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Meiotic chromosomes: it takes two to tango

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Meiosis is a special type of cell division that produces haploid gametes from diploid parental cells. Chromosome number is reduced during meiosis because a single round of DNA replication is followed by two rounds of chromosome segregation (Fig. 1). Fusion of two gametes during sexual reproduction restores the diploid chromosome complement.

The second division of meiosis (the equational division) resembles mitosis: Sister chromatids separate and segregate. The first division, however, is unique. Reductional chromosome segregation at meiosis I differs from mitosis and meiosis II in a number of respects. First, sister chromatids remain associated with each other. Second, the two copies of the same chromosome (called homologous chromosomes or homologs) behave in a coordinate fashion, such that one chromosome moves to one pole of the spindle apparatus and its homolog moves to the opposite pole. This coordination in chromosome behavior depends on complex processes and elaborate structures that bring homologs together during meiotic prophase and hold them together until the transition between metaphase I and anaphase I. In most organisms, the relevant processes include alignment of homologs, assembly of the synaptonemal complex (SC, described below), genetic recombination, and the formation of chiasmata (stable connections between homologs formed at the sites of crossovers). These events occur during a very lengthy prophase that is divided into a series of substages based on changes in chromosome morphology (Table 1). This article reviews our current knowledge of the processes and structures that promote and maintain interactions between homologs and thereby ensure proper reductional chromosome segregation. Emphasis is placed on observations made in recent years, particularly those that have enhanced our understanding of the molecular mechanisms underlying meiotic chromosome behavior.

Homolog pairing

Understanding how homologous chromosomes find and recognize each other during meiotic prophase is one of the most fascinating and challenging problems in studies of meiosis. Despite intensive investigation, no clear picture of this process has yet emerged. This lack of clarity is probably attributable (at least in part) to the fact that cells employ several different mechanisms to effect pairing and different organisms rely to varying extents on each mechanism.

Presynaptic alignment

In many organisms, homolog pairing is clearly distinct from chromosome synapsis. (Throughout this review, pairing refers to the side-by-side alignment of homologs, perhaps at a distance, whereas synapsis refers to the intimate association of chromosomes specifically in the context of the SC.) Presynaptic alignment is evidenced by a parallel alignment of homologs at a distance that exceeds the width of the SC (Zickler 1977; Loidl 1990; Scherthan et al. 1992; Weiner and Kleckner 1994; Barlow and Hulten 1996). In some organisms, homologs align along their entire lengths prior to the initiation of synapsis; in many others, pairing and then synapsis occur on a segment-by-segment basis. Several observations indicate that pairing not only precedes, but is separable from synapsis. First, in certain meiotic mutants, chromosomes pair but fail to synapse (Moreau et al. 1985; Loidl et al. 1994; Weiner and Kleckner 1994; Nag et al. 1995). Second, in triploids (or trisomes), all three homologs line up side by side, but only two chromosomes engage in synapsis in any given region (for review, see Loidl 1990). Third, the SC can form between nonhomologous chromosomes (for review, see von Wettstein et al. 1984), whereas pairing (by definition) involves homologs.

Premeiotic pairing

To what extent does homolog pairing in nonmeiotic (vegetative or somatic) cells contribute to chromosome pairing in meiosis? In *Drosophila* and other Dipterans, homologs pair early during embryogenesis and they remain paired throughout subsequent cell cycles (Lifschytz and Haraven 1982; Hiraoka et al. 1993; Dernburg et al. 1996a). This pairing is not disrupted in meiotic cells; instead, chromosomes undergo a gradual transition from somatic pairing to SC formation (Wandall and Svendsen 1985).

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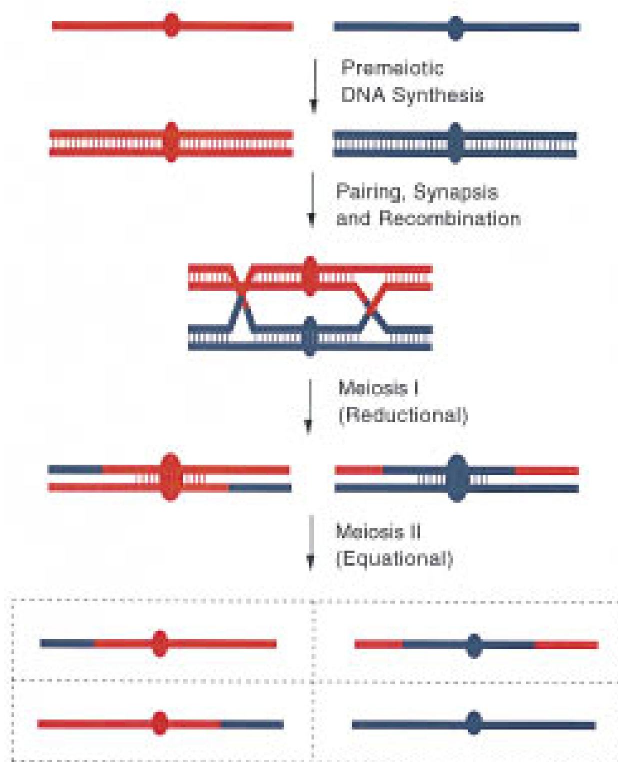

Figure 1. Diagram of meiotic chromosome segregation. Shown is a single pair of homologous chromosomes (one chromosome in red, the other in blue). Each solid line represents a single chromatid; the hatched lines indicate sister chromatid cohesion.

Evidence for homolog associations in nonmeiotic cells of the budding yeast *Saccharomyces cerevisiae* and the fission yeast *Schizosaccharomyces pombe* has been obtained by fluorescence in situ hybridization (FISH) using chromosome-specific probes. In diploid cells of fission yeast, homologs occupy a limited territory within the nucleus with separate territories occupied by different pairs of homologs (Scherthan et al. 1994). In budding yeast, homologs appear to be closely apposed at multiple sites along their lengths (Weiner and Kleckner 1994). Recent studies indicate that chromosomes in vegetative cells of *S. cerevisiae* are nonrandomly positioned, with centromeres tightly clustered together and telomeres distributed in the other half of the nucleus (J. Loidl, pers. comm.). Thus, nuclear architecture may contribute to the apparent pairing observed in premeiotic yeast cells. Consistent with this hypothesis, only centromeric regions show a high level of pairing in diploid cells of *S. pombe* (Scherthan et al. 1994).

In many organisms, chromosomes are not paired premeiotically. Particularly compelling demonstrations come from recent FISH analyses of pairing in the last somatic mitosis preceding meiosis. These results clearly demonstrate that homologs are not paired in premeiotic cells of maize, mice and humans (Scherthan et al. 1996; Bass et al. 1997). In those fungi in which meiosis immediately follows the fusion of two haploid nuclei to form a zygote, homolog pairing must be restricted to meiotic cells. However, at least in *Ascobolus* and *Neurospora,* dispersed repeated sequences are inactivated (by mutation or methylation) in the haploid nuclei of heterokaryons (for review, see Rossignol and Faugeron 1994). Thus, in these organisms, genome-wide searching for homology must occur both during meiosis and during the few cell divisions that intervene between mating and nuclear fusion.

Is recombination required for pairing?

Crossing over promotes proper meiotic chromosome segregation, but gene conversion (i.e., nonreciprocal recombination) has no effect on the fidelity of segregation. Speculation about the biological function of gene conversion led to the hypothesis that conversion promotes homolog pairing (Smithies and Powers 1986). Invasion of a single-stranded DNA tail into an intact DNA duplex

Table 1. *Events in meiotic prophase*

Stage in meiotic prophase	Chromosome morphology and SC morphogenesis	Bouquet formation	DSB repair	Cytological signs of recombination
Leptotene	axial elements begin to develop	telomeres begin to cluster	DSBs appear	early nodules
Zygotene	chromosome synapsis initiates	telomeres tightly clustered	DSBs disappear	early nodules
Pachytene	chromosomes fully synapsed	telomeres disperse	double Holliday junctions	late nodules
Diplotene	SC disassembled; chromosomes condense		mature recombinants	chiasmata
Diakinesis	further chromosome compaction			chiasmata

The precise sequence of events varies somewhat from one organism to another. Meiotic DSB repair has been studied exclusively in *S. cerevisiae,* whereas most observations of recombination nodules and all observations of chiasmata have been made in other organisms. (SC) Synaptonemal complex; (DSB) double-strand break.

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would provide a means to assess the similarity between two DNA molecules. Homolog recognition, sometimes resulting in gene conversion, would establish a connection between homologs and thereby promote chromosome synapsis. The phenotypes of mutants defective in crossing over, but proficient in gene conversion and synapsis, seemed to support the hypothesis that conversion and crossing over differ in mechanism and function (Carpenter 1984; Engebrecht et al. 1990). However, gene conversion-mediated homolog pairing now seems unlikely, at least in *S. cerevisiae.*

Physical analyses of recombination intermediates and products in yeast indicate that gene conversion and crossing over occur at the same time, and both are initiated by double-strand breaks (DSBs) (Storlazzi et al. 1995). Thus, these data argue against a gene conversion-specific recombination pathway. Also, yeast mutants that are defective in the formation or processing of DSBs (and therefore lack single-stranded tails competent for strand invasion) nevertheless undergo a significant amount of meiotic homolog pairing (Loidl et al. 1994; Weiner and Kleckner 1994; Nag et al. 1995). Additional evidence for interactions between homologs that are independent of recombination comes from studies of DSB induction in diploids that are either homozygous or heterozygous at the DSB site. Heterozygosity decreases the frequency of DSBs, suggesting that homolog recognition precedes and promotes the initiation of recombination (Xu and Kleckner 1995; Rocco and Nicolas 1996).

Pairing at multiple sites along chromosomes

Observations in budding yeast suggest that meiotic chromosome pairing involves a genome-wide homology search in which most or all DNA sequences are capable of ''probing'' all other sequences in the genome. If a single yeast gene is inserted at an ectopic location, recombination between the inserted sequence and its counterpart at the normal chromosomal location is strongly induced in meiosis (e.g., Jinks-Robertson and Petes 1985; Lichten et al. 1987). In some cases, the frequency of these ectopic recombination events is nearly as high as that of recombination between genes at equivalent positions on homologous chromosomes. Ectopic recombination events also occur at high frequency during meiosis in mice (Murti et al. 1994).

FISH analyses of chromosome pairing in yeast provide additional evidence that sites capable of pairing are numerous and widely dispersed along the lengths of chromosomes (Scherthan et al. 1994; Weiner and Kleckner 1994). Many different segments of DNA can pair in meiotic prophase (independent of chromosome condensation and SC formation), and pairing at one site is unaffected by pairing at another site (≤150 kbp away) on the same chromosome. In *S. cerevisiae,* the total number of pairing sites per meiotic cell is estimated to be ~190 (or one every 65 kbp), which is similar to the total number of recombination events that occur (~260). This correspondence (and other considerations) has led to the hypothesis that the sites of early pairing later serve as sites for the initiation of recombination (Weiner and Kleckner 1994; Kleckner 1996).

Genetic and cytological studies of several plants also indicate that pairing sites are numerous and fairly uniformly distributed along chromosomes. In several species, pairing has been visualized by electron microscopic analysis of silver-stained spread nuclei. Prior to the initiation of SC formation, parallel chromosome cores appear to be connected to each other at multiple sites along each chromosome pair (e.g., Gillies 1985; Albini and Jones 1987; Anderson and Stack 1988). Studies of pairing partner switches in triploids and trisomic strains also suggest that most or all chromosomal segments are capable of pairing (Vincent and Jones 1993). A similar conclusion has been reached based on genetic analysis of maize variants carrying chromosome rearrangements (Maguire 1986).

Early meiotic pairing may involve the formation of unstable side-by-side (paranemic) joints between intact DNA duplexes (Kleckner and Weiner 1993; Kleckner 1996). Such reversible associations would provide a mechanism to deal with the interchromosomal tangles that are expected to result when uncondensed chromosomes (meandering through the nucleus) initiate pairing at multiple sites. Unstable interactions could be sufficient to align chromosomes because homologs would be held together at multiple sites along their length. Interactions between ectopic repeats would usually be displaced by homologous interactions as paranemic joints are broken and reformed. The RecA strand exchange protein of bacteria is capable of forming homology-dependent paranemic joints (West 1992) of the sort hypothesized by this model; however, none of the RecA homologs in yeast is required for meiotic chromosome pairing (Kleckner 1996).

Meiotic pairing centers

Although meiotic pairing sites appear to be numerous and widespread in many species, there are certain organisms in which only particular sites on chromosomes can promote homolog pairing. In no system is this more obvious than in the nematode, *Caenorhabditis elegans* (Zetka and Rose 1995a).

Studies of chromosome rearrangements in worms have demonstrated that each chromosome contains a single site that is necessary to promote recombination and synapsis along the length of the chromosome (for review, see Zetka and Rose 1995a). This site is referred to as a homolog recognition region or HRR; in every case, it is located at one end of the chromosome. Models for HRR function must take into account the observation that the HRR functions reasonably well even when present on only one of the two homologs (Villeneuve 1994). The most likely explanation for HRR activity is that this region promotes homolog pairing, perhaps by acting as a loading site for a protein complex that is involved in homology searching and is capable of movement along the chromosome (Villeneuve 1994). However, the possibility cannot be excluded that the HRR serves instead to

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promote synapsis and/or recombination between homologs that have already paired.

Special pairing centers also exist in *Drosophila.* There are four such sites on the X chromosome (Hawley 1979).

Pairing of achiasmate chromosomes

In certain exceptional organisms, some or all pairs of chromosomes routinely fail to undergo meiotic recombination. Proper segregation of these chromosomes is achieved through special mechanisms that are independent of chiasma formation. The best studied examples are found in *Drosophila,* in which there is no meiotic recombination in males and the tiny 4th chromosome never recombines in females (for review, see Hawley and Theurkauf 1993). Recent studies have identified some of the *cis*-acting sequences required for pairing and segregation of these achiasmate chromosomes.

Pairing of the X and Y chromosomes in male flies is mediated exclusively by the repeated sequences specifying the ribosomal RNAs (for review, see McKee 1996; see also Ren et al. 1997). One block of tandem repeats on the X chromosome interacts with a similar block on the Y. Analysis of flies containing transgenic insertions of ribosomal DNA has demonstrated that sequences both necessary and sufficient for pairing reside in a 240-bp sequence located in the intergenic spacer region. This sequence contains a promoter for RNA polymerase I and is present in 6–12 tandem repeats in each intergenic spacer. As few as six copies of the 240-bp unit confer measurable pairing ability, and pairing activity increases with increasing copy number.

Progress has also been made in identifying the sites required for chromosome 2 pairing in males (for review, see McKee 1996). Analysis of flies in which segments of chromosome 2 have been transposed to the Y chromosome indicates a widespread distribution of weak pairing capacity throughout the euchromatin of chromosome 2. Superimposed on this background of weak pairing sites is a strong site that corresponds to multiple copies of a repeat unit encoding the major histones. Thus, in male flies, pairing of both sex chromosomes and autosomes appears to involve tandem arrays of transcriptionally active sequences. Perhaps the relevant promoters share a common chromatin structure that makes them particularly accessible to proteins involved in pairing.

In female flies, pairing and segregation of the 4th chromosome depends on heterochromatin (Hawley et al. 1993). Efficient disjunction of engineered minichromosomes requires 1000 kb pairs of overlap in centromere-proximal heterochromatin and is unaffected by euchromatin or by differences in chromosome size (Karpen et al. 1996). Cytological analysis demonstrates that segregation of the 4th chromosomes is preceded by a physical association between chromosomes from zygotene through metaphase I (Carpenter 1975; Dernburg et al. 1996b). The mechanism of heterochromatin-mediated homolog pairing is unknown. It is unlikely to rely strictly on a DNA homology search mechanism because sequences present in heterochromatin are not unique to a particular chromosome pair.

A role for telomeres in homolog pairing

In many organisms, meiotic chromosomes form a bouquet in which the ends of chromosomes are attached to a small region of the nuclear envelope (for review, see Dernburg et al. 1995). Bouquet formation may facilitate homolog pairing by bringing homologous subtelomeric sequences into parallel alignment within a limited region of the nuclear volume. The bouquet forms abruptly during late leptotene and persists throughout zygotene; telomeres disperse again during pachytene (Table 1) (Dernburg et al. 1995; Scherthan et al. 1996; Bass et al. 1997). At least in some organisms, bouquet formation is a two-step process in which telomeres first attach to the nuclear envelope and then move along the envelope to a common location (Scherthan et al. 1996). Bouquet formation is coincident with homolog pairing and precedes the initiation of chromosome synapsis (Scherthan et al. 1996; Bass et al. 1997). Two observations suggest that telomere movements are mediated by microtubules. First, the base of the bouquet is juxtaposed to the microtubule-organizing center (Dernburg et al. 1995). Second, microtubule-destabilizing agents interfere with telomere movements and homolog pairing (for review, see Loidl 1990; Dernburg et al. 1995).

Additional evidence for telomere-mediated chromosome movement comes from studies of *S. pombe* (Chikashige et al. 1994, 1997; Scherthan et al. 1994). Time-lapse images of living cells have demonstrated that the nucleus is dragged back and forth over the length of the cell several times during meiotic prophase, producing elongated ''horse tail'' nuclei (Chikashige et al. 1994). Present at the leading edge of the nucleus is the spindle pole body, to which all of the telomeres are attached. Microtubule arrays emanate from the spindle pole body to both ends of the cell; coordinated shortening and lengthening of the two microtubule arrays pushes and/or pulls the nucleus back and forth (Svoboda et al. 1995). It has been suggested that nuclear movement, with the associated stirring and stretching of chromosomes, facilitates homolog alignment in fission yeast (Scherthan et al. 1994). Consistent with this hypothesis, a mutation that impairs telomere clustering substantially reduces meiotic recombination (Shimanuki et al. 1997).

Telomeres also play a role in homolog pairing in *S. cerevisiae* (B. Rockmill and G.S. Roeder, unpubl.). Recent results suggest that interactions between homologous chromosomes trigger a checkpoint that prevents meiotic nuclear division until all chromosomes are paired. A circular chromosome and its linear homolog are unable to activate this checkpoint, demonstrating that efficient homolog recognition requires both chromosomes to have ends. A protein that might play a role in homolog pairing in budding yeast is Tam1/Ndj1, which localizes specifically to the ends of meiotic chromosomes (Fig. 2D) (Chua and Roeder 1997; Conrad et al. 1997). A *tam1/ndj1* mutation causes a delay in chromo-

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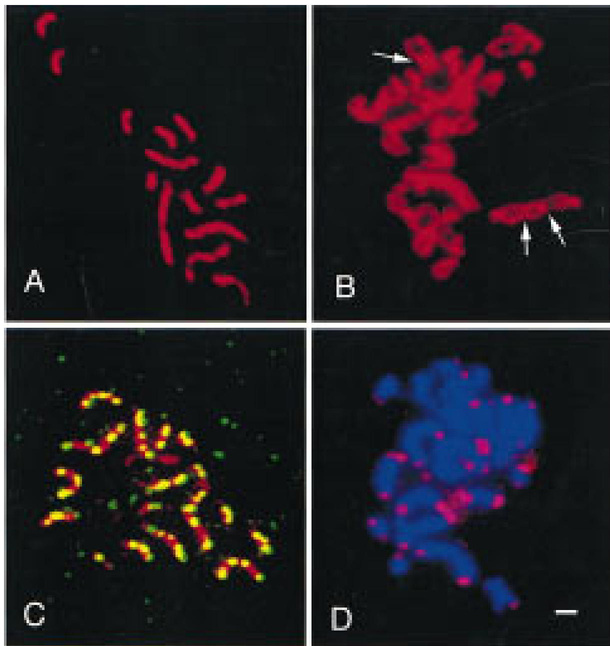

Figure 2. Localization patterns of the Zip1, Red1, Msh4, and Tam1 proteins in *S. cerevisiae.* (*A*) Spread chromosomes from wild-type cells stained with antibodies to Zip1. (*B*) Spread chromosomes from the *zip1* mutant stained with antibodies to Red1. Parallel axial elements are connected at axial associations (arrows). Red1 staining is more continuous in the *zip1* mutant than in wild type. (*C*) Spread chromosomes from wild type stained with antibodies to Zip1 (red) and epitope-tagged Msh4 (green). (*D*) Spread chromosomes from wild type stained with a DNA-binding dye (blue) and antibodies to Tam1 (red). All nuclei are in pachytene. Bar, 1 µm. Photographs provided by Kuei-Shu Tung (*A*), Albert Smith (*B*), Janet Novak (*C*), and Penelope Chua (*D*) (Yale University, New Haven, CT). Figure 2B is reproduced, with permission, from *The Journal of Cell Biology* (1997, vol. 136, pp. 963) (The Rockefeller University Press, NY).

some synapsis and increases the frequency of chromosome pairs that fail to recombine.

The SC

A conspicuous landmark of the meiotic landscape is the SC, a ribbon-like structure that results from the intimate association between homologous chromosomes during meiotic prophase (Fig. 3) (for review, see von Wettstein et al. 1984; Heyting 1996). Early in prophase, the two sister chromatids of a single chromosome develop a common proteinaceous core called an axial element. As meiosis progresses, the axial elements derived from homologous chromosomes become closely connected to each other along their entire lengths by proteins that constitute the central region of the SC (Fig. 4). Within mature SC, axial elements are referred to as lateral elements, and these are separated from each other by a uniform distance of ~100 nm. Each SC is surrounded by a halo of chromatin loops that are anchored to the lateral elements. Very little

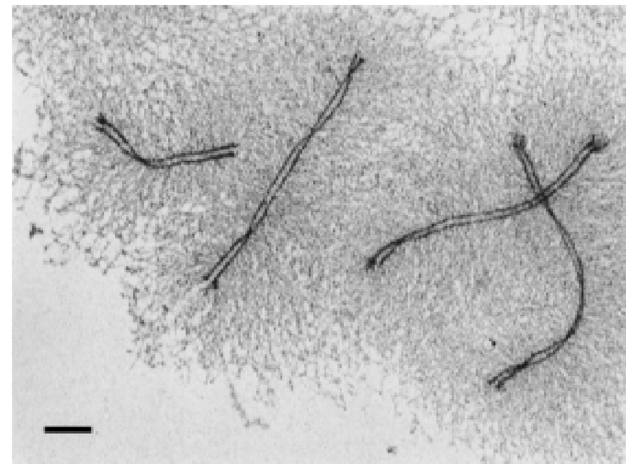

Figure 3. Synaptonemal complexes from the moth, *Hyalophora columbia.* Shown are four SCs from a single nucleus; the two on the right are overlapping. Chromosomes were surface spread, stained with silver nitrate, and examined in the electron microscope. Each SC consists of two parallel lateral elements (dark lines) surrounded by chromatin loops. Bar, 1 µm. Photograph provided by Peter Moens (York University, Toronto, Ontario, Canada). Figure 3 is reproduced, with permission, from *Meiosis* (1987, ed. P.B. Moens) (Academic Press, Inc., Orlando, FL).

DNA passes through the central region of the SC (Vazquez Nin et al. 1993).

Special cytological techniques have identified substructures within the central region of the SC (Fig. 4) (for review, see Schmekel and Daneholt 1995). A central el-

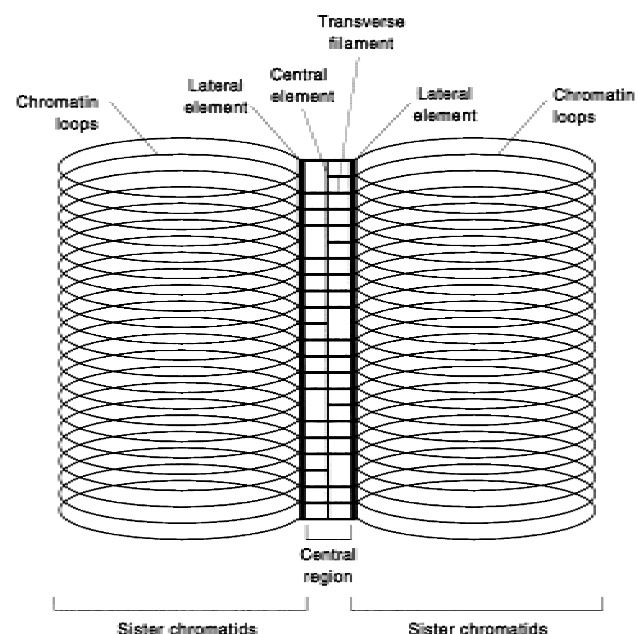

Figure 4. Diagram of the SC.

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ement lies parallel to and equidistant between the two lateral elements. The central region also contains a number of regularly spaced transverse filaments that lie perpendicular to the long axis of the complex. Many of these filaments traverse the entire width of the SC, from one lateral element to the other, whereas others terminate at the central element.

In recent years, several protein components of the SC have been identified and characterized. In yeast, genes encoding SC proteins have been identified in screens for meiotic mutants. In plants and animals, SC components have been isolated from preparations of purified SCs. Antibodies to SC components serve as valuable tools in investigating the structure and assembly of the complex, and in exploring the temporal and spatial relationships between chromosome synapsis and other meiotic processes. Studies of yeast mutants that lack structural components of the SC are providing insight into the functions of the complex.

The central region of the SC

Genes that encode putative components of the transverse filaments of the SC have been cloned from both yeast and mammals. These include the *ZIP1* gene of *S. cerevisiae,* the *SCP1* gene of rats, and homologs of *SCP1* from hamsters (Syn1), mice, and humans (Meuwissen et al. 1992, 1997; Sym et al. 1993; Dobson et al. 1994; Liu et al. 1996). These proteins range in size from 875 to 997 amino acids and each contains a long central region of extended coiled-coil motif. Thus, it is generally assumed that each of these proteins forms a homodimer consisting of an elongated rod-shaped domain flanked by small globular domains, analogous to the structure of myosin and intermediate filament proteins. The predicted amino acid sequences of the four mammalian proteins are 74%–93% identical to each other. Although similar in overall structure, the Zip1 protein is no more similar to SCP/Syn1 than expected for any two proteins containing coiled coils. The *ZIP1* and *SCP1* genes are expressed specifically in meiotic prophase cells (Meuwissen et al. 1992; Sym et al. 1993).

What is the evidence that Zip1 and SCP1/Syn1 are components of transverse filaments? First, these proteins localize to synapsed chromosomes but not to unsynapsed axial elements (Fig. 2A, 5A) (Meuwissen et al. 1992; Sym et al. 1993; Dobson et al. 1994). Second, a *zip1* null mutant assembles full-length axial elements that are homologously paired but not intimately synapsed (Fig. 2B) (Sym et al. 1993; Nag et al. 1995). Third, mutations that increase the length of the Zip1 coiled coil lead to corresponding alterations in the width of the SC (Sym and Roeder 1995). Fourth, epitope-mapping experiments demonstrate that SCP1 and Syn1 lie perpendicular to the long axis of the complex with their carboxyl termini located in the lateral elements and their amino termini positioned near the middle of the central region (Dobson et al. 1994; Liu et al. 1996; Schmekel et al. 1996). These data suggest that two SCP1/Syn1 dimers lying head to head, and perhaps slightly overlapping, span the width of the SC from one lateral element to the other. The amino-terminal globular domains of these proteins may constitute the central element of the SC.

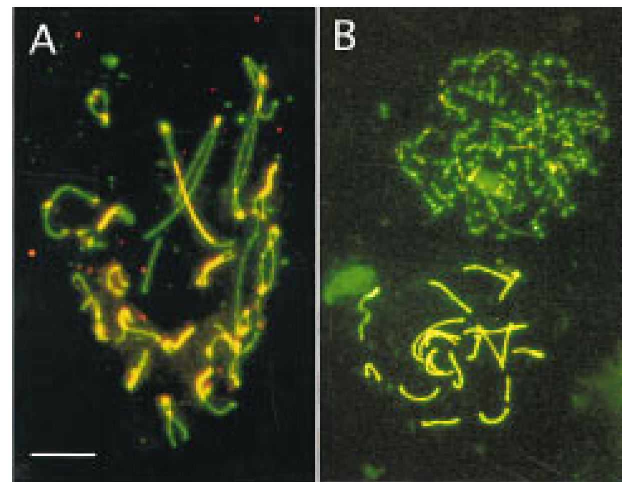

Figure 5. Localization patterns of the Syn1, Cor1, and Rad51 proteins in mouse spermatocytes. (*A*) A spread nucleus in early diplotene stained with antibodies to Cor1 (green) and Syn1 (red). Regions of overlap between the two proteins appear yellow. Thus, yellow staining indicates synapsed chromosomal segments, while green staining represents chromosomal segments that have desynapsed. (*B*) Two spread nuclei stained with antibodies to Rad51 (green) and Cor1 (red). The nucleus on top is in late leptotene; the nucleus on the bottom is in early pachytene. Regions of overlap between the two proteins appear yellow. The leptotene nucleus shows many Rad51 foci and a few short segments of axial elements. In the pachytene nucleus, both Rad51 and Cor1 are localized fairly continuously along the lengths of chromosomes. Bar, 10 μm. Photographs provided by Peter Moens (York University, Toronto, Ontario, Canada). The nuclei in Figure 5B are reproduced, with permission, from *Chromosoma* (1997) (Springer-Verlag, New York, NY).

Other proteins that localize to the SC central region are SC65 and SC48 from rats (Chen et al. 1992; Smith and Benavente 1992); SC48 has been postulated to be a component of transverse filaments. The *dy* mutant of maize may also define a component of transverse filaments, since a *dy* mutation increases the width of the SC central region (Maguire et al. 1991).

The lateral elements of the SC

The best-characterized component of the lateral elements of the SC is the Cor1 protein of hamsters and the homologous SCP3 protein from rats (Dobson et al. 1994; Lammers et al. 1994). The meiosis-specific Cor1/SCP3 protein is ~250 amino acids in length, and a significant portion of the carboxy-terminal half of the protein is predicted to form a coiled coil. Cor1/SCP3 has been shown to interact with itself both in vitro and in the yeast two-hybrid system; this interaction requires a region of coiled coil (Tarsounas et al. 1997). In meiotic cells, Cor1/SCP3 localizes to unsynapsed axial elements and to the lateral

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elements of mature SCs (Dobson et al. 1994; Lammers et al. 1994; Liu et al. 1996). Unexpectedly, Cor1/SCP3 does not dissociate from chromosomes as the SC disassembles (Fig. 5A) (Dobson et al. 1994; Moens and Spyropoulos 1995). From diplotene through metaphase I, Cor1/SCP3 remains associated with the cores of chromosomes, although the pattern of staining with anti-Cor1 antibodies becomes progressively fainter and more discontinuous. During the same time period, Cor1 accumulates near centromeres. By anaphase I, Cor1 is no longer detectable along chromosome cores. The protein dissociates from centromeres abruptly at anaphase II. This localization pattern suggests a role for Cor1/SCP3 in meiotic chromosome segregation (see below).

In *S. cerevisiae,* the meiosis-specific Red1 protein is associated with unsynapsed axial elements and with mature SCs (Fig. 2B) (Smith and Roeder 1997). Red1 localizes somewhat discontinuously along the lengths of pachytene chromosomes, which is not the result expected if Red1 is an integral building block of axial/lateral elements. However, Red1 is tightly associated with the cores of meiotic chromosomes and it is required for the formation of axial/lateral elements (Rockmill and Roeder 1990; Smith and Roeder 1997). These observations have led to the hypothesis that Red1 nucleates the formation of axial elements, thus promoting the assembly of other proteins responsible for continuous linear elements (Smith and Roeder 1997). A number of observations suggest a direct interaction between Red1 and the Hop1 protein, which is also a component of meiotic chromosomes (Hollingsworth et al. 1990). Red1 and Hop1 localize to the same sites, and Hop1 requires Red1 for its assembly onto chromosomes (Smith and Roeder 1997). In addition, overproduction of Red1 suppresses certain *hop1* non-null mutants (Hollingsworth and Johnson 1993; Friedman et al. 1994). Unlike Red1, Hop1 is not required for axial element formation though it is required for synapsis (Hollingsworth and Byers 1989; F. Klein and B. Byers, pers. comm.). Red1 dissociates from chromosomes as the SC disassembles (i.e., at the same time as Zip1); Hop1 departs chromosomes even earlier (Smith and Roeder 1997).

Assembly and function of the SC must be highly regulated and several observations suggest a role for protein phosphorylation in such regulation. First, Cor1/SCP3 is a phosphoprotein whose extent of phosphorylation changes throughout pachytene (Lammers et al. 1995). Second, the meiosis-specific protein kinase encoded by the yeast *MEK1/MRE4* gene is required for proper SC assembly (Rockmill and Roeder 1991), and genetic assays indicate a direct interaction of Mek1/Mre4 with Hop1 and/or Red1 (Hollingsworth et al. 1997; J. Bailis and G.S. Roeder, unpubl.). In addition, Red1 interacts with a protein phosphatase in the two-hybrid system (Tu et al. 1996). Interaction of Cor1/SCP3 with a ubiquitin-conjugating enzyme raises the possibility that ubiquitin-mediated proteolysis also plays a role in SC morphogenesis or disassembly (Tarsounas et al. 1997).

Other components of lateral elements include the 170-kD protein encoded by the rat SCP2 gene (Heyting 1996) and a protein(s) from lilies recognized by a monoclonal antibody (Anderson et al. 1994). Topoisomerase II, which is a component of mitotic chromosome scaffolds, also localizes to the lateral elements of the SC (Earnshaw et al. 1985; Moens and Earnshaw 1989).

Chromatin organization

The DNA of synapsed chromosomes is organized into a series of chromatin loops, each attached at its base to a lateral element (Figs. 3 and 4). Chromatin loop size varies significantly among species, ranging from 0.5 μm (from base to top) in *S. cerevisiae* to 14 μm in grasshopper (for review, see Moens and Pearlman 1988). Variation in loop size results in substantial differences in the amount of DNA per unit length of SC—for example, 12,000 kbp of DNA per micron of SC length in humans versus 500 kbp per micron of SC in yeast. This regulation of chromatin packaging implies the existence of specific DNA sequences that serve as SC attachment sites. However, isolation and characterization of DNA sequences that remain tightly associated with the SC after DNase digestion has failed to identify any sequences that are unique to meiotic chromosome cores (Moens and Pearlman 1990; Pearlman et al. 1992). Nevertheless, there must be some specificity to binding because some DNA sequences lack SC attachment sites. When a large piece of prokaryotic DNA is inserted into a mouse chromosome, the insert gives rise to an unusually large loop that appears to be anchored to the SC only by the adjacent eukaryotic DNA (Heng et al. 1994).

A number of observations indicate that DNA sequence is not the only (perhaps not even the primary) determinant of loop size. Chromosomal geography and host cell are also important factors. Within a single chromosome, loop size is two to three times smaller near telomeres than it is in interstitial regions (Heng et al. 1996). This effect is attributable to chromosomal position (not sequence) because telomeric sequences inserted at interstitial sites display the same packaging ratio as the surrounding chromatin (Heng et al. 1996). When an artificial chromosome consisting mostly of human DNA is propagated in yeast, the human DNA adopts the loop size characteristic of yeast DNA (Loidl et al. 1995). These observations suggest the existence of multiple potential attachment sites whose use is variable and influenced by many factors.

There is an inverse correlation between the density of chromatin packaging and the rate of meiotic crossing over (i.e., the more DNA per SC length, the lower the rate of exchange). For example, the average recombination rate in yeast [~0.26 map units (mu) per kbp] is nearly 300 times that in humans (0.0009 mu/kbp), while the amount of DNA per unit length of SC in humans is about 25 times that in yeast (for review, see Loidl et al. 1995). In human females, both the length of the SC complement (which is inversely related to loop size) and the rate of meiotic recombination are twice those in males (Wallace and Hulten 1985). When human DNA is introduced into yeast, it adopts both the packaging ratio

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and the recombination rate typical of yeast DNA (Loidl et al. 1995; Sears et al. 1992). A lower density of packing (i.e., smaller loop size) increases the relative amount of DNA that is contained within the SC. SC-associated sequences may have greater access to the recombination machinery, which localizes over the central region of the complex (von Wettstein et al. 1984).

The DSB repair pathway of meiotic recombination

The DNA lesions that serve to initiate meiotic recombination in *S. cerevisiae* have been unambiguously identified as DSBs. Meiotically induced DSBs have been observed at a number of recombination hotspots (Sun et al. 1989; Cao et al. 1990; Goldway et al. 1993; Bullard et al. 1996), and these breaks appear and disappear with the kinetics expected for an early intermediate in the exchange process (Padmore et al. 1991). The overall frequency of DSBs and their distribution throughout the genome are generally consistent with the observed frequency and distribution of meiotic recombination events (Baudat and Nicolas 1997; Klein et al. 1996; Wu and Lichten 1994).

According to the DSB repair model of recombination (Fig. 6), double-strand cleavage is followed by exonucleolytic digestion to expose single-stranded tails with 3′ termini. These single-stranded tails invade an uncut homologous duplex where they promote repair synthesis followed by branch migration to produce two Holliday junctions. Resolution of these junctions in opposite directions results in a reciprocal crossover between markers that flank the region of strand exchange. In yeast, many of the intermediates postulated by the DSB repair model have been demonstrated physically, and mutants blocked at different steps in the repair process have been identified (Fig. 6).

Initiation

Mutations in at least nine different yeast genes lead to a failure to induce meiotic DSBs (Fig. 6). Until recently, however, the gene product directly involved in cleavage remained elusive. Identification of the relevant protein was made possible by the characterization of a number of mutants (Fig. 6) in which DSBs are induced but their subsequent processing to expose single-stranded tails is blocked. In these mutants, the 5′ termini of the broken molecules are covalently linked to protein (de Massy et al. 1995; Keeney and Kleckner 1995; Liu et al. 1995). Analysis of purified DNA–protein complexes has dem-

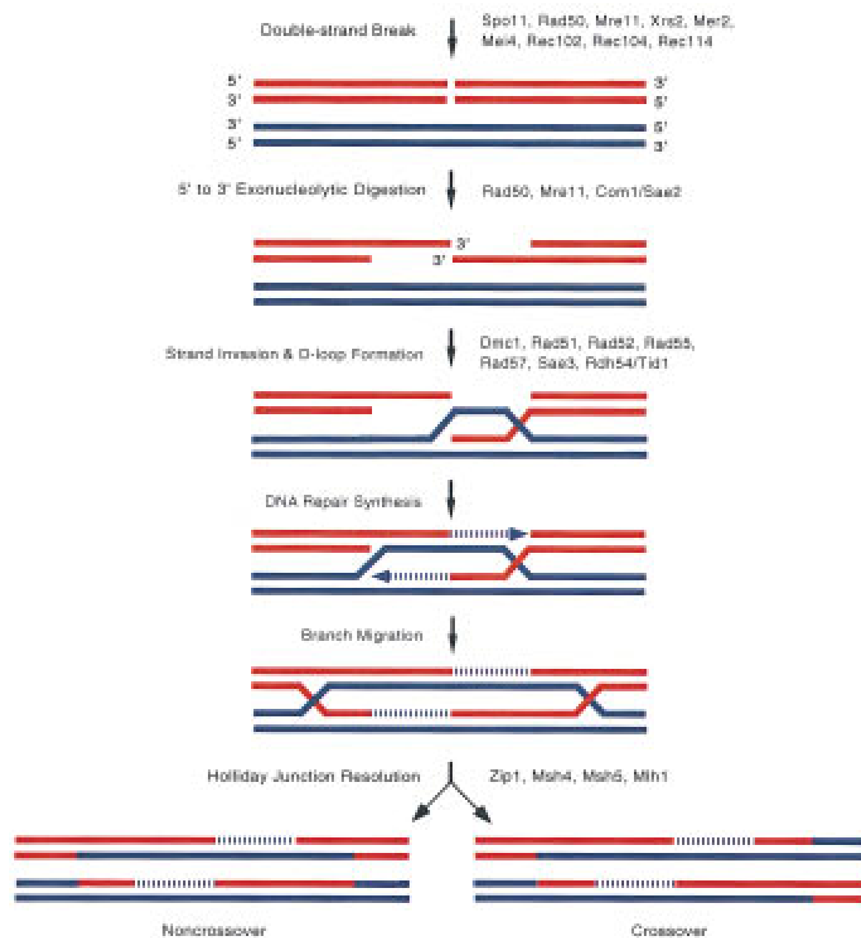

Figure 6. DSB repair model of meiotic recombination (Szostak et al. 1983; Sun et al. 1991). Shown are two double-stranded DNA molecules (one in red, the other in blue). Gene products are indicated only in cases where a corresponding mutant has been demonstrated to be defective at a specific step by genetic and/or physical assays. Other gene products are implicated based on in vitro activities and/or mitotic phenotypes. Not all of the gene products shown are absolutely required at the step indicated. For the noncrossover product shown on the *bottom left,* both Holliday junctions were resolved by cleavage of inside strands. For the crossover product shown on the *bottom right,* the Holliday junctions on the *left* and *right* were resolved by cleavage of inside and outside strands, respectively. References to gene products are as follows: Spo11 (Cao et al. 1990), Rad50 (Alani et al. 1990), Mre11 (Johzuka and Ogawa 1995; Nairz and Klein 1997), Xrs2 (Ivanov et al. 1992), Mer2 (Rockmill et al. 1995a), Mei4 (Menees and Roeder 1989), Rec102/104/114 (Bullard et al. 1996), Com1/Sae2 (McKee and Kleckner 1997a; Prinz et al. 1997), Dmc1 (Bishop et al. 1992; Rockmill et al. 1995b), Rad51 (Shinohara et al. 1992), Sae3 (McKee and Kleckner 1997b), Rdh1/Tid1 (Shinohara et al. 1997), Rad52 (Ogawa et al. 1993a), Rad55/57 (Schwacha and Kleckner 1997), Zip1 (Sym and Roeder 1994), Msh4 (Ross-Macdonald and Roeder 1994), Msh5 (Hollingsworth et al. 1995), and Mlh1 (Hunter and Borts 1997).

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onstrated that the attached protein is Spo11 (Keeney et al. 1997), one of the gene products previously shown to be required for the initiation of meiotic recombination (Klapholz et al. 1985; Cao et al. 1990). The Spo11 protein is homologous to a novel family of type II topoisomerases (Bergerat et al. 1997), suggesting that DSBs are formed by a topoisomerase-like transesterification reaction rather than by endonucleolytic hydrolysis. Furthermore, the fact that topoisomerase-mediated breaks are directly reversible raises the possibility that a meiotic DSB can be reversed in the absence of a suitable partner with which to recombine (Keeney et al. 1997).

Exonucleolytic digestion

After double strand cleavage, the ends of the broken molecule must be resected by a 5′-to-3′ exonucleolytic activity. Mutations in three genes—*RAD50, MRE11,* and *COM1/SAE2*—lead to a failure of DSB resection (Fig. 6) (Alani et al. 1990; McKee and Kleckner 1997a; Nairz and Klein 1997; Prinz et al. 1997). In the case of *RAD50* and *MRE11,* only certain non-null alleles confer this phenotype; null mutants result in a failure of DSB induction (Alani et al. 1990; Johzuka and Ogawa 1995; Nairz and Klein 1997). Thus, Rad50 and Mre11 are required for both the formation and processing of meiotic DSBs. Rad50 and Mre11 interact with each other in the two-hybrid system (Johzuka and Ogawa 1995) and they are homologous to the *E. coli* SbcC (Rad50) and SbcD (Mre11) proteins (Sharples and Leach 1995). The SbcC/SbcD complex acts as an exonuclease on double-stranded DNA (Connelly and Leach 1996), suggesting that a complex containing Rad50 and Mre11 is indeed the exonuclease responsible for DSB processing in yeast. Consistent with this hypothesis, the *rad50* mutant is defective in the resection of DSBs induced by a site-specific endonuclease in vegetative yeast cells (Ivanov et al. 1994).

Strand invasion

Four yeast genes encode homologs of the bacterial RecA strand exchange enzyme—*RAD51, RAD55, RAD57,* and *DMC1.* Mutations in all four genes can lead to defects in the repair of resected DSBs (Bishop et al. 1992; Shinohara et al. 1992; Schwacha and Kleckner 1997), but biochemical studies suggest that Rad51 is the enzyme that catalyzes the invasion of single-stranded tails into an uncut DNA duplex (Fig. 6). Purified Rad51 protein promotes strand exchange in vitro (Sung 1994) and forms nucleoprotein filaments that are similar to those formed by RecA (Ogawa et al. 1993b). Rad51-promoted strand exchange requires the yeast single-stranded DNA-binding protein and is stimulated by a heterodimer consisting of Rad55 and Rad57 (Sung 1997). Processing of resected DSBs in meiosis also requires Rad52 and Rdh54/Tid1 (Ogawa et al. 1993a; Shinohara et al. 1997). Purified Rad52 binds to both single- and double-stranded DNA and promotes the annealing of complementary single strands (Mortensen et al. 1996). In the two-hybrid system, Rad52 and Rad55 interact with Rad51, and Rdh54/Tid1 interacts with Dmc1 (Milne and Weaver 1993; Hays et al. 1995; Johnson and Symington 1995; Dresser et al. 1997).

Double Holliday junctions

The DSB repair model predicts the formation of a joint molecule containing two Holliday junctions, one on each side of the region of strand exchange (Fig. 6). Such joint molecules have been isolated by two-dimensional gel electrophoresis; subsequent analysis demonstrated that each of the component single strands is intact and nonrecombinant with respect to markers flanking the region of strand exchange (Schwacha and Kleckner 1994). However, digestion of joint molecules with a Holliday junction-cleaving enzyme from bacteria generates individual DNA duplexes, half of which are recombinant for the flanking markers (Schwacha and Kleckner 1995). This is the result expected for random resolution of both Holliday junctions.

Heteroduplex DNA and mismatch repair

The demonstration of double Holliday junctions would seem to vindicate the DSB repair model; however, studies of heteroduplex DNA make it necessary to question certain aspects of the model. According to the model shown in Figure 6, hybrid DNA (containing one strand from each of the two recombining duplexes) is formed on both sides of the initiating DSB. Furthermore, hybrid DNA to the left of the DSB should be on a different chromatid than hybrid DNA to the right of the DSB. In genetic studies, however, these expectations were not met. Instead, most events were found to be one-sided; when two-sided events were detected, both regions of hybrid DNA were on the same chromatid (Porter et al. 1993; Gilbertson and Stahl 1996). The DSB repair model also predicts that hybrid DNA is formed in advance of the formation of Holliday junctions. The results of physical assays, however, indicate that heteroduplex is produced around the time that Holliday junctions are resolved (Goyon and Lichten 1993; Nag and Petes 1993). Attempts have been made to reconcile these observations with the basic tenets of the DSB repair model, but the explanations proposed remain to be tested (Porter et al. 1993; Schwacha and Kleckner 1995; Gilbertson and Stahl 1996).

Although the timing of heteroduplex DNA formation is still being debated, a great deal is known about proteins that effect the correction of mismatched base pairs (for review, see Kolodner 1996). Mismatch repair in yeast requires three homologs of the bacterial MutS protein (Msh2, Msh3, and Msh6) and two homologs of MutL (Pms1 and Mlh1). Early steps in mismatch repair include recognition of a mismatch by a heterodimer consisting of Msh2 and either Msh3 or Msh6 (Marsischky et al. 1996), followed by binding of a heterodimer of Pms1 and Mlh1 (Prolla et al. 1994b). Later steps in mismatch repair are less well characterized, but the recent identification of

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an exonuclease (Exo1) that interacts with Msh2 marks progress in this direction (Tishkoff et al. 1997).

Are DSBs universal initiators of meiotic recombination?

To date, meiosis-specific DSBs have been demonstrated only in *S. cerevisiae,* but there is reason to believe that this mechanism of recombination initiation applies across species. The *S. pombe rec12* and *rad32* genes are homologs of the *S. cerevisiae SPO11* and *MRE11* genes, respectively, and these genes are required for meiotic recombination in fission yeast (Lin and Smith 1994; Tavassoli et al. 1995). Numerous homologs of *S. cerevisiae* genes involved in DSB repair have been identified in multicellular organisms; where it has been examined, gene expression was found to be strongly induced in meiotic cells (e.g., Shinohara et al. 1993; Petrini et al. 1995; Dolganov et al. 1996; McKee et al. 1996; Stassen et al. 1997). In several different fungi, sites that act as initiators of meiotic recombination have been shown to serve as recipients (rather than donors) of genetic information during gene conversion (for review, see Lichten and Goldman 1995), as predicted by the DSB repair model.

Recombination nodules

Recombination nodules are small, electron-dense structures that are observed in association with meiotic chromosomes (Carpenter 1988). There are two classes of nodules that differ in their time of appearance, number, and distribution. Nodules are classified as early if they are present during leptotene or zygotene; nodules present during pachytene are classified as late (Table 1). There is an excellent correspondence between the number and distribution of late nodules and the number and distribution of crossovers (Carpenter 1988), leading to the hypothesis that late nodules are multienzyme complexes that catalyze crossing over. Compared to late nodules, early nodules are more abundant and sometimes different in shape. Early nodules have been postulated to mark the sites of all strand exchange reactions, whereas late nodules represent only those strand exchange events that will be resolved as crossovers.

Early nodule components

Two proteins postulated to be components of early nodules in budding yeast are Dmc1 and Rad51. These RecA-like proteins localize to discrete spots on meiotic chromosomes (Bishop 1994). Rad51 is required for the localization of Dmc1 and many foci contain both proteins (Bishop 1994; Dresser et al. 1997). Rad51/Dmc1 foci are present at the same time as DSBs and they require DSBs for their assembly. The foci disappear as chromosomes synapse. In wild-type cells, the average number of Rad51/Dmc1 foci (~50) is significantly less than the total number of recombination events (~260). This difference may be due to the transient nature of Rad51/Dmc1 complexes.

Homologs of the yeast *RAD51* gene have been identified in multicellular organisms, and antibodies to these proteins have demonstrated that Rad51 forms discrete foci on chromosomes during the zygotene stage of meiosis in mice, humans, lilies, and chickens (Fig. 5B) (Ashley et al. 1995; Terasawa et al. 1995; Barlow et al. 1997; Moens et al. 1997). A lily homolog of the Dmc1 protein also localizes to spots on zygotene chromosomes, and these foci overlap extensively with the sites of Rad51 deposition (Terasawa et al. 1995). The Rad51 protein of higher eukaryotes does not always dissociate from chromosomes as they synapse; instead, at least in some organisms, Rad51 staining becomes fairly uniform along the lengths of synapsed chromosomes (Fig. 5B) (Ashley et al. 1995; Terasawa et al. 1995; Ikeya et al. 1996; Moens et al. 1997).

Localization of Rad51 and Dmc1 to foci on zygotene chromosomes by fluorescence microscopy does not prove that these proteins are components of early nodules because nodules (as classically defined) cannot be detected in the light microscope. Recently, an antibody that recognizes the Rad51 and Dmc1 proteins of lilies was used to localize these proteins in the electron microscope using antibodies tagged with gold particles. The results clearly demonstrate the presence of Rad51 and/or Dmc1 in early nodules (Anderson et al. 1997). Together with the requirement for Rad51 for DSB repair in yeast and the in vitro activity of the Rad51 protein (see above), these observations provide strong support for the hypothesis that early nodules mark the sites of genetic recombination events.

Late nodule components

A protein that may be a component of late recombination nodules in yeast is the MutS homolog, Msh4. A *msh4* null mutation reduces crossing-over (about twofold) but has no effect on gene conversion or mismatch repair (Ross-Macdonald and Roeder 1994). The protein localizes to discrete spots on chromosomes predominantly during the pachytene stage of meiosis (Fig. 2C) (Ross-Macdonald and Roeder 1994). Other candidates for late nodule components are Msh4 and Mlh1. *msh5* and *mlh1* mutations also confer modest decreases in crossing-over, and genetic analysis indicates that Msh4, Msh5, and Mlh1 act in the same pathway (Hollingsworth et al. 1995; Hunter and Borts 1997). In addition to its role in crossing over, Mlh1 is required for the correction of mismatched base pairs present in heteroduplex DNA (Prolla et al. 1994a), suggesting a link between mismatch repair and the stabilization or resolution of Holliday junctions.

There is good evidence that the mouse Mlh1 protein (a homolog of *S. cerevisiae* Mlh1) is a component of late nodules (Baker et al. 1996). This protein localizes to discrete foci on mouse chromosomes during the pachytene stage of meiosis, and the number of foci corresponds to the number of crossovers. In mice carrying a knockout of the *MLH1* gene, homologous chromosomes separate from each other prematurely (in diplotene), suggesting a

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defect in crossing-over and a consequent failure to establish chiasmata. Like yeast Mlh1, the mouse Mlh1 protein is required for mismatch repair (Edelmann et al. 1996).

The relationship between recombination and synapsis

Recombination is required for synapsis in budding yeast

Traditionally, it has been assumed that chromosome synapsis is required for meiotic recombination. However, recent studies in yeast indicate that this assumption is incorrect. Time course analyses indicate that recombination and synapsis are concurrent events in budding yeast (Table 1) (Padmore et al. 1991; Schwacha and Kleckner 1994, 1995). DSBs with single-stranded tails appear early in prophase, prior to the formation of mature SC, and disappear in zygotene as synapsis initiates. Joint molecules are present during pachytene, and mature recombinants are produced near the end of pachytene as the SC disassembles.

Several observations indicate that synapsis is not required for recombination; instead, steps in the recombination pathway appear to be required for synapsis. First, the *zip1* mutant undergoes a wild-type number of meiotic recombination events, despite the absence of mature SC (Sym et al. 1993; Sym and Roeder 1994). Furthermore, *S. pombe* and *Aspergillus nidulans* undergo high levels of meiotic recombination, though they fail to make SC (Egel-Mitani et al. 1982; Bahler et al. 1993). Haploid strains of budding yeast sustain the normal level of DSBs, demonstrating that the initiation of recombination does not depend on prior interactions between homologs (de Massy et al. 1994; Gilbertson and Stahl 1994). Finally, yeast mutants defective in DSB repair display defects in synapsis, with mutants blocked at earlier steps in the repair pathway showing more severe defects in synapsis. Mutants that do not sustain DSBs fail to make SC (Alani et al. 1990; Cao et al. 1990; Loidl et al. 1994; Rockmill et al. 1995a). Mutants that make DSBs that remain unprocessed assemble a limited amount of SC, largely between nonhomologous chromosomes (Alani et al. 1990; Loidl et al. 1994; Nairz and Klein 1997; Prinz et al. 1997). Mutants that make DSBs with single-stranded tails assemble nearly wild-type amounts of apparently normal SC, but synapsis is substantially delayed (Bishop et al. 1992; Rockmill et al. 1995b; Shinohara et al. 1992). Because many of the mutants defective in both synapsis and meiotic recombination are also radiation sensitive, it is likely that the primary defect is in DSB repair and that the defect in SC formation is secondary.

The dependence of synapsis on recombination is probably not unique to budding yeast. Several radiation-sensitive mutants of *Coprinus* are defective in both meiotic recombination and SC formation (Pukkila et al. 1992; Ramesh and Zolan 1995). Also, mice defective in the mismatch repair gene *PMS2* exhibit abnormal chromosome synapsis (Baker et al. 1995).

The fact that synapsis is not required for meiotic recombination does not preclude a role for the SC in facilitating recombination or promoting certain classes of recombinants. Although the yeast *zip1* mutant undergoes the wild-type number of recombination events, there is a two- to threefold reduction in the fraction of these events that are resolved in favor of crossing over (Sym and Roeder 1994; Storlazzi et al. 1996). In the *red1* mutant, in which there is no SC or axial elements, recombination is reduced about 10-fold (Rockmill and Roeder 1990; Xu et al. 1997).

Does synapsis initiate at the sites of genetic recombination events?

In most organisms, synapsis initiates at a few sites along each chromosome pair, and SC extension in both directions from each initiation site leads to full synapsis. One way to account for the dependence of synapsis on recombination is to suppose that synapsis initiates at the sites of genetic recombination events. There is some evidence to support this hypothesis.

As noted above, cytological studies of early prophase chromosomes in several organisms has demonstrated that homologs are held together at multiple sites prior to the initiation of SC formation (Gillies 1985; Albini and Jones 1987; Anderson and Stack 1988). An early recombination nodule is usually located at the point of convergence between axial elements, referred to hereafter as an axial association. During early stages of synapsis, each short stretch of independently initiated SC is associated with a nodule. Furthermore, there is a general correspondence between the order in which different chromosome segments form axial associations and the order in which they synapse. In light of the evidence indicating that early nodules mark the sites of strand exchange (see above), these cytological observations support the view that synapsis initiates at the sites of recombination events.

In spread meiotic chromosomes from the *zip1* mutant, each pair of homologs is aligned side by side and intimately connected at a few sites (Sym et al. 1993). Based on similarities to the axial associations observed in other organisms, it is postulated that these connections serve as sites of synaptic initiation (Rockmill et al. 1995b). The observation that the RecA-like proteins Dmc1 and Rad51 are required for the formation of axial associations provides one indication that synapsis initiates at the sites of recombination events (Rockmill et al. 1995b). Additional information comes from studies of the Zip2 protein (P. Chua and G.S. Roeder, unpubl.), which localizes to axial associations and is required specifically for the initiation of synapsis. In a mutant in which DSB processing is blocked, Zip2 colocalizes with proteins involved in the formation and processing of DSBs, arguing strongly that synapsis initiates at DSB sites. However, it should be noted that the number of axial associations and the number of Zip2 foci (both ~40) are significantly less than the number of DSBs (~260).

In some organisms, there is a clear 1:1 correspondence between SC initiation sites and crossovers (as reflected

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in late recombination nodules and/or chiasmata) (Stack and Soulliere 1984; Zickler et al. 1992). This situation applies to wild-type *Sordaria;* furthermore, certain mutations that reduce recombination in this organism effect similar reductions in the number of SC initiations (Zickler et al. 1992). In maize heterozygous for an inversion, the frequency of crossing over within the inverted segment is the same as the frequency of homologous synapsis (Maguire and Riess 1994). However, a 1:1 correspondence between crossovers and SC initiations is certainly not the rule. In many organisms, the number of sites of synaptic initiation is in considerable excess of the number of crossovers (Jones 1984). There are also numerous instances in which synapsis initiates predominantly near chromosome ends, whereas crossovers are not similarly localized (e.g., Albini and Jones 1987; Ashley 1994; Moens 1969a). The fact that some synaptic initiation events are not associated with crossing over does not preclude the possibility that initiation is accompanied by nonreciprocal recombination.

Recombination-deficient mutants of Drosophila *are proficient in chromosome synapsis*

Recent studies indicate that the dependence of synapsis on recombination, as suggested in studies of yeast, does not apply to *Drosophila* females (K. McKim and S. Hawley, pers. comm.). In this system, two mutations (*mei-W68* and *mei-P22*) that eliminate meiotic recombination have no effect on synapsis. As noted above, chromosomes in flies are already paired along their lengths prior to entry into meiosis. Perhaps under these circumstances, the conditions required for SC formation can be relaxed without risk of synapsis between nonhomologous chromosomes.

Regulation of the frequency and distribution of meiotic recombination events

Recombination hot spots

Meiotic recombination events are not uniformly distributed throughout the genome (for review, see Lichten and Goldman 1995). Instead, the frequency of meiotic exchange per unit physical distance can vary by several orders of magnitude from one region to another, even within a single chromosome. Considerable attention has focused on recombination hot spots, which are sites or regions in which recombination occurs at frequencies significantly higher than the average for the overall genome.

In *S. cerevisiae,* hot spots correspond to the sites of the meiosis-specific DSBs that initiate recombination. DSBs do not occur at a specific DNA sequence, but rather are dispersed throughout a region of 50–200 bp at each locus examined (de Massy et al. 1995; Liu et al. 1995; Xu and Kleckner 1995; Xu and Petes 1996). Almost all breaks occur in intergenic regions that contain transcription promoters, but transcription is not required for DSB induction (White et al. 1992; Wu and Lichten 1994). Hot spots correspond to nuclease-hypersensitive sites in chromatin isolated from vegetative cells, and these regions undergo meiosis-specific modifications that increase their susceptibility to nuclease digestion (Ohta et al. 1994; Wu and Lichten 1994; Fan and Petes 1996). However, an open chromatin configuration must not be the only determinant of DSB formation because there is an imperfect correlation between the level of nuclease hypersensitivity and the probability of cleavage (Wu and Lichten 1995; Fan and Petes 1996).

A well-characterized recombination hotspot in *S. pombe* is defined by the *ade6–M26* mutation. Unlike other eukaryotic hot spots, *M26* activity depends on a specific DNA sequence: 5′-ATGACGT-3′ (Schuchert et al. 1991). This heptamer serves as a binding site for a heterodimeric protein, Mts1/Mts2, whose activity is required for hot spot activity (Wahls and Smith 1994; Fox et al. 1997). Chromatin structure appears to play a role in regulating recombination in fission yeast, just as it does in budding yeast. The *M26* mutation causes a dramatic increase in meiotic induction of a nuclease hypersensitive site in the *ade6* promoter, and it creates a new hypersensitive site at the position of the *M26* mutation (located ~400 bp downstream) (Mizuno et al. 1997). Both the promoter and *M26* are required for hot spot activity (Zahn-Zabal et al. 1995). The position of the lesion that initiates recombination, either in the presence or in the absence of the *M26* mutation, is not known.

Little is known about the molecular basis of hot spot activity in systems other than fungi. In many organisms, recombination is concentrated in gene-rich regions (e.g., Civardi et al. 1994; Gill et al. 1996). In contrast, in *C. elegans,* recombination occurs preferentially in gene-poor regions (Barnes et al. 1995); mutation of the *rec-1* gene abolishes this bias (Zetka and Rose 1995b). In mice and human males, crossing over occurs at higher-than-average frequencies near telomeres (for review, see Ashley 1994). Curiously, these telomere-proximal recombination exchanges are not associated with detectable recombination nodules, suggesting that these events are mechanistically distinct from other exchanges. A special case of a recombination hot spot is the pseudoautosomal region that serves as the site of pairing and exchange between the X and Y chromosomes in mammals (for review, see Rappold 1993).

Crossover interference

Meiotic crossovers rarely occur close together. When two exchanges occur on the same chromosome arm, they are almost always widely spaced. This interference between crossovers must involve the transmission of an inhibitory signal from one crossover site to nearby potential sites of crossing over. It has been suggested that the SC serves as the conduit for signal transmission (for review, see Egel 1995). Consistent with this hypothesis, the *zip1* mutation abolishes interference (Sym and Roeder 1994). Although it is possible Zip1 plays a role in

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interference that is independent of its function in synapsis (Storlazzi et al. 1996), the simplest interpretation of this result is that *zip1* eliminates interference by preventing SC formation. A number of other observations are consistent with a role for the SC in interference. *S. pombe* and *A. nidulans* fail to make SC and do not exhibit interference (Egel-Mitani et al. 1982; Bahler et al. 1993; Kohli and Bahler 1994). The *as1* and *asb* mutants of tomato display defects in both synapsis and interference (Moens 1969b; Havekes et al. 1994). In the *tam1* mutant of *S. cerevisiae,* synapsis is delayed and interference is decreased (Chua and Roeder 1997).

Regardless of the mechanism of signal transmission, there must be proteins present at the sites of crossing over that initiate and receive the signal. A candidate for such a protein is the yeast Msh4 protein (a putative late nodule component, see above). The *msh4* mutant makes SC, but interference is nearly completely eliminated (Ross-Macdonald and Roeder 1994; P. Ross-Macdonald and G.S. Roeder, unpubl.).

In most organisms, small chromosomes undergo more recombination per unit of physical distance than large chromosomes (Kaback et al. 1989; Jones 1984). The enhanced rate of exchange on small chromosomes may serve to ensure that every pair of chromosomes sustains at least one crossover to promote its correct disjunction at meiosis I. Studies in *S. cerevisiae* suggest a regulatory mechanism that responds directly to chromosome size. When a chromosome is bisected to produce two smaller chromosomes, the amount of recombination per kilobase pairs increases even though the chromosomal sequences are unchanged (Kaback et al. 1992).

Crossover interference and the nonrandom distribution of crossovers among chromosomes may be mechanistically related (Kaback et al. 1989, 1992; Egel 1995). By preventing excess exchanges on large chromosomes, interference might ensure that crossovers (presumably limited in number) are distributed in such a way that every chromosome pair undergoes at least one exchange. In support of such a mechanistic link, mutations that reduce or eliminate interference randomize the distribution of crossovers among chromosomes such that some chromosome pairs fail to crossover and therefore nondisjoin (Sym and Roeder 1994; Egel 1995; Chua and Roeder 1997).

Sister versus nonsister exchange

Meiotic recombination events are also nonrandom with respect to the involvement of sister versus nonsister chromatids. Studies in a variety of organisms indicate that recombination events between nonsister chromatids exceed exchanges between sisters by 3- to 10-fold (for review, see Petes and Pukkila 1995). A preference for exchange between nonsisters makes telological sense, as only crossovers between nonsisters establish the connections necessary to ensure proper chromosome segregation. In *S. cerevisiae,* the repeated rRNA genes do not undergo synapsis, and sister chromatid events exceed nonsister exchanges in ribosomal DNA (Petes and Pukkila 1995). These observations suggest that SC-associated proteins play a role in specifically promoting exchange between nonsisters; in particular, Red1, Dmc1, and Hop1 are implicated in this control (Rockmill et al. 1995b; Schwacha and Kleckner 1997; Smith and Roeder 1997). The frequency of recombination between sister chromatids is substantially increased during meiosis in haploid yeast, suggesting that the normal constraints on sister chromatid recombination are relaxed in the absence of interactions between homologs (Loidl and Nairz 1997; Wagstaff et al. 1985).

Meiotic chromosome segregation

Co-orientation by pulling

The meiosis I division is distinct from mitosis and meiosis II in that sister chromatids remain associated with each other, whereas homologous chromosomes move to opposite poles of the spindle apparatus. Proper chromosome segregation at meiosis I depends on crossing over to establish chiasmata, which are stable connections between homologs that persist after the SC has disassembled and recombination intermediates have been resolved (Table 1) (for review, see Hawley 1988). During prometaphase, homologous chromosomes can become attached to microtubules from the same or opposite spindle poles. Only attachment to microtubules from opposite poles results in a stable configuration that is maintained until anaphase. If homologs attach to microtubules from the same pole they dissociate and try again. The recognition that chromosomes are properly oriented depends on the mechanical tension that results when homologs are pulled toward opposite spindle poles, and this pulling is resisted by chiasmata. The importance of tension has been demonstrated by artificially applying tension to homologs that are attached to the same spindle pole. If a micromanipulating needle is used to apply an opposing force then the otherwise unstable monopolar attachment is stabilized (Nicklas 1974).

How does tension signal that homologs are correctly oriented? The answer appears to be tension-sensitive protein phosphorylation. Antibodies specific for a phosphorylated kinetochore protein light up the kinetochores of chromosomes that are incorrectly oriented. However, once tension is achieved (either naturally or artificially) the kinetochore protein becomes dephosphorylated (Nicklas et al. 1995). Thus, the mechanical tension that depends on chiasmata is converted to a chemical signal at kinetochores. A similar mechanism is used to assess the orientation of sister chromatids on the mitotic spindle apparatus (for review, see Gorbsky 1995).

Chiasma function

A chiasma corresponds to the site of reciprocal breakage and rejoining of two nonsister chromatids (Jones 1984). How does a chiasma hold homologs together? One model invokes a role for sister chromatid cohesion: homologs are held together at chiasmata because sister

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chromatids are glued to each other in regions distal to chiasmata. An alternative view is that homologs are held together only in the immediate vicinity of the crossover by chiasma binder proteins. Recent studies in organisms as diverse as yeast, fruit flies, and humans demonstrate that crossovers near the ends of chromosomes are less effective than centromere-proximal exchanges in ensuring proper meiosis I disjunction (Koehler et al. 1996; Lamb et al. 1996; Ross et al. 1996). These observations support the view that chiasma function depends on sister chromatid cohesion, as such a model predicts that terminal chiasmata will be less stable. Also, the behavior of acentric fragments resulting from recombination in paracentric inversions of maize is consistent with cohesion along chromatid arms serving to stabilize chiasmata (Maguire 1995). The pattern of segregation of the acentric fragment indicates an association with sister chromatids rather than with the site of the crossover.

Experiments in maize have led to the proposal that mature SC is required for proper sister chromatid cohesion in meiosis (for review, see Maguire 1990; see also Maguire et al. 1991). Maize mutants in which chromosomes desynapse prematurely or fail to synapse altogether undergo precocious separation of sister chromatids. In trisomic strains of maize, the chromosome that lacks a pairing partner displays premature sister separation. However, mature SC is clearly not required for meiotic sister chromatid cohesion in all organisms. In the *zip1* mutant of yeast and the *c(3)G* mutant of *Drosophila,* precocious sister separation is infrequent, despite the failure of SC formation (Baker et al. 1976; Sym and Roeder 1994). Also, grasshopper chromosomes that lack pairing partners do not undergo precocious sister separation (Suja et al. 1992).

Even in organisms in which mature SC is not required for sister chromatid cohesion, axial/lateral elements may play an important role in keeping sister chromatids together. In the *red1* mutant of yeast (which fails to make axial elements), chromosomes that have undergone crossing over nevertheless missegregate, suggesting a failure of chiasma function (Rockmill and Roeder 1990). The persistent localization of the rodent Cor1 lateral element component along chromosome cores until metaphase of meiosis I is consistent with a role for this protein in promoting cohesion along chromosome arms (Dobson et al. 1994; Moens and Spyropoulos 1995). Wild-type *S. pombe* does not make SC, but it assembles linear elements that are assumed to be closely related to axial/lateral elements (Bahler et al. 1993). The *S. pombe rec8* mutant fails to make linear elements and undergoes precocious separation of sister chromatids at high frequency (Molnar et al. 1995).

One gene that is known to be important for meiotic sister chromatid cohesion is the *ord* gene of *Drosophila* (Miyazaki and Orr-Weaver 1992; Bickel et al. 1997). Loss of *ord* function leads to separation of sister chromatids prior to metaphase I and consequent random segregation of chromosomes at both divisions. It is not known whether Ord serves as a structural component of meiotic chromosomes.

Sister chromatid cohesion at meiosis II

Meiotic sister chromatid cohesion is released in two stages (Miyazaki and Orr-Weaver 1994). Cohesion along chromosome arms is released at anaphase I, whereas cohesion near centromeres is maintained until anaphase II (Fig. 1). This stepwise separation of sister chromatids implies the operation of two types of chromatid cohesion that differ in mechanism and/or regulation. The Mei-S332 protein of *Drosophila* acts specifically at the second stage to ensure cohesion in the centromeric regions of meiotic chromosomes. In *mei-S332* mutants, homologs undergo normal recombination and they segregate correctly at the first division of meiosis (and in mitosis). However, sister chromatids frequently separate from each other during anaphase of meiosis I and then segregate randomly at meiosis II (Kerrebrock et al. 1992). Analysis of Mei-S332 tagged with green fluorescent protein demonstrates that the gene product localizes specifically to the centromeric regions of meiotic chromosomes (Kerrebrock et al. 1995). Mei-S332 associates with centromeres beginning in late meiotic prophase and it disappears abruptly at anaphase II, just as sister chromatids separate from each other.

The localization of Cor1 specifically to centromeric regions from anaphase I until anaphase II suggests that this protein may perform a function similar to Mei-S332 (Dobson et al. 1994; Moens and Spyropoulos 1995). The phenotypes conferred by certain *ord* alleles in *Drosophila* clearly demonstrate that the Ord protein participates in chromatid cohesion in centromeric regions in addition to its function in promoting cohesion along chromosome arms (Bickel et al. 1997).

Achiasmate chromosome segregation

If chiasmata are required for the proper orientation of homologs on the meiosis I spindle, then how do the fourth chromosomes of *Drosophila* (which are always nonrecombinant) segregate correctly? Insight comes from studies of the *nod* gene, which is required for the segregation of achiasmate chromosomes in female flies but not for the segregation of homologs joined by chiasmata (for review, see Hawley and Theurkauf 1993).

Nod is a kinesin-like protein, and a number of observations suggest that Nod is a plus-end directed microtubule motor (i.e., that Nod directs movement away from spindle poles) (Zhang et al. 1990). At prometaphase and subsequent stages of meiosis, Nod localizes along the lengths of all chromosomes (Afshar et al. 1995). At prometaphase, chromosomes 4 leave the mass of chromosomes at the metaphase plate and begin to move poleward. At metaphase, the 4th chromosomes are positioned on opposite half spindles between the metaphase plate and the spindle poles (Theurkauf and Hawley 1992). In the absence of Nod, chromosomes 4 are displaced from the spindle apparatus, apparently by migrating precociously off the ends of the spindle (Theurkauf and Hawley 1992). Thus, the microtubule motor activity of Nod is proposed to provide an anti-poleward force that

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counterbalances the poleward forces exerted at the kinetochore. By pushing the fourth chromosomes toward each other, Nod compensates for the absence of chiasmata.

Nod activity is not restricted to chromosomes 4. In 5%–10% of meioses, the X chromosomes fail to recombine, yet the rate of X nondisjunction is <0.1%. As is the case for the 4th chromosomes, correct segregation of nonrecombinant X chromosomes depends on heterochromatin-mediated pairing during prophase and Nod-mediated ejection from the spindle poles at metaphase (Dernburg et al. 1996b; Hawley et al. 1993).

Meiotic checkpoint control

To ensure success at the reductional division, meiotic events must be properly coordinated. As in the mitotic cell cycle, checkpoint machinery operates in meiosis to ensure that one event does not occur until the preceding event has been completed. To date, two different checkpoints have been shown to operate in meiosis. The recombination checkpoint ensures that cells do not exit pachytene until recombination intermediates have been resolved. The metaphase checkpoint prevents cells from exiting metaphase I until all chromosome pairs have been properly oriented on the spindle apparatus.

The recombination checkpoint

In *S. cerevisiae,* several mutants that confer defects in recombination (e.g., *zip1, dmc1, sae3*) cause cells to arrest at the pachytene stage with unrepaired DSBs or unresolved Holliday junctions (Bishop et al. 1992; Sym et al. 1993; Storlazzi et al. 1996; McKee and Kleckner 1997b). Mutations that prevent the initiation of recombination (e.g., *spo11*) allow these mutants to sporulate, because the double mutants (e.g., *spo11 dmc1*) fail to generate the recombination intermediates that trigger the meiotic checkpoint. Arrest in *dmc1* and *zip1* is also bypassed by mutations in genes required for mitotic cell cycle checkpoints that respond to unrepaired DSBs (Lydall et al. 1996). Such mutations (e.g., *rad24*) allow cells to undergo nuclear division despite the presence of recombination intermediates. Recent observations suggest that the meiotic checkpoint machinery monitors recombination intermediates in a specific chromosomal context that depends on SC-associated proteins (Xu et al. 1997).

Evidence for monitoring of meiotic recombination events in multicellular organisms comes from studies of the *ATM* gene, which is required for mitotic checkpoints that arrest cells in response to DNA damage (for review, see Meyn 1995). In wild-type mice, the Atm protein associates with meiotic chromosomes in a pattern similar to that of Rad51 (Keegan et al. 1996). In mice carrying an *ATM* knockout, chromosome synapsis is delayed and meiotic chromosomes become fragmented (Xu et al. 1996). A mutation in the *Drosophila mei-41* gene, a homolog of *ATM* (Hari et al. 1995), affects both the number and morphology of recombination nodules (Carpenter 1979). Rad51 has been shown to interact (at least in somatic cells) with the checkpoint protein, p53 (Sturzbecher et al. 1992).

Though there is a checkpoint that monitors ongoing recombination events, there is, unexpectedly, no checkpoint to ensure that recombination is initiated. Mutants of budding yeast that fail to make any DSBs nevertheless undergo both meiotic divisions (e.g., Klapholz et al. 1985; Alani et al. 1990; Rockmill et al. 1995a). The consequence is massive chromosome missegregation and the production of inviable meiotic products.

The metaphase checkpoint

As described above, the proper orientation of chromosomes on the metaphase I spindle depends on the tension that results when homologs conjoined by chiasmata are pulled toward opposite spindle poles. In spermatocytes of the praying mantid, a single chromosome that is not under tension causes cells to delay at metaphase I and eventually degenerate without forming sperm (Li and Nicklas 1995). If a micromanipulating needle is used to apply tension to the misattached chromosome then anaphase ensues. The kinetochore-associated protein that is phosphorylated specifically in chromosomes not under tension (see above) is proposed to serve as a signal to the checkpoint machinery (Nicklas et al. 1995).

Meiotic chromosomes frequently missegregate in humans, leading to a variety of birth defects and a very high frequency of miscarriages (for review, see Hassold et al. 1996). The vast majority of aneuploidies are the result of chromosome missegregation during meiosis in females. Studies in mice suggest that this sex specificity is attributable to a less efficient monitoring of meiotic chromosome behavior in females as compared to males (Hunt et al. 1995). In male mice, the presence of an unpaired chromosome causes cells to arrest at metaphase of the first meiotic division. In contrast, oocytes from female mice complete the first division even if one chromosome lacks a pairing partner.

Perspectives

For decades, meiosis was predominantly the province of cytologists. Meiotic structures were characterized extensively at the cytological level but theories as to their function were difficult to test in the absence of suitable genetic and molecular tools. During the past several years, however, meiosis has increasingly become the focus of genetic, molecular, and biochemical studies. Genes encoding recombination enzymes and structural components of meiotic chromosomes have been cloned and sequenced. Mutants in meiosis-specific genes have been identified and characterized in a variety of organisms. Genes identified in model organisms such as fungi, flies, and worms have been used to clone homologs from higher eukaryotes, thereby facilitating molecular and cell biological studies in these systems. With the ability to construct mouse knockouts, genetic analysis of meiosis in mammals is now an area of intense investigation.

Recent years have witnessed remarkable advances in

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our understanding of the meiotic process. Given the numerous genetic and molecular tools generated by these recent studies and increasingly sophisticated methods of analysis, we can expect even more dramatic progress in the years to come.

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