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Prelude to a Division

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Abstract

Accurate segregation of chromosomes during meiosis requires physical links between homologs. These links are usually established through chromosome pairing, synapsis, and recombination, which occur during meiotic prophase. How chromosomes pair with their homologous partners is one of the outstanding mysteries of meiosis. Surprisingly, experimental evidence indicates that different organisms have found more than one way to accomplish this feat. Whereas some species depend on recombination machinery to achieve homologous pairing, others are able to pair and synapse their homologs in the absence of recombination. To ensure specific pairing between homologous chromosomes, both recombination-dependent and recombination-independent mechanisms must strike the proper balance between forces that promote chromosome interactions and activities that temper the promiscuity of those interactions. The initiation of synapsis is likely to be a tightly regulated step in a process that must be mechanically coupled to homolog pairing.

Keywords

meiosis; homologous chromosomes; pairing; synapsis; recombination; meiotic bouquet

INTRODUCTION

In most eukaryotes, sexual reproduction accomplishes two goals: (*a*) the production of haploid gametes from a diploid cell so that a diploid genome will be regenerated upon fertilization and (*b*) the shuffling of genetic information, which gives rise to novel combinations of alleles that underlie adaptation and natural selection. Meiosis produces haploid gametes from a diploid cell by executing two successive chromosome segregation events after a single round of replication: meiosis I, a reductional division in which homologs are partitioned, and meiosis II, an equational division when sister chromatids segregate away from each other (Figure 1). Meiotic chromosome missegregation can lead to

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aneuploidy among the resulting gametes, which is usually lethal to any zygote that results upon fertilization. In humans, approximately one-third of miscarriages occur owing to genetic imbalances in the embryo that result from chromosome segregation errors during meiosis. Some aneuploidy may be tolerated by the developing zygote but, in humans, invariably results in developmental disabilities and/or infertility (Hassold & Hunt 2001).

Sister chromatid cohesion, introduced during DNA replication, enables sisters to stay together and eventually to segregate from each other during the equational division of meiosis (Figure 1c), much as it does during mitotic division. However, for homologous pairs of sister chromatids to partition accurately during the reductional division, they must first establish physical linkages that enable their kinetochores to biorient, or attach to opposite poles of the meiosis I spindle (Figure 1a). These links are established after meiotic DNA replication, during an extended prophase period in which each chromosome becomes physically paired with its homologous partner. In most organisms, this pairing is reinforced by the assembly of the synaptonemal complex and culminates in crossover recombination between homologs.

How each chromosome finds, recognizes, synapses with, and selectively undergoes exchange of genetic material with its unique homologous partner remains one of the outstanding mysteries of meiosis. Although many of the details of this pairing process remain to be clarified, work in diverse organisms has revealed two general classes of pairing mechanisms: those that require early events in recombination and those that do not. Recent work has demonstrated that recombination-dependent and recombination-independent pairing pathways both involve a balance between mechanisms that promote pairing and opposing mechanisms that prevent inappropriate chromosome interactions. When these forces are in proper balance, pairing between homologs is selectively stabilized by synapsis. When the system breaks down, reinforcement of homologous interactions often fails, but more revealingly, interactions between nonhomologous partners can become aberrantly stabilized.

Our purpose here is to highlight recent evidence for distinct mechanisms that contribute to homologous interactions during meiosis. In particular we emphasize how these mechanisms progressively and selectively stabilize initially tenuous interactions between homologs to culminate in synapsis and/or crossover recombination. As the molecular mechanisms and structural intermediates are defined, we can begin to consider the meiotic progression from unpaired chromosomes to fully conjoined homologs as we would any other metabolic pathway, and we can think in terms of critical transition points, thermodynamic barriers, and rate-limiting steps along the way. On the basis of this paradigm, recognition between homologous chromosomes is accomplished through the reversibility of early steps along the pathway, during which homology is assessed and inappropriate interactions are rejected.

The Progression of Chromosome Interactions

We start by defining a number of terms, because their use in the literature is inconsistent and our goal here is to be as consistent and unambiguous as possible. We describe chromosomes undergoing alignment, encounters, pairing, synapsis, and recombination (Figure 2).

We define alignment (Figure 2*b*) as the polarization of chromosomes within the nucleus such that chromosome arms are arrayed in parallel. In most organisms, homolog alignment during meiosis is thought to be an active process that initiates at the onset of meiotic prophase, in many cases mediated by associations between chromosomes and the nuclear envelope. As we discuss below, alignment probably plays the dual roles of promoting appropriate inter-homolog contacts and restricting ectopic (or nonallelic) interactions.

Encounters (Figure 2*c*) represent an early step in establishing stable chromosome interactions. We use this term to mean transient, highly reversible contacts between chromosome loci, whether homologous or nonhomologous. These may be mediated through passive means, including diffusion, and may also be facilitated through active rearrangement of chromosomes within the nucleus. Real-time imaging can reveal the frequency and duration of encounters between homologous sequences (e.g., Ding et al. 2004), but interactions between nonhomologous sequences are more difficult to measure.

Pairing (Figure 2*d*) is the most difficult term to define rigorously because it is used in the literature to encompass diverse mechanisms operating on an enormous range of size scales. We restrict our use of this term to describe the local stabilization of homologous encounters, sometimes referred to as close, stable homolog juxtaposition (CSHJ) (Peoples et al. 2002). By this definition, pairing interactions are sufficiently stable that they can be observed cytologically in fixed samples even in the absence of synapsis (e.g., MacQueen et al. 2002, 2005; Rockmill et al. 1995). Pairing can also be detected experimentally after the fact through recombination events, which can be generated either by the endogenous meiotic recombination apparatus or by engineered recombinases, such as the Cre/*loxP* system (e.g., Peoples et al. 2002). The stability and reversibility of pairing interactions can be measured more directly by real-time imaging (Ding et al. 2004), but only a few studies to date have used this approach. When pairing interactions are established at multiple points between two chromosomes, this results in intimate association along their entire lengths; we do not use the term pairing here to describe this more global phenomenon.

Synapsis (Figure 2*g*) specifically refers here to the assembly of the synaptonemal complex, a conserved protein matrix that normally forms between paired homologs, reinforcing their interaction. The term synapsis is frequently used outside the meiosis field to describe DNA recombination intermediates involving strand exchange, but we avoid this ambiguity here. The formation of the synaptonemal complex between homologs is unique to meiosis and occurs in most organisms that undergo sexual reproduction. Axial elements assemble between the sisters of replicated chromosomes prior to, or concomitant with, pairing; once the synaptonemal complex has fully assembled, these protein cores are often referred to as lateral elements. Synapsis is completed when transverse filament proteins and additional components load to form the central element of the synaptonemal complex by bridging the axial elements of homologous chromosomes (Figure 3*b*). The resulting zipper- or ladder-like structure can be visualized in spread preparations or thin sections by transmission electron microscopy, which reveals axial elements separated by ~100 nm (reviewed in Zickler & Kleckner 1999) (Figure 3*a*). Components of the transverse filaments have been identified in several species, and although they lack obvious sequence conservation, they are all proteins with high coiled-coil formation potential (reviewed in Colaiacovo 2006). The transverse

filaments may be composed of only a single protein, as in budding yeast (Zip1) (Sym et al. 1993) and *Drosophila* [c(3)G] (Page & Hawley 2001). Elegant experiments with Zip1 have revealed that the distance between synapsed chromosomes is determined by the length of its coiled-coil portion (Sym & Roeder 1995). Multiple proteins may compose the transverse filaments in other species; for example, multiple predicted coiled-coil components of the synaptonemal complex central element have been identified so far in *Caenorhabditis elegans* (Colaiacono et al. 2003, MacQueen et al. 2002, Smolikov et al. 2007) and in mammals (reviewed in Costa & Cooke 2007).

Meiotic recombination is initiated by a conserved topoisomerase-like enzyme, Spo11, which introduces programmed double-strand breaks (DSBs) into the genome (reviewed in Neale & Keeney 2006) (Figure 5*b*, below). DSBs usually pose a hazard to genome integrity.

However, the enzymes that repair breaks through conservative homologous recombination are highly upregulated during meiosis. This machinery is also modulated during meiosis so that use of the sister chromatid as a template is inhibited and the homologous chromosome becomes the preferred donor for recombinational repair. DSBs initiate two different pathways of meiotic recombination, leading to either crossovers, which involve the reciprocal exchange of sequences flanking the repair sites, or noncrossovers (also referred to as simple gene conversions), which transfer local information, typically spanning a few hundred base pairs, from one homolog to the other (reviewed in Neale & Keeney 2006). Mounting evidence indicates that the choice between crossover and noncrossover outcomes is determined very early in the process, possibly at or soon after the time of break formation (Borner et al. 2004, Martini et al. 2006), and that the intermediates in the two pathways are also distinct (Allers & Lichten 2001, Hunter & Kleckner 2001). This view has been supplanting an older paradigm in which a common recombination intermediate could be resolved to give either a gene conversion or a crossover (Szostak et al. 1983). Whereas crossovers create persistent physical links (chiasmata) between homologs, simple gene conversions do not.

We define these terms above on the basis of collective evidence that these processes are distinct but coordinated. A challenge in integrating results from different studies is that many of the assays that are routinely used to analyze meiosis actually measure events that occur downstream of these processes, such as crossover frequency, progeny survival, or chromosome nondisjunction. The quantitative effects of pairing or synapsis defects on each of these outputs may not be linear or obvious. In part, this is because the consequences of defects in meiotic chromosome transactions can be nondisjunction, cell cycle arrest, or cell death, depending on the activities of meiotic checkpoints. As a clearer view of the pathway leading to homolog synapsis emerges, the effects of mutations on the assembly and stability of specific intermediates in this pathway will likely be more systematically examined.

Coordination between Pairing and Synapsis

In most organisms, local sites of homolog pairing are eventually reinforced by assembly of the synaptonemal complex, which results in global apposition of homologous chromosomes. The initiation of synapsis is likely to be a committed step in homolog association. Cytogenetic evidence from *Neurospora* and mice indicates that chromosomes can undergo

synaptic adjustment to eliminate inversion loops. Synaptic adjustment presumably involves depolymerization and repolymerization of the synaptonemal complex (Bojko 1990, Davisson et al. 1981), but this occurs during mid- to late pachytene (Moses et al. 1982), perhaps after the search for a homologous partner has been completed. There is also evidence for preliminary synaptonemal complex formation near centromeres in budding yeast that is clearly reversible (Tsubouchi & Roeder 2005). However, once initiated, synaptonemal complex formation usually appears to be highly processive and potentially insensitive to homology, which probably reflects the tendency of synaptonemal complex components to self-assemble into polymers (Baier et al. 2007, Ollinger et al. 2005). This implies that synapsis initiation is likely to be a tightly regulated event, with large kinetic and/or thermodynamic barriers that must be overcome.

Mutation of transverse filament components in both *C. elegans* and budding yeast abrogates synapsis but does not eliminate intimate, local associations between homologs (MacQueen et al. 2002, 2005; Rockmill et al. 1995). Conversely, mutation of certain genes, including *HOP2* (Leu et al. 1998) or *MND1* (Tsubouchi & Roeder 2002) in budding yeast and *htp-1* (Martinez-Perez & Villeneuve 2005) or *sun-1* (Penkner et al. 2007) in *C. elegans*, results in promiscuous synapsis between nonhomologs. The effects of these mutations further indicate that synaptonemal complex assembly does not depend on homology per se and that pairing and synapsis are discrete processes that can be genetically uncoupled. Ongoing analyses of these mutant situations are providing important insight into the mechanisms that restrict synaptonemal complex assembly to paired homologous chromosomes.

Taken together, this evidence indicates that the initiation of synapsis is coupled to the establishment of stable homolog pairing. Although homolog pairing may not be sufficient for synapsis initiation, it is normally a prerequisite to overcome the kinetic and/or thermodynamic barriers to synapsis. The goal of the cell is thus to calibrate pairing and synapsis initiation mechanisms such that appropriate, homologous pairing interactions reliably trigger the synaptonemal complex to polymerize, whereas nonhomologous interactions are transient or unstable enough that this rarely occurs.

RECOMBINATION-INDEPENDENT PAIRING MECHANISMS

Abundant evidence exists that all organisms employ mechanisms that promote meiotic homolog interactions in the absence of DSBs or other recombination intermediates. At least two recombination-independent phenomena may contribute to proper chromosome segregation during meiosis: (a) interactions between chromosomes and the nuclear envelope and (b) interchromosomal interactions between heterochromatic regions of the genome.

Interactions between Chromosomes and the Nuclear Envelope

Cytologically observed interactions between chromosomes and the nuclear envelope are a widely conserved feature of meiotic prophase. Such interactions have been recognized for more than 100 years, but their contributions to homolog pairing and synapsis remain a subject of speculation and debate (reviewed in Scherthan 2001). Current experimental efforts to understand how chromosomes are actively rearranged in this phase of meiosis are

revealing mechanisms that promote some interactions between chromosomes while limiting others.

Formation of the meiotic bouquet—In many organisms, the onset of meiotic prophase is accompanied by a chromosome configuration in which chromosome ends associate with the nuclear envelope, resulting in a roughly parallel alignment of the chromosome arms, particularly in regions of the genome near the telomeres (Figure 4). In some species, these chromosome attachment sites form a tight cluster, leading to the description of this stage as the meiotic bouquet because the chromosomes resemble a bouquet of flowers with gathered stems (reviewed in Zickler & Kleckner 1998). Although clustering of telomeres is frequently cited as a defining attribute of the meiotic bouquet, the degree of clustering varies from highly pronounced (Figure 4*a,b*) to more subtly polarized (Figure 4*c–e*) within the nucleus, suggesting that attachment to the nuclear envelope may play a more conserved, and therefore more critical, role. In most organisms with discrete microtubule-organizing centers, clustered telomeres are observed adjacent to these structures (reviewed in Zickler & Kleckner 1998).

This reconfiguration of chromosome organization coincides with the onset of alignment, pairing, and synapsis, and its contribution to these events is currently an area of vigorous investigation. Genetic and cytological analysis indicates that the bouquet stage involves three discrete but interdependent processes: nuclear envelope attachment, clustering of chromosome ends, and cytoskeleton-mediated chromosome movement. Each of these steps appears to contribute to proper homolog pairing.

Many of the insights into the molecular basis and purpose of bouquet formation have come from studies in fission yeast. This organism has an unusual meiosis in that it lacks synaptonemal complex formation, and the entire nucleus oscillates dramatically along the long axis of the cell for the duration of meiotic prophase in what is called horsetail movement (Chikashige et al. 1994). This phenomenon is probably a manifestation of mechanisms that underlie bouquet formation in other species, although such dramatic motion of the entire nucleus is unusual. More recently, experiments in synaptic organisms including *C. elegans* (Penkner et al. 2007; A. Sato, C.M. Phillips & A.F. Dernburg, unpublished), *Saccharomyces cerevisiae* (Chua & Roeder 1997; Conrad et al. 1997, 2007), plants (Corredor et al. 2007, Cowan & Cande 2002, Golubovskaya et al. 2002), and mammals (Ding et al. 2007, Liu et al. 2004, Schmitt et al. 2007) have shed light on both the conservation and the diversity of bouquet organization and function.

In most organisms, formation of the meiotic bouquet is thought to be mediated by association between telomeric repeats and nuclear envelope components. Molecular evidence for telomere involvement comes from *Schizosaccharomyces pombe*, in which mutations in the genes encoding constitutive telomere-associated proteins, including Taz1p, Rap1p, and Rik1p, disrupt bouquet formation and impair meiotic segregation (Cooper et al. 1998, Nimmo et al. 1998, Tuzon et al. 2004). Telomere shortening in telomerase-deficient mice has also been linked to meiotic defects (Liu et al. 2004). In a variety of other organisms, telomere repeats have been implicated in the bouquet primarily by their

localization to the nuclear envelope cluster (Bass et al. 1997; reviewed in Scherthan 2001, Ding et al. 2007, Schmitt et al. 2007).

In addition to normal telomere structure, formation of the bouquet in fungi requires the expression of meiosis-specific proteins that form a bridge between telomeres and the nuclear envelope. These proteins include Ndj1 in budding yeast (Chua & Roeder 1997, Conrad et al. 1997) and Bqt1p and Bqt2p in fission yeast (Chikashige et al. 2006). Interestingly, none of the meiosis-specific components identified to date show conservation between budding and fission yeast or have obvious homologs in other species.

In the nematode *C. elegans*, a bouquet-like configuration also appears to play a major role in homolog pairing. Surprisingly, in this species the bouquet is mediated not by the telomeres, but instead by a distinct region on each chromosome known as the homolog recognition region or pairing center. Recent work has shown that pairing centers comprise a region of each chromosome enriched in short, repetitive sequences that are recognized by specific members of a zinc-finger protein family (Phillips & Dernburg 2006, Phillips et al. 2005; C.M. Phillips & A.F. Dernburg, unpublished). Further evidence indicates that these pairing centers mediate nuclear envelope attachment to fulfill their roles in stabilizing homolog pairing and facilitating synapsis (Phillips & Dernburg 2006, Phillips et al. 2005).

Some of the nuclear envelope components involved in bouquet formation are clearly conserved across evolution. The first of these to be identified were Sad1 (Niwa et al. 2000) and Kms1 (Shimanuki et al. 1997) in *S. pombe*. These transmembrane proteins were initially identified as components of the spindle pole body, the fungal microtubule-organizing center, which is embedded in the nuclear envelope. These proteins contain a SUN domain and a KASH domain, respectively. SUN domain proteins (named for founding members Sad1 and UNC-84) have recently been implicated in meiotic telomere attachment and/or homolog synapsis in mice (Ding et al. 2007) and *C. elegans* (Penkner et al. 2007; A. Sato, C.M. Phillips & A.F. Dernburg, unpublished).

SUN and KASH domains (the latter named for Klarsicht/ANC-1/Syne homology) are thought to interact physically within the lumen of the nuclear envelope, between the inner and outer nuclear membranes. The SUN domain protein usually extends into the nucleoplasm, whereas the KASH domain is connected to a protein that spans the outer nuclear envelope to the cytoplasm. Pairs of SUN/KASH proteins link nuclear components to either the microtubule cytoskeleton or actin structures in the cytoplasm in a variety of cell types (Starr & Fischer 2005). Kms1 interacts with dynein, a cytoplasmic, minus-end-directed microtubule motor. These proteins are required for the telomere clustering and horsetail movement of *S. pombe* nuclei during meiosis, respectively (Shimanuki et al. 1997, Miki et al. 2002, Yamamoto et al. 1999). In *C. elegans*, SUN-1 interacts with the KASH domain protein ZYG-12 to link chromosomes, via their pairing centers, to microtubules and cytoplasmic dynein (A. Sato, C.M. Phillips & A.F. Dernburg, unpublished). Surprisingly, dynein is dispensable for meiotic prophase in *S. cerevisiae* (Lui et al. 2006), and the meiotic bouquet is insensitive to microtubule drugs but is disrupted by latrunculin, which results in actin depolymerization (Trelles-Sticken et al. 2005). Latrunculin also reversibly disrupts telomere-led chromosome movement during meiotic prophase (Scherthan et al. 2007). This

leads to the provocative conclusion that different cytoskeletal elements may govern telomere-led meiotic chromosome movements in different organisms, despite the widespread conservation of the bouquet.

Pro- and antipairing functions of the meiotic bouquet—The most detailed analyses of the functional contributions of the bouquet come from fission yeast. This is due to the early identification of bouquet components in this organism, the dramatic horsetail movements associated with bouquet formation, and the amenability of these yeast cells to real-time fluorescence imaging. Meiotic chromosome pairing dynamics have been directly analyzed by the use of locus-specific fluorescent probes, both in wild-type cells and in a variety of meiotic mutants. Homologous loci repeatedly associate and dissociate in wild-type cells, eventually becoming more stably associated (Ding et al. 2004). Cells that lack *Rec12* (the *S. pombe* ortholog of *SPO11*) show initial kinetics and frequencies of homologous association similar to those of wild-type cells. However, in contrast to wild-type cells, the number of cells showing associations between homologous loci does not increase with progression through prophase but remains constant over time. This analysis of the dynamics of homolog pairing confirms that transient encounters between homologous chromosomes are governed by recombination-independent mechanisms but are ultimately stabilized by recombination-dependent mechanisms (Ding et al. 2004).

Mutations in *S. pombe* that disrupt telomere attachment during meiotic prophase severely reduce the frequency of encounters between homologs. The primary defect is a failure to align chromosomes. Loci on chromosome arms exhibit the most severe defect, whereas centromeres, which may have an independent pairing mechanism, still pair efficiently (Ding et al. 2004). The attachment of telomeres to the nuclear envelope seems to bring chromosomes into register with their homologs at interstitial loci. This both promotes homologous interactions and limits interactions with other chromosomes, as revealed by the fact that mutations that reduce the interaction between homologous chromosomes also result in an increase in ectopic recombination (Davis & Smith 2006, Niwa et al. 2000). These relatively simple sorting and stabilization mechanisms may be particularly effective in *S. pombe*, owing to its small number of chromosomes ($2n = 6$), the pronounced length differences among them, and the high levels of meiotic recombination in this organism.

Mutations that disrupt telomere clustering, but not nuclear envelope attachment, in either *S. pombe* or maize impair synapsis and/or recombination (Golubovskaya et al. 2002, Niwa et al. 2000, Shimanuki et al. 1997). This may reflect a direct role for clustering in mediating homolog interactions. Alternatively, clustering may be an indication that the chromosome attachments are interacting productively with other components, such as the cytoskeleton. For example, most clustering-defective mutations in fission yeast also perturb the integrity of the spindle pole body (Jin et al. 2002, Niwa et al. 2000, Shimanuki et al. 1997). Surprisingly, disrupting nuclear movement in *S. pombe* by mutation of the microtubule motor dynein has even more severe consequences for homolog pairing than loss of telomere attachment, even at centromeres (Ding et al. 2004). This indicates that nuclear movement alone can promote homolog encounters independently of telomere-mediated alignment. Unlike telomere-clustering mutants, dynein mutants do not show an increase in ectopic recombination. One interpretation is that in the absence of nuclear oscillation, chromosomes

align owing to telomere attachment but fail to pair properly (Davis & Smith 2006). Alternatively, microtubule-dependent nuclear movement may promote encounters among all chromosomes so that both allelic recombination and ectopic recombination are reduced in its absence. This would predict that the elevated ectopic recombination levels in mutants that disrupt telomere attachment should depend on nuclear oscillation.

The meiotic bouquet appears to play a less critical role in aligning homologs in *S. cerevisiae*. Although a telomere-mediated bouquet is detected during early meiotic prophase (Dresser & Giroux 1988, Trelles-Sticken et al. 1999), this bouquet can be disrupted experimentally with only subtle consequences for the cell. Deletion of the *NDJ1* gene, which encodes a meiosis-specific telomere component, results in a prophase delay and reduces telomere localization at the nuclear periphery (Trelles-Sticken et al. 2000) but has only modest effects on pairing, synapsis, and recombination (Chua & Roeder 1997, Conrad et al. 1997). An increase in ectopic recombination is also detected in *ndj1* mutant cells, suggesting that homolog discrimination may be perturbed (Goldman & Lichten 2000). However, only an approximately 2-fold increase in ectopic recombination is observed, compared with the 18-fold increase in bouquet mutants of fission yeast (Davis & Smith 2006, Goldman & Lichten 2000). As in wild-type cells, an inverse relationship between the distance of loci from the telomere and the frequency of ectopic recombination is seen in this mutant (Goldman & Lichten 2000, Schlecht et al. 2004). This relationship suggests that some aspects of telomere-mediated homolog alignment or constraint are retained in the absence of Ndj1.

A general model for bouquet formation and function that is consistent with available data is as follows: Meiosis-specific proteins establish links between chromosomes and components of the inner nuclear envelope, which either contain SUN domains or interact with SUN domain proteins. A bridge across the double bilayer of the envelope is formed by interactions between the SUN domain protein and a KASH domain protein. These bridging proteins tend to aggregate within the nuclear envelope via association with each other or with components of the microtubule-organizing center. This results in telomere clustering, which contributes to homolog alignment and thereby to pairing. However, the key purpose of this bridge may be to connect chromosomes to cytoskeletal components that drive nuclear and/or chromosome movement, which is important for cells to reap the full benefit of the bouquet. The bouquet therefore contributes to chromosome alignment and increases the overall frequency of chromosome encounters, which promote proper pairing, particularly at regions proximal to the attachment sites.

Interactions between Centromeric Regions

Beyond mediating associations with the nuclear envelope, specific chromosome regions have been speculated to play additional roles in homolog segregation during meiosis. Centromeric chromosome regions are known to be “sticky,” in that they tend to aggregate or form pairwise associations in a variety of cell types (Ding et al. 2004, Martinez-Perez et al. 2001, Scherthan et al. 1994), including non-meiotic cells (reviewed in McKee 2004). This behavior may stem from the enrichment of particular chromatin components, such as cohesins, or possibly from the enrichment of specific sequence-binding or epigenetically targeted proteins in the regions flanking the centromeres. The evidence that centromeric

associations play a role in mediating partner choice or segregation during meiosis is limited and somewhat enigmatic.

In budding yeast, centromeres have been implicated in a distributive disjunction mechanism that segregates pairs of heterologous chromosomes, which are unable to recombine and synapse (Dawson et al. 1986, Kemp et al. 2004). Physical association between the centromeres of nonhomologous partner chromosomes precedes their segregation (Kemp et al. 2004), and this physical contact may contribute to the biorientation of these chromosomes in the absence of chiasmata. Even during wild-type meiosis, centromeres establish pairwise associations that are initially nonspecific but eventually resolve to homologous associations, presumably by partner switching. This progression from random to homologous pairing of centromeres requires *SPO11* activity (Tsubouchi & Roeder 2005), as does homologous synapsis in this organism (Giroux et al. 1989), indicating that such a progression is dependent on the same recombination-based mechanism that regulates homolog pairing. This may imply that the recombination machinery operates in centromeric regions or that recombination-based homology assessment elsewhere along the chromosomes eventually directs proper centromere pairing.

Nonhomologous centromere pairing requires the activity of the synaptonemal complex component Zip1 (Tsubouchi & Roeder 2005), which may indicate that Zip1 plays a functional role in homolog sorting. Alternatively, the centromeric associations may persist long enough to allow reversible loading of the synaptonemal complex, which further stabilizes pairwise associations, at least long enough to enable their detection. In other words, these nonhomologous associations may reflect the promiscuity of synaptonemal complex formation at stabilized contact sites between nonhomologous chromosome pairs, rather than representing a productive step along the pathway to homologous synapsis. This transient synaptonemal complex formation may need to be repressed to prevent extensive synapsis between nonhomologous chromosomes.

Martinez-Perez et al. (2001) have described a similar phenomenon in allohexaploid wheat. In these plant species, each of the 7 ancestral chromosomes has become triplicated, resulting in a diploid number of 42. The chromosomes within the triploid sets do not exchange information during meiosis and have consequently diverged enough to become distinct homeologs. During meiotic prophase, each chromosome faces the problem of identifying its unique homolog not only from unrelated chromosomes but also from its four homeologs. The centromeres initially cluster in sets of six, which then resolve to homologous pairwise interactions (Martinez-Perez et al. 2001). This centromere sorting was proposed to be an active process underlying homologous synapsis in this organism. However, recent work indicates that this resolution does not depend on homology at the centromere, but rather at subtelomeric regions (Corredor et al. 2007), and also is sensitive to disruption of the telomeric bouquet by colchicine treatment (Corredor & Naranjo 2007). These findings indicate that the homologous pairing of centromeres does not drive the process of pairing and synapsis but instead is a consequence of these mechanisms. Because centromeres usually contain abundant repeats that are not unique to individual chromosomes, and thus are not optimal sites at which to assess pairwise homology, this makes teleological sense.

In fission yeast, evidence that centromeric regions are sticky during meiosis comes from observations of homolog pairing in both fixed and living cells (Ding et al. 2004, Scherthan et al. 1994). In the absence of recombination, homologous centromeres are more stably associated than interstitial regions of the chromosomes. Although homologous pairwise associations between centromeric regions in *S. pombe* are facilitated by telomere clustering and by telomere-led horsetail movement, such associations do not depend as strongly on these forces as do associations at other loci and are also more stable in the absence of DSBs (Ding et al. 2004). The pairwise association of homologous centromeres is likely facilitated by the disparate lengths of each of the three chromosome pairs. Whether centromere-specific chromatin structure or kinetochore formation contributes to their propensity to pair has not yet been tested. When recombination fails, these pairwise associations may contribute to faithful disjunction of homologs, which is slightly more robust than would be expected if the chromosomes segregated at random (Molnar et al. 2001). However, this has also not been formally tested, for example, by moving one of two homologous centromeres to a different chromosomal position to inhibit centromeric pairing.

A role for pericentric regions in mediating homolog interactions is more clearly established in *Drosophila* oocytes. Chromosomes pair along their lengths during early meiotic prophase, as in other species. Following the pachytene stage, the chromosomes condense to form a compact structure called a karyosome. The euchromatic arms separate from each other, but interactions between homologous heterochromatic regions persist until the end of meiotic prophase (Dernburg et al. 1996). In the absence of chiasmata, these persistent associations can mediate highly accurate biorientation and disjunction of homologs (reviewed in McKee 2004). Nevertheless, successful exchange between at least one or two of the chromosome pairs is critical for establishment of a bipolar spindle capable of partitioning the achiasmate chromosomes (reviewed in Hawley et al. 1993). There is no indication that heterochromatin contributes to the initial association or synapsis of homologs in *Drosophila* oocytes, and so heterochromatin is not considered to play a role in pairing by our definition.

We draw the following conclusions from these studies: (a) Centromeric and pericentric regions have a propensity to form both heterologous and homologous interactions during meiotic prophase. (b) Although it is known that persistent centromere pairing contributes to achiasmate chromosome segregation in female flies and potentially in budding yeast, it is not yet known whether it plays a role in homologous synapsis in any organism. (c) Their sticky nature may contribute to pairing and synapsis by promoting global alignment of chromosomes from centromere to telomere, which may facilitate evaluation of homology at interstitial regions.

Recombination-Independent Mechanisms Are Sufficient to Promote Homologous Synapsis in Some Organisms

In many organisms, the recombination-independent activities that promote homolog associations (described above) are probably necessary but not sufficient for homologous chromosome synapsis. In budding yeast, plants, and mammals, DSBs (Baudat et al. 2000, Giroux et al. 1989, Grelon et al. 2001, Romanienko & Camerini-Otero 2000) and subsequent strand invasion (Bishop et al. 1992; Li et al. 2004, 2007; Pittman et al. 1998; Yoshida et al.

1998) are required for efficient homologous synapsis, as discussed in more detail below. However, in *C. elegans* (Dernburg et al. 1998) and the fruit fly *Drosophila melanogaster* (McKim et al. 1998), timely and apparently normal homologous synapsis occurs even when DSB formation is blocked by mutation. If recombination machinery is necessary in other organisms to promote interactions that are sufficiently stable to overcome the barriers to synapsis, then it follows that *Drosophila* and *C. elegans* must have other ways to selectively stabilize pairing.

In *C. elegans* meiocytes, stable homologous pairing interactions are detected at the pairing center regions of chromosomes in the absence of both synaptonemal complex formation and DSBs (MacQueen et al. 2002). This pairing depends on interactions between homologous pairing centers and also on a family of zinc-finger proteins that bind to these chromosome regions (MacQueen et al. 2005, Phillips & Dernburg 2006, Phillips et al. 2005). Indirect evidence suggests that these stabilized interactions act as sites of synapsis initiation because chromosomes that are homologous in their pairing center regions but otherwise dissimilar will undergo complete synapsis (MacQueen et al. 2005). Although the pairwise interactions between pairing centers do not require DSBs or transverse filament components, they do require nuclear envelope attachment and interaction with the microtubule cytoskeleton, hallmarks of the influence of the meiotic bouquet (Penkner et al. 2007; A. Sato, C.M. Phillips & A.F. Dernburg, unpublished). Recognition between homologs may be facilitated by the organization of pairing centers, which are composed of short repeats interspersed with unique single-copy DNA sequences (C.M. Phillips & A.F. Dernburg, unpublished). However, the mechanism that mediates selective homologous recognition between these sites is unknown.

Evidence that synapsis is normally inhibited until homologs are properly associated in *C. elegans* comes from analysis of mutations in two different genes, *htp-1* and *sun-1*. HTP-1 is a component of the axial/lateral elements of the synaptonemal complex. Loss of HTP-1 function results in promiscuous loading of transverse filament components between heterologous autosomes (Couteau & Zetka 2005, Martinez-Perez & Villeneuve 2005). Interestingly, the X chromosomes still pair and synapse appropriately (Martinez-Perez & Villeneuve 2005), which is possibly related to the observed loading of the X chromosome pairing center protein HIM-8 earlier in prophase than the autosomal pairing center ZIM proteins (Phillips & Dernburg 2006; R. Kasad & A.F. Dernburg, unpublished). SUN-1 is a component of the inner nuclear envelope that is likely to interact directly or indirectly with the meiotic pairing centers. A point mutation in, or RNAi depletion of, *sun-1* during meiosis results in a phenotype very similar to that of *htp-1* deletions, except that all chromosomes, including the X chromosomes, undergo nonhomologous synapsis. Further analysis indicates that SUN-1 is necessary for normal levels of pairing (Penkner et al. 2007; A. Sato, C.M. Phillips & A.F. Dernburg, unpublished); this may reflect a direct involvement of SUN-1 in pairing or, alternatively, that SUN-1 is necessary to sustain the phase of meiosis during which pairing is actively promoted. A parsimonious explanation for the phenotypes associated with *sun-1* and *htp-1* mutations is that these proteins are both components of a checkpoint that coordinates pairing and synapsis by testing for paired homologs before

synapsis initiation is permitted (Martinez-Perez & Villeneuve 2005, Penkner et al. 2007; A. Sato, C.M. Phillips & A.F. Dernburg, unpublished).

In *Drosophila*, intimate associations between homologs are detected in somatic interphase cells, i.e., in the absence of either DSBs or synapsis (Dernburg et al. 1996, Fung et al. 1998, Hiraoka et al. 1993), but it remains unclear whether the mechanisms that promote somatic pairing (which remain poorly understood) also lead to stable homolog pairing in meiosis. It is possible that synaptonemal complex formation in *Drosophila* oocytes is promoted by activities at particular regions along the chromosome arms, although this remains uncertain (Gong et al. 2005, Hawley 1980, Sherizen et al. 2005). There is no evidence to date of a bouquet stage in *Drosophila* oocytes or that the nuclear envelope plays any role in pairing, but a recent report indicates that chromosomes do interact with the nuclear envelope during early meiosis (Lancaster et al. 2007), so this remains an open question.

RECOMBINATION-DEPENDENT MECHANISMS

In organisms that rely on recombination to generate local sites of homolog pairing, the early events of meiotic recombination promote close, stable homolog juxtaposition (CSHJ). The formation of DSBs by Spo11, the resection of DNA to reveal single-stranded DNA, and the invasion of this single-stranded DNA into the intact DNA duplex of a homologous chromosome, as catalyzed by conserved recombinases, generate intermediates that intimately link homologs. At least two enzymatic mechanisms appear to negatively regulate pairing in budding yeast: the helicase Sgs1 and the meiosis-specific protein dimer composed of Hop2 and Mnd1. Strong evidence suggests that both of these mechanisms disassemble or destabilize inappropriate recombination intermediates to ensure proper homolog pairing.

Interhomolog Recombination Promotes Pairing

Early FISH experiments in budding yeast suggested that initial pairwise interactions between homologous chromosomes can occur in the absence of recombination (Loidl et al. 1994, Nag et al. 1995, Weiner & Kleckner 1994). These tenuous interactions likely reflect the alignment of chromosomes resulting from bouquet formation. This idea is consistent with results from fission yeast, in which the bouquet promotes tenuous contacts between homologs but not stable associations (Ding et al. 2004). However, this has not yet been formally tested—for example, by FISH analysis in a double mutant in which bouquet formation and recombination have been disrupted.

The development of cytological and recombination-based assays to directly observe CSHJ has revealed the primacy of recombination in mediating homolog pairing in budding yeast. In mutants that fail to assemble the synaptonemal complex, the axes of homologous chromosomes, which can be visualized by immunofluorescence, are closely associated at several sites along their length. The appearance of these axial associations depends on regions of homology, DSB formation, and the activity of the strand-exchange proteins Dmc1 and Rad51, all of which are required for the early steps in meiotic recombination (Rockmill et al. 1995).

A site-specific recombination assay has corroborated the essential role of meiotic recombination in promoting CSHJ. This assay measures recombination events generated by the Cre recombinase at engineered *loxP* sites at homologous or heterologous chromosome sites, and can therefore be used in cells deficient in normal meiotic recombination. Because Cre-mediated recombination does not involve strand-exchange intermediates that might themselves promote pairing, this assay is thought to report on pairing without influencing it (S. Burgess, personal communication). As detected by this assay, CSHJ requires DSBs, *DMC1* (Peoples et al. 2002), *RAD51* (Lui et al. 2006), and axial element proteins (Peoples et al. 2002). Consistent with cytological analysis of axial associations, CSHJ can be detected in the absence of synapsis and crossovers (Peoples et al. 2002), indicating that the stabilization of homolog pairing depends on the initiation of crossovers, but not on their completion.

This site-specific recombination assay has also been used to evaluate the contribution of recombination-independent mechanisms of homolog interactions, such as bouquet formation. Deletion of *NDJ1*, the meiosis-specific telomere component that mediates bouquet formation in budding yeast, results in slightly reduced CSHJ, indicating some influence of telomere organization on homolog pairing. However, this influence is not detected in the absence of DSBs, suggesting that the telomereled reorganization of chromosomes may facilitate pairing but that recombination-dependent mechanisms are essential to achieve stable homolog pairing in budding yeast (Peoples-Holst & Burgess 2005).

Recombination between homologous chromosomes requires heteroduplex formation, and it is easy to imagine that these transient intermediates may be employed to assess homology to contribute to homolog pairing. Following DSB formation (Figure 5a) and resection (Figure 5b), strand-exchange proteins, along with accessory proteins, coat the resulting single-stranded 3' DNA end to create a nucleoprotein filament (Figure 5c). This filament invades an intact DNA duplex. If homologous, this invaded DNA segment provides the template for DSB repair; if nonhomologous, invasion is nonproductive and transient. Productive strand invasion leads to either crossover (Figure 5d–f) or noncrossover (Figure 5g–i) recombination (reviewed in Neale & Keeney 2006). Although recombination intermediates in the noncrossover pathway have not been detected, random spore analysis confirms a popular hypothesis that a majority of noncrossovers result from DNA synthesis following strand invasion (McMahill et al. 2007) (Figure 5g–i). The formation of a crossover further stabilizes the linkage between homologs through the formation of a double Holliday junction (DHJ), whose resolution is eventually catalyzed by an unknown enzyme (Figure 5e, f).

As mentioned above, strand exchange is central to CSHJ. This activity is carried out by Rad51 and Dmc1, eukaryotic homologs of the bacterial RecA protein. Rad51 is the dominant player in mitotic recombination, when the preferred substrate for repair is the sister chromatid (Aboussekhra et al. 1992, Shinohara et al. 1992). In organisms that utilize DSB-dependent mechanisms to stabilize homolog pairing and initiate synapsis, DMC1 is required for meiotic recombination, and its activity is coordinated with that of Rad51, probably to direct it toward interhomolog repair (Bishop 1994, Bishop et al. 1992). In organisms in which DSB-independent mechanisms are sufficient to accomplish homologous

synapsis, Rad51 appears to act as the only strand-exchange protein during meiosis (Stahl et al. 2004).

Editing of Homolog Pairing

The pairing promoted by recombination intermediates is likely edited by mechanisms that minimize the occurrence of these intermediates between inappropriate partners. Evidence for this comes from analysis of Sgs1 during meiosis in budding yeast. Sgs1 is a homolog of the human Bloom Syndrome helicase (BLM), a member of the RecQ family (Ellis et al. 1995, Watt et al. 1996). Mutations in *SGS1* produce the unusual phenotype of elevated numbers of axial associations in the absence of synapsis (Rockmill et al. 2003) and increased ectopic recombination in the Cre recombinase-based CSHJ assay (Lui et al. 2006). Mutation of *SGS1* also results in a mitotic hyper-recombination phenotype (Gangloff et al. 1994, Ira et al. 2003) similar to defects observed in the cancer-prone cells from Bloom Syndrome patients (Chaganti et al. 1974). These findings indicate that Sgs1 antagonizes recombination, most likely by destabilizing recombination intermediates. Consistent with this idea, mammalian BLM can catalyze dissolution of crossover intermediates into non-crossovers in vitro, in concert with topoisomerase IIIa (Plank et al. 2006, Wu et al. 2005). The activity of Sgs1 during meiosis appears to be important for disassembly of inappropriate recombination intermediates, particularly those between sister chromatids (Jessop et al. 2006, Oh et al. 2007, Rockmill et al. 2003). One noteworthy finding is that Sgs1 antagonizes recombination intermediates that form between homologous sequences (e.g., between sister chromatids and closely spaced interhomolog recombination events) as well as potentially nonhomologous sequences, suggesting that Sgs1 modulates pairing by raising the energetic requirements for all recombination, appropriate and otherwise.

An additional player in the editing of homolog pairing is the Hop2/Mnd1 complex. Hop2 and Mnd1 were initially implicated as negative regulators of homolog pairing and synapsis by the extensive nonhomologous synapsis observed when either of the *HOP2* or *MND1* genes is mutated in budding yeast (Leu et al. 1998, Tsubouchi & Roeder 2002). Further characterization in both budding yeast and mice showed that these mutants fail to repair DSBs (Leu et al. 1998, Petukhova et al. 2003). In principle, a defect in repair could be a consequence of failed pairing. However, the defect in recombination can be observed in the absence of synapsis (Tsubouchi & Roeder 2003), indicating a direct role for the Hop2/Mnd1 complex in recombination. When the *HOP2* and *MND1* genes are disrupted in mice or plants, asynapsis results (Kerzendorfer et al. 2006, Panoli et al. 2006, Petukhova et al. 2003), suggesting that the Hop2/Mnd1 complex is responsible for promoting homolog interactions in these organisms. Moreover, this complex can both stabilize and stimulate the strand-exchange activity of either Dmc1 or Rad51 nucleoprotein filaments (Chi et al. 2007, Pezza et al. 2007), although it stimulates a Dmc1-dependent reaction more robustly than a Rad51-dependent reaction (Petukhova et al. 2005). The absence of axial associations in *hop2 zip1* mutant cells would also support a role for Hop2 in promoting strand-exchange reactions (Leu et al. 1998).

However, analysis of the Hop2/Mnd1 complex in budding yeast suggests a more complex contribution of Hop2/Mnd1 to recombination. In the absence of *HOP2*, Dmc1 and Rad51

accumulate on chromosomes (Leu et al. 1998, Tsubouchi & Roeder 2002). Disruption of *RAD51*, *DMC1*, or both of these genes in a *hop2* mutant results in significant suppression of the *hop2* mutant phenotype. However, only mutation of *DMC1* restores spore viability to the *hop2* mutant (Tsubouchi & Roeder 2003). These experiments indicate that in *hop2* mutants, Dmc1, and to a lesser degree Rad51, promotes both appropriate and inappropriate strand-exchange reactions. The increase in ectopic recombination in *hop2 rad51* and *mnd1 rad51* mutants (Henry et al. 2006) supports a role of the Hop2/Mnd1 complex in rejecting nonhomologous Dmc1-containing recombination intermediates to contribute to proper homolog pairing.

Ectopic recombination is not observed in *mnd1 dmc1* double mutants (Henry et al. 2006), suggesting that when recombination intermediates include only Dmc1, they exhibit greater promiscuity. These data offer a potential explanation for the presence of *HOP2* and *MND1* in organisms that also include *DMC1*: If Dmc1 acts as a less selective recombinase than Rad51, it may require additional regulators, such as Hop2/Mnd1, to modulate its activity. Moreover, these data may provide an explanation for why organisms that rely on DSBs to accomplish homolog pairing, such as budding yeast, mammals, and plants, require both Dmc1 and Rad51 to complete meiotic recombination.

Homologous chromosomes must search for and identify their unique partner within the limited time frame of meiotic prophase. For organisms that rely on the recombination machinery to carry out this task, the presence of a more promiscuous recombinase, whose activity can be checked in situations in which homology is not satisfied, may facilitate homology assessment. Surprisingly, however, Rad51 can substitute for Dmc1 if overexpressed (Tsubouchi & Roeder 2003), albeit with some delays in meiotic progression (Niu et al. 2005). Nevertheless, there are mechanisms in place to ensure that Dmc1 is the dominant recombinase in budding yeast meiosis: The protein Hed1 colocalizes with Rad51 to inhibit Rad51 activity in meiosis (Tsubouchi & Roeder 2006). Aside from its promiscuity, does Dmc1 confer an additional advantage to the process of interhomolog pairing and recombination in these organisms?

The homology search occurs concomitantly with other events in meiotic chromosome behavior, such as the establishment of a block to sister chromatid exchange (BSCE). This block is imposed by the formation of the axial core between sister chromatids and potentially by the development of higher-order chromosome structure that limits access to sister chromatids (Schwacha & Kleckner 1997, Thompson & Stahl 1999, Zierhut et al. 2004). Dmc1 may be preferred to promote interhomolog recombination while this block is still being established. Such a model is consistent with the minor role Dmc1 plays in meiotic DSB repair in *S. pombe* (Young et al. 2004), an organism in which there is no apparent interhomolog bias and intersister repair intermediates predominate (Cromie et al. 2006). Moreover, this model may also explain why Rad51 can suffice in organisms in which synapsis occurs independently of recombination. For example, in *C. elegans* and *Drosophila*, most DSB formation occurs on already synapsed or synapsing chromosomes (Colaiacovo et al. 2003, Jang et al. 2003), when BSCE is likely to be fully established by axial elements capable of sustaining synaptonemal complex assembly.

The ability of overexpressed Rad51 to substitute for Dmc1 indicates that Rad51 can also catalyze interhomolog recombination. Schwacha & Kleckner (1997) suggested the existence of two mechanisms to introduce interhomolog recombination: one that directs recombination only between homologs and an alternate pathway that introduces intersister interactions with some interhomolog byproducts. Additional work by Tsubouchi & Roeder (2003) suggests that this first mechanism involves Dmc1, Rad51, Hop2, and Mnd1 whereas the primarily intersister pathway is dependent solely on Rad51.

Other than overexpression, other experimental manipulations also appear to upregulate the function of Rad51. Deletion of *HED1*, a negative regulator of Rad51 (Tsubouchi & Roeder 2006), or overexpression of Rad54, which probably promotes turnover and availability of Rad51 (Bishop et al. 1999), also suppresses recombination and sporulation defects in *dmc1* mutants. Elevated activity of Rad51 may mediate enough interhomolog recombination, along with many more intersister events, to suppress the defects of the *hop2* and *dmc1* mutants. Alternatively, Rad51 may repair DSBs preferentially by interhomolog mechanisms at a later stage of meiosis, once the block to sister chromatid exchange is fully established. Three lines of evidence support this possibility: (a) The ability of Rad51 overexpression to suppress a *dmc1* mutant depends on functional BSCE (Niu et al. 2005), (b) the repair of DSBs in *dmc1* mutants overexpressing Rad51 occurs later than in wild-type cells and is accompanied by a delay in meiosis I progression (Niu et al. 2005), and (c) the formation of crossovers is also delayed in a *hed1 dmc1* double mutant (Tsubouchi & Roeder 2006).

The role of the Hop2/Mnd1 complex remains somewhat unclear. Its biochemical characterization clearly shows a positive function in stimulating Dmc1 and Rad51 recombinase activity and stabilizing the resulting recombination intermediates. Conversely, mutational analysis in budding yeast indicates that Hop2/Mnd1 functions as an editor during pairing and recombination, destabilizing inappropriate recombination intermediates. These results could be reconciled if Hop2/Mnd1 facilitates Dmc1 function in both directions so that it promotes strand exchange but also helps to liberate Dmc1 and Rad51 from recombination intermediates. The complex may be aided in this capacity by additional modulators of Dmc1, such as Tid1, that affect the dissociation of these recombinases from sites of double-stranded DNA (Holzen et al. 2006). However, localization of the Hop2/Mnd1 dimer to chromatin independent of DSBs (Tsubouchi & Roeder 2002, Zierhut et al. 2004) suggests that the complex may modulate Dmc1/Rad51 activity indirectly, perhaps by affecting chromatin structure. In support of this idea, the fission yeast *HOP2* homolog *meu13+* affects homolog pairing dynamics independently of recombination (Nabeshima et al. 2001).

In summary, homolog pairing in budding yeast is a consequence of the stabilization of recombination intermediates between regions of homology. Early recombination intermediates, rather than crossovers per se, are necessary and sufficient to intimately pair homologs even in the absence of synapsis. The formation of DSBs and the strand-exchange reaction catalyzed by Rad51 and Dmc1 serve to link homologs, whereas enzymatic activities, including Sgs1 and Hop2/Mnd1, ensure that these linkages occur between appropriate partners. Many of these conclusions are likely to extend to mammals and plants, although no assay for CSHJ currently exists in these organisms.

Synapsis Initiation

Homolog pairing, as accomplished by DSB formation and strand exchange, is by itself not sufficient to satisfy the barrier to synapsis. Additional experiments in budding yeast have suggested that it is the subset of DSBs that will become crossovers that act as sites of synapsis initiation (Fung et al. 2004). This link between crossover formation and synapsis initiation is supported in a variety of organisms by observations of synapsis defects resulting from mutation of genes that can initiate recombination but fail to make crossovers (de Vries et al. 1999, Edelman et al. 1999, Higgins et al. 2004, Kneitz et al. 2000, Novak et al. 2001).

In principle, the formation of a crossover intermediate could stabilize interhomolog interactions to overcome a kinetic barrier to synapsis. Alternatively, there may be an enzymatic mechanism that couples crossover commitment to synapsis initiation. Analysis of the *ZIP3* and *UBC9* genes in budding yeast suggests that SUMOylation may be involved in this coupling. *ZIP3* is a member of a synapsis initiation complex (SIC) (Agarwal & Roeder 2000, Fung et al. 2004) that includes the additional proteins Zip2 and Zip4 (Chua & Roeder 1998, Tsubouchi et al. 2006) and is required for both chromosome synapsis and crossover formation (Agarwal & Roeder 2000). These SIC proteins colocalize at chromosomal foci prior to synapsis. In synapsis-defective mutants such as *zip1*, SIC proteins colocalize at some sites of axial associations (Agarwal & Roeder 2000, Chua & Roeder 1998, Tsubouchi et al. 2006), reinforcing the idea that not all sites of stable homolog pairing have the capacity to initiate synapsis. Zip3 contains a ring-finger domain, suggesting that it has ubiquitin or SUMO ligase activity (Perry et al. 2005). Cheng and colleagues verified that Zip3 acts as a SUMO ligase in vitro and showed that the transverse element protein Zip1 can bind to SUMO moieties (Cheng et al. 2006). Crippling the SUMOylation pathway by mutating an additional component of the SUMO conjugation pathway, *UBC9*, results in defective synapsis without reducing crossovers (Hooker & Roeder 2006), suggesting that the SUMO ligase activity of Zip3 may be required only for its role in synapsis. Caveats of this interpretation are that *UBC9* is essential and these conclusions are based on a non-null allele.

The direct targets of Zip3 are unknown, but cytological experiments and two-hybrid assays (Cheng et al. 2006, Hooker & Roeder 2006) suggest a mechanism for synapsis initiation. Zip3, in concert with other proteins, stabilizes those strand-exchange intermediates designated to become crossovers [termed single-end invasions (SEIs)]. Simultaneously, Zip3-regulated SUMOylation of proteins along these paired chromosomes (for instance, axial element proteins) restricts Zip1 polymerization to properly paired homologs that have initiated crossover formation. This is consistent with the timing of the appearance of SEIs in wild-type meiosis, which is concomitant with synaptonemal complex formation (Hunter & Kleckner 2001). SUMOylation of some target(s) by Zip3, in response to the formation of crossovers, may thereby provide a means to overcome the thermodynamic barriers to synapsis initiation in budding yeast (de Carvalho & Colaiacovo 2006).

Situations that give rise to nonhomologous synapsis, e.g., mutations in *HOP2* or *MND1*, may result in either inappropriate SUMOylation or SUMO-independent polymerization of Zip1. Inappropriate stabilization of Dmc1-containing strand-exchange intermediates may mimic SEIs and lead to synaptonemal complex assembly. The absence of cytologically

detectable axial associations in *hop2 zip1* double mutants indicates that these putative intermediates would have to be relatively short-lived (Leu et al. 1998). Alternatively, synapsis initiation mechanisms typically inhibited during wild-type meiosis (i.e., synaptonemal complex formation at centromeres) may be responsible for the synapsis observed in these mutant backgrounds. Localization of synapsis initiation components, such as Zip2, -3, and -4, in *hop2* or *mnd1* mutants will likely provide insight into this aberrant synapsis initiation.

In contrast to budding yeast, deletion of *HOP2* in mice (Petukhova et al. 2003) or of *MND1* in plants (Kerzendorfer et al. 2006, Panoli et al. 2006) results in asynapsis with very low levels of nonhomologous synapsis, suggesting that the kinetic requirements to initiate synapsis may be more stringent in these organisms. In plants and mammals, there may be additional conditions that need to be met to initiate synapsis, aside from the transient stabilization of strand-exchange intermediates. This additional level of regulation in these organisms may reflect the greater complexity of their genomes; the existence of considerable homologous sequence on nonhomologous chromosomes would provide more possibilities for incorrect Dmc1-containing strand-exchange intermediates and potential synapsis initiation sites.

WHY SYNAPSE AT ALL?

Given that stable homolog pairing and crossover recombination can occur in the absence of synapsis, and normally do so in *S. pombe* and other fungi, why do chromosomes synapse in most known organisms? As with all teleological questions, we cannot answer this one conclusively. A long-standing and still potentially valid idea is that the synaptonemal complex mediates control of crossover placement, also known as crossover interference, which is important for proper segregation. Evidence for this is somewhat correlative: Organisms that lack synapsis, including *S. pombe* and *Aspergillus nidulans*, also lack crossover interference. Moreover, recent results have shown that the relationship between synaptonemal complex and crossover regulation is not as straightforward as previously believed. For example, at least some interference can be imposed in the absence of normal synaptonemal complex polymerization in yeast, mice, and other organisms (Borner et al. 2004, de Boer et al. 2007, Fung et al. 2004, Osman et al. 2006). Despite these interesting cases, it remains possible that synaptonemal complex formation plays important roles in controlling the number and position of crossover events.

The primary function of the synaptonemal complex may be to enable the cell to globally monitor interhomolog associations, which, as described throughout this review, are initially mediated through local interactions. By refraining from completing crossovers between homologous sequences until this assurance is obtained, the cell may be able to minimize the ectopic crossover events that would lead to chromosome translocations. According to this view, it is in the interest of the cell to make synapsis a prerequisite for the completion of crossing over. This is consistent with the observation that late nodules, cytological manifestations of crossover resolution, are rarely seen in the absence of the synaptonemal complex (reviewed in Zickler & Kleckner 1999). In *Drosophila*, separation-of-function alleles of the transverse filament protein c(3)G have demonstrated that the domains of the

protein necessary for crossovers can be uncoupled from domains essential for synapsis (R.S. Hawley, personal communication). Such evidence reinforces the idea that crossover resolution and synapsis are not inherently codependent but that the proteins of the synaptonemal complex have evolved to couple these events. In some organisms, crossovers can form in the absence of the synaptonemal complex, but these events involve different intermediates (Cromie et al. 2006) and are resolved by a different enzymatic mechanism than those that occur in the context of the synaptonemal complex (Berchowitz et al. 2007, de los Santos et al. 2003, Higgins et al. 2008, Osman et al. 2003, Smith et al. 2003).

SYNTHESIS

We discuss above the interaction of homologous chromosomes during the meiotic process as a dynamic process in which unstable but appropriate associations between homologs are progressively reinforced and incorrect partner choices are rejected such that assembly of the synaptonemal complex and crossover recombination occur only between homologous chromosomes. Studies of the dramatic horsetail movement in fission yeast initially illuminated how the polarized arrangement of chromosomes into the bouquet facilitates interactions between homologous loci and limited associations between nonhomologous regions. It is highly likely that tenuous interactions between homologs in other species are also promoted by telomere attachment to the nuclear envelope and associated chromosome dynamics. These interactions are stabilized by recombination-dependent or -independent mechanisms, which usually lead to homolog synapsis.

Budding yeast, in which recombination-independent mechanisms play only a subtle role in pairing and synapsis, may represent an extreme case. Mutations that perturb formation of the bouquet have modest effects on homolog pairing, synapsis, and recombination in this species (Chua & Roeder 1997, Conrad et al. 1997, Goldman & Lichten 2000, Schlecht et al. 2004). Alternatively, the nonhomologous centromeric associations that have been observed early in meiosis in this organism (Tsubouchi & Roeder 2005) may also contribute to the alignment of chromosomes; in the absence of both telomere attachment to the nuclear envelope and centromere coupling (i.e., a *ndj1 zip1* double mutant), a more severe defect in homolog alignment, as assayed by levels of ectopic recombination above those in either single mutant, might be apparent.

The ecdysozoans *C. elegans* and *D. melanogaster* present an interesting counterpoint to budding yeast, in that recombination-independent mechanisms are sufficient to achieve homolog pairing and synapsis. Investigations of meiosis in these organisms raise a fundamental issue: How is homology assessed in the (presumed) absence of strand invasion? Furthermore, if homologs can recognize each other without recombination, to what extent do these mechanisms operate in organisms that couple homolog synapsis to recombination?

It is likely that the smattering of model organisms that have been analyzed in depth does not represent the full range of pairing mechanisms used during meiosis. There are numerous known exceptions, such as *Drosophila* males, in which homologs pair and synapse in the absence of both crossovers and the synaptonemal complex. Given that the goal of pairing homologous chromosomes is intrinsic to meiosis, it is curious how the details of these

mechanisms have diverged in fundamental ways even among those few species that have been investigated. As we learn more about how pairing is achieved and coupled to synapsis, it will also be interesting to see what emerges from studies of more deeply rooted eukaryotes, which do not share a common ancestor with these familiar species.

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Glossary

Pairing	also referred to as close, stable homolog juxtaposition (CSHJ); the local stabilization of homolog interactions that can be observed in the absence of synapsis
Synaptonemal complex	a morphologically conserved structure composed of axial (or lateral) elements and transverse elements; normally forms between pairs of homologous chromosomes during meiosis and structurally enforces homolog pairing
Crossover recombination	also known as genetic exchange, a reciprocal recombination event between two chromatids on homologous chromosomes that results

	in local gene conversion and exchange of the arms flanking the site of initiation. Crossover events result in chiasmata (singular: chiasma), which link homologs during the first meiotic division
Synapsis	assembly of the synaptonemal complex
Alignment	the polarization of chromosomes in the nucleus such that homologous interactions are favored and nonhomologous contacts are inhibited
Meiotic recombination	includes both noncrossover (also known as gene conversion) and crossover events
Double-strand break (DSB)	essential initiating event in all meiotic recombination; catalyzed by Spo11 a conserved topoisomerase-like enzyme that acts as a dimer to simultaneously cut both strands of a DNA helix (chromatid)
Gene conversion	a recombination event involving local, unidirectional transfer of information from one nonsister chromatid to another; describes meiotic recombination events that are not accompanied by crossovers

SUMMARY POINTS

1. Pairing and synapsis are distinct processes that must be coordinated to ensure that synapsis selectively enforces interactions between homologous chromosomes.
2. The initiation of synapsis is probably a tightly regulated event during meiosis and is therefore subject to large thermodynamic or kinetic barriers. Mutations that uncouple pairing and synapsis can illuminate both the physical nature of the barriers and the intermediates that allow them to be overcome.
3. Homology is likely “recognized” through both the stabilization of appropriate interactions and the rejection of nonhomologous contacts. Defects in either the stabilization or the rejection machinery may result in failed or inappropriate pairing and synapsis.
4. Recombination-independent and -dependent mechanisms contribute to the assessment of homology during meiotic prophase. Most organisms probably employ a combination of both mechanisms to accomplish homolog pairing.

FUTURE ISSUES

1. What are the relative contributions of recombination-independent mechanisms to homolog pairing and synapsis in organisms that ultimately use recombination-dependent mechanisms to stabilize pairing and initiate synapsis? Does the recombination machinery play a role in organisms that can accomplish pairing and synapsis in the absence of Spo11-induced DSBs?
2. How is homology assessed in organisms that rely solely on recombination-independent mechanisms to accomplish pairing and synapsis?
3. What are the molecular mechanisms responsible for overcoming the barrier to synapsis?
4. To what extent are common mechanisms to stabilize pairing and initiate synapsis present in all organisms? Do organisms repress some of these mechanisms so that others appear to dominate?

Figure 1.

Meiotic chromosome segregation. (a) Meiotic cells of diploid organisms contain two copies of every chromosome, one inherited from each parent (*red* and *blue*). After DNA replication, sister chromatids are linked by cohesion (*purple circles*). Genetic exchange between nonsister chromatids generates chiasmata, which, in conjunction with sister chromatid cohesion, link homologous chromosomes through metaphase I. (b) Dissolution of cohesion distal to the chiasmata during meiosis I enables homologous chromosome segregation. (c) The remaining cohesion is removed during meiosis II to enable separation of sister chromatids.

Figure 2.

A pairing pathway. Intermediates in the pairing pathway are depicted: (a) unpaired homologs (one *red* and one *blue*), (b) alignment, (c) encounters between homologous chromosomes, and (d) stabilized pairing. The pathway concludes with synapsis and/or homolog recombination (g). Alignment is often facilitated by formation of the bouquet, more specifically the attachment of chromosome ends to the nuclear envelope (b). Paired homologs can be stabilized by recombination-independent mechanisms (e.g., pairing at *cis*-acting loci such as pairing centers) (e) or recombination-dependent mechanisms (i.e., axial associations) (f).

Figure 3.

The synaptonemal complex. (a) Transmission electron micrograph of a synaptonemal complex from *Caenorhabditis elegans*, which appears as a zipper-like track flanked by electron-dense patches of chromatin. (b) Schematic of the synaptonemal complex. The axial/lateral elements (red) assemble between sister chromatids prior to or concomitant with pairing. The transverse filaments (purple) polymerize between paired homologs to complete synapsis.

Figure 4.

Examples of the meiotic bouquet. Images of the bouquet in (a) *Schizosaccharomyces pombe*, (b,c) *Saccharomyces cerevisiae*, (d) *Zea mays*, (e) *Caenorhabditis elegans*, and (f) *Mus musculus*. In some organisms, such as *S. pombe* (a), tight clustering of the telomeres is obvious. However, in other organisms, such as *Z. mays* (d), *C. elegans* (e), and *M. musculus* (f), clustering of chromosome ends is less pronounced. *S. cerevisiae* exhibit a mixture of “tight” (b) and “loose” (c) bouquet arrangements during prophase. The arrow in panel c indicates the spindle pole body. DNA is shown in blue, telomeres or chromosome ends are shown in green, and SUN (Sad1, Mps3, and SUN-1) or KASH (ZYG-12) domain proteins are indicated in red, except for in the *Z. mays* image, in which only the telomeres are shown. Images are reprinted and/or adapted from Chikashige et al. 2006 (a), Conrad et al. 2007 (b,c), Bass et al. 1997 (d), and Ding et al. 2007 (f), respectively, with permission from The Rockefeller University Press (d) and Elsevier (a and f).

Figure 5. Meiotic recombination. (a–c) Double-strand break (DSB) formation and resection. DSB formation is catalyzed by the Spo11 enzyme (orange ovals) (b). Endonuclease activity releases Spo11 covalently bound to an oligonucleotide, and 5'-to-3' exonuclease activity exposes single-stranded (ss) 3' ends. Recombinases such as Rad51 and/or Dmc1 coat the ssDNA tail and catalyze strand invasion into the intact DNA duplex of a homologous chromosome (c). (d–f) Crossover pathway. Invasion of the Rad51/Dmc1-containing nucleoprotein filament results in an asymmetric strand-exchange intermediate (d). DNA synthesis (dashed line) is primed from the invading 3' end. The second end is captured and primes DNA synthesis. Ligation produces a double Holliday junction (DHJ) (e). The DHJ is resolved by an unknown enzyme to produce a mature crossover with the exchange of flanking DNA (f). (g–i) Noncrossover pathway by synthesis-dependent strand annealing

(SDSA). Strand invasion (*g*) and DNA synthesis (*h*) are inferred but have not been experimentally detected. The newly synthesized DNA strand is displaced and anneals with the other DSB end; break repair is accomplished by DNA synthesis and ligation.

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