Annu. Rev. Cell Dev. Biol. 2004. 20:525–58
doi: 10.1146/annurev.cellbio.19.111301.155141

First published online as a Review in Advance on June 24, 2004

THE GENETICS AND MOLECULAR BIOLOGY OF THE SYNAPTONEMAL COMPLEX

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Key Words meiosis, synapsis, chromosome pairing, meiotic recombination, cohesins

■ **Abstract** The synaptonemal complex (SC) is a protein lattice that resembles railroad tracks and connects paired homologous chromosomes in most meiotic systems. The two side rails of the SC, known as lateral elements (LEs), are connected by proteins known as transverse filaments. The LEs are derived from the axial elements of the chromosomes and play important roles in chromosome condensation, pairing, transverse filament assembly, and prohibiting double-strand breaks (DSBs) from entering into recombination pathways that involve sister chromatids. The proteins that make up the transverse filaments of the SC also play a much earlier role in committing a subset of DSBs into a recombination pathway, which results in the production of reciprocal meiotic crossovers. Sites of crossover commitment can be observed as locations where the SC initiates and as immunostaining foci for a set of proteins required for the processing of DSBs to mature crossovers. In most (but not all) organisms it is the establishment of sites marking such crossover-committed DSBs that facilitates completion of synapsis (full-length extension of the SC). The function of the mature full-length SC may involve both the completion of meiotic recombination at the DNA level and the exchange of the axial elements of the two chromatids involved in the crossover. However, the demonstration that the sites of crossover formation are designated prior to SC formation, and the finding that these sites display interference, argues against a role of the mature SC in mediating the process of interference. Finally, in at least some organisms, modifications of the SC alone are sufficient to ensure meiotic chromosome segregation in the complete absence of meiotic recombination.

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INTRODUCTION

To accomplish the meiotic process, pairs of homologous chromosomes must align (or pair) by mechanisms that are incompletely understood. Whereas some processes of pairing are dependent on the formation of double-strand breaks (DSBs), which also initiate the recombination process, others are DSB independent. Both classes of pairing mechanisms culminate in the process of synapsis, in which a large protein structure, referred to as the synaptonemal complex (SC), comes to lie between paired chromosomes and connects them along their entire lengths. Although the SC is not required for pairing maintenance in yeast (Sym et al. 1993, Nag et al. 1995), it is required to stabilize meiotic pairing as the cell enters pachytene in at least one organism (*Caenorhabditis elegans*) (MacQueen et al. 2002). Moreover, the modification of the SC in organisms as disparate as *Bombyx mori* and marsupial males (and perhaps in *Drosophila* females, as well) facilitates

the segregation of homologs even in the absence of crossing over (Rasmussen 1977, Page et al. 2003, Harris et al. 2003).

This review describes the processes that lead to the formation of the SC, our understanding of the structure of the SC, and the function of the core components of the SC. We emphasize the relationship of processes that underlie formation of chromosome axes to the assembly of the SC and discuss the roles of SC components in mediating the maturation of recombination intermediates into mature crossovers. To illustrate our discussion, we have diagrammed these processes along a timeline of meiotic prophase (Figure 1). Our goal is not to survey the entire meiotic process, nor the mechanisms that underlie either recombination or segregation (those processes are covered in recent reviews: Zickler & Kleckner 1998, 1999; Lichten 2001; Hassold & Hunt 2001; McKim et al. 2002; Champion & Hawley 2002; Page & Hawley 2003; Petronczki et al. 2003), but rather to focus solely on the role of the SC in meiosis.

Changes in Chromosome Structure During Meiotic Prophase

Chromosomes undergo an intricate series of structural changes during meiosis (Zickler & Kleckner 1998). Prior to entering meiosis, the chromosomes are replicated during an extended premeiotic S-phase. Meiotic prophase is traditionally divided into stages on the basis of changes to chromosome morphology visible by light microscopy. At the first of these stages, leptotene, individual chromosomes are recognizable as long thin strands that have begun condensing but do not yet show signs of homologous alignment. As chromosomes individualize and condense during early prophase, the sister chromatids become organized along structures called axial elements (AEs).

In most organisms, the interaction of meiotically induced DNA DSBs with matching sequences on the homologous chromosome brings the AEs of homologous chromosomes into alignment during early- to mid-leptotene. The sites of these interactions are visualized as ~400-nm interaxis bridges (Albini & Jones 1987, Tesse et al. 2003). These bridges, which likely contain a DSB already engaged in a nascent interaction with its partner DNA, occur in large numbers (Hunter 2003, Franklin et al. 1999, Tarsounas et al. 1999). As leptotene proceeds, a small fraction of these bridges appears to be matured into structures known as axial associations (AAs), which connect the paired lateral elements (LEs) (Rockmill et al. 1995). These AAs will eventually nucleate the formation of the SC (i.e., as synapsis initiation sites) between intimately associated AEs. The AEs are thus incorporated into SC structure as part of the LEs. The regions of synapsis expand along the chromosome until synapsis is complete and the entire length is joined together by the SC.

By the beginning of pachytene, the chromosomes achieve a state known as synapsis, which refers to a tight continuous association along the chromosome length in which the four chromatids are aligned and held together by the SC. At this point the SC consists of the paired LEs, which are connected by transverse filaments running between them (Figure 2). In most electron microscopy (EM) studies of the SC at pachytene, a central element appears as an electron-dense linear structure

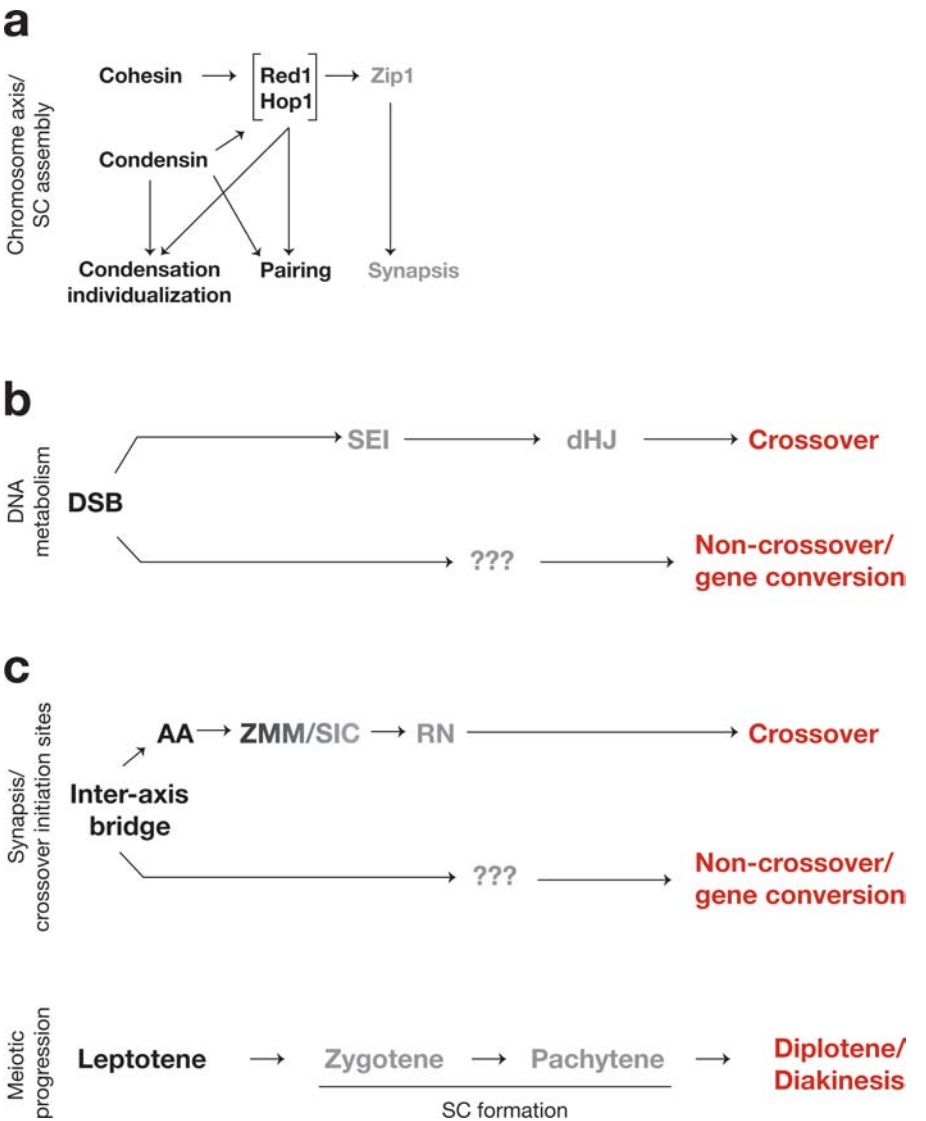

Figure 1 Three schematic road maps of the meiotic process, useful for positioning specific events relative to each other during meiotic prophase. (*a*) A schematic diagram for the events required for the assembly of the chromosome axes and SC. (*b*) A schematic diagram for the events required for the repair of meiotic DSBs. (*c*) A schematic diagram for the process of crossover differentiation and synaptic initiation at the level of axial associations. For reference, the approximate stages of early meiotic prophase are listed at bottom.

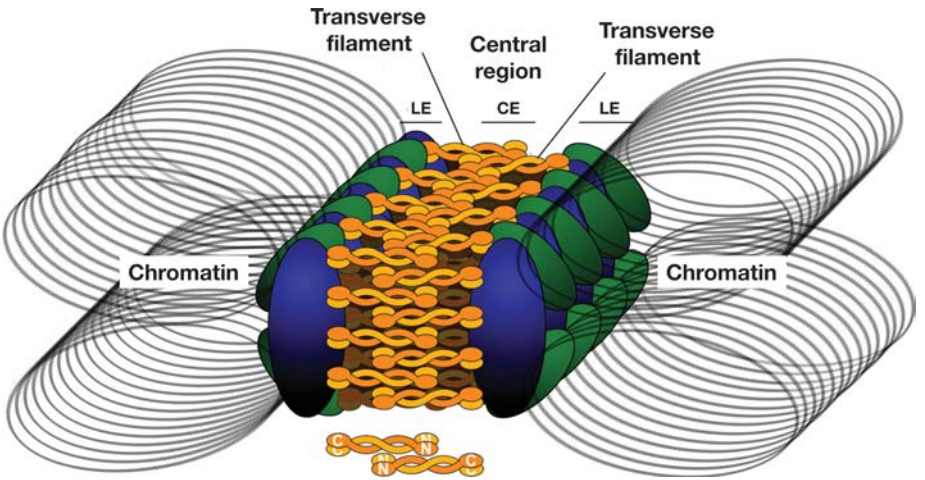

Figure 2 Model of SC structure. Shown is a cross section of a segment of the SC with lateral elements (LE), transverse filaments, central element (CE), and central region. The arrangement of transverse filament proteins, as determined experimentally for Zip1p and SCP1, is shown at bottom. Also shown is a hypothetical arrangement of cohesins/condensins (*blue ovals*) and other LE proteins (*green ovals*) along the LEs.

running down the center of the SC. Following pachytene, meiotic chromosomes in many organisms undergo a phase of decondensation called diplotene, during which the SC disassembles and homologs often separate, except at chiasmata. Chiasmata, the physical manifestations of reciprocal meiotic recombination events, continue to hold homologous chromosomes together during diakinesis as the chromosomes condense prior to the onset of metaphase I.

The Processes of Alignment and Pairing

As reviewed by Burgess (2002) and Page & Hawley (2003), the degree to which DSB-dependent and DSB-independent pairing mechanisms are employed in meiosis appears to vary among organisms. Although DSB-dependent interactions represent the primary mode of establishing pairing in *Saccharomyces cerevisiae*, at least some types of homolog pairing interactions occur in the absence of DSBs (Peoples et al. 2002, Burgess 2002). Similarly, in *Coprinus cinereus*, a significant amount of homolog pairing occurs even when meiotic DSBs are lacking (Celerin et al. 2000), despite the fact that DSBs are essential for proper synapsis.

In contrast to yeast, homolog pairing occurs normally in *C. elegans* and in both sexes of *Drosophila melanogaster* in the complete absence of DSBs (Dernburg et al. 1998, McKim et al. 1998, MacQueen et al. 2002, Vazquez et al. 2002). *Caenorhabditis elegans* chromosomes enter meiosis unpaired and then undergo a rapid alignment. This alignment requires neither the initiation of recombination

nor the function of proteins that will later facilitate synapsis (MacQueen et al. 2002). Similarly, in *Drosophila* females, the existence of prior somatic pairing associations may well circumvent the need for DSB-dependent homology searches. It seems likely that the lack of a requirement for the creation of recombination intermediates for synapsis in these organisms may reflect the ability of flies and worms to use other DSB-independent means to mediate homolog recognition.

The Creation of DSBs and Maturation into Recombination Intermediates

Recombination is initiated by DSBs created by the Spo11 protein in yeast and its homologs in other organisms (Keeney et al. 1997, McKim & Hayashi-Hagihara 1998, Dernburg et al. 1998, Romanienko & Camerini-Otero 2000, Grelon et al. 2001). The decision as to whether breaks will be repaired along a pathway that leads to reciprocal meiotic crossovers or to nonreciprocal gene conversion events appears to be made quite early, at or about the time of DSB formation (Allers & Lichten 2001, Hunter & Kleckner 2001, but see Börner et al. 2004 for review). Although the events that lead to gene conversion remain undefined, it is clear that the maturation of DSBs to crossovers involves the resection of the DSB to form a gap (White & Haber 1990) followed by the formation of two intermediates, single-end invasions (SEIs) and double Holliday junctions (dHJs), arising from successive single-strand events occurring at each end of the double-strand gap (Hunter & Kleckner 2001, Schwacha & Kleckner 1995). Both intermediates are long lived and, at least in yeast, their successive appearance and disappearance are correlated with the progression of meiotic prophase (Figure 1). Thus in yeast, DSBs occur prior to the appearance of any SC at leptotene; the appearance of SEIs is concomitant with the initiation of SC formation and completed by the end of SC formation; dHJ formation occurs during pachytene, and the resolution of dHJs to mature crossovers occurs at the end of pachytene.

As discussed by Blat et al. (2002), the maturation of DSBs to crossovers is paralleled by changes in axial cores of meiotic chromosomes, such that "interruption of DNA via a DSB may be accompanied by interruption of the underlying axis at the corresponding position." Presumably, the events that mature a DSB to an SEI and then to a dHJ are also coupled with events that produce a matching axial break on the exchange partner and then heal these breaks to produce an axial exchange. Moreover, as suggested by Blat et al. (2002), it seems likely that these axial changes determine which DSBs will become committed to the crossover pathway.

The Relationship of Double-Strand Break Formation to Synapsis

In yeast, the creation of DSBs by Spo11p, and thus the initiation of recombination, is required for synapsis (Giroux et al. 1989, Keeney et al. 1997). Subsequent studies in many other organisms also demonstrated the dependence on DSBs for

synapsis (Lichten 2001, Burgess 2002). In the absence of functional Spo11 protein, synapsis can be restored if DSBs are induced by other means, as has been shown experimentally for *spo11* mutants in both *Coprinus* and mouse (Celerin et al. 2000, Romanienko & Camerini-Otero 2000). Most likely, further processing of the DSBs is also required for proper synapsis. Analysis of yeast mutants that are impaired in these steps show various SC formation defects (Zickler & Kleckner 1999, Burgess 2002). Homologous DNA sequence alone is also not sufficient for proper synapsis. The yeast proteins Hop2p and Mnd1p are required for ensuring synapsis between homologous sequences and preventing synapsis between nonhomologous chromosomes (Leu et al. 1998; Nabeshima et al. 2001; Gerton & DeRisi 2002; Tsubouchi & Roeder 2002, 2003; Petukhova et al. 2003).

Synapsis occurs normally in the absence of meiotic DSBs in *C. elegans* and *Drosophila* females (Dernburg et al. 1998, McKim et al. 1998). In *C. elegans*, unpaired chromosomes entering meiosis rapidly align and synapse in the absence of recombination initiation (MacQueen et al. 2002). Synapsis of chromosomes in *Drosophila* females may depend on the existence of prior somatic pairing associations. In both cases, synapsis is achieved without the need for DSBs, indicating that other strategies may be employed to assemble a SC structure. Despite using a different mechanism to achieve synapsis, the assembly and structure of the SC in these organisms is indistinguishable from what is observed in DSB-dependent synapsis. However, as detailed below, synapsis is not required for DSB formation in either *Drosophila* or *C. elegans*. In both cases, DSBs form at normal or near normal frequency in the absence of SC formation (Colaiácovo et al. 2003, Jang et al. 2003—but see below).

The Recombination Nodule

Recombination nodules (RNs) were originally identified as electron-dense ovoid structures associated with SCs (Carpenter 1975). Many subsequent investigations identified two types of RNs, early nodules and late nodules. Early nodules (ENs) are ~100-nm diameter spherical or ellipsoidal structures associated with axial elements and the SCs from as early as late leptotene until mid-pachytene. Late nodules (LNs) are variable in shape and appear later during pachytene and in lower numbers than ENs (Zickler & Kleckner 1999, Moens et al. 2002). Anywhere from several hundred to several thousand evenly spaced ENs may appear per cell, depending on the species studied. The timing and locations of EN appearance during meiosis has suggested their involvement in early recombinational interactions, possibly in the pairing of homologous chromosomes (Albini & Jones 1987, Carpenter 1987).

Comparisons of cytological and genetic studies established a strong correlation between LNs and crossovers or chiasmata (Carpenter 1975, Albini & Jones 1988, Zickler & Kleckner 1999). Indeed, several lines of evidence strongly support the view that LNs mark the sites of those DSBs that will be matured into crossover events. First, the number and distribution of LNs parallels the number and distribution of genetically observed crossovers in both wild-type meiosis and in meioses in

which the level or distribution of exchanges has been perturbed by another means (Carpenter 1975, 1987). Second, several studies in yeast suggest that a group of proteins specifically involved in crossover maturation (but not in gene conversion), namely Zip1p, Zip2p, Zip3p, Msh4p, and Msh5p, are components of LNs (Ross-Macdonald & Roeder 1994, Novak et al. 2001, Fung et al. 2004). Similarly, the MLH1 protein has been shown to be a component of mammalian LNs (Moens et al. 2002). Third, late RNs in yeast display interference, as do meiotic crossovers (Agarwal & Roeder 2000, Fung et al. 2004).

SITES OF CROSSOVER COMMITMENT AND SYNAPTIC INITIATION

Synaptonemal complex formation appears to be initiated at AAs (Sym et al. 1993, Rockmill et al. 1995) corresponding to sites at which DSBs have been committed to a repair pathway that will result in the production of reciprocal exchanges (crossovers). These sites can be observed cytologically in early zygotene of a number of organisms (Moens 1969, Rasmussen & Holm 1978, Hasenkampf 1984, Stack & Anderson 1984, Loidl & Jones 1986, Albini & Jones 1987, Tarsounas et al. 1999).

Axial associations can be visualized in yeast only at pachytene in the presence of *zip1* mutants that block assembly of the central region of the SC (Sym et al. 1993, Rockmill et al. 1995). Four lines of evidence argue that AAs correspond to the sites of those DSBs that will mature into meiotic crossovers. First, in yeast the occurrence of AAs is Spo11p dependent; these structures do not arise in the absence of recombination initiation (Agarwal & Roeder 2000). Second, the RecA homologs Rad51p and Dmc1p are required to establish AAs (Rockmill et al. 1995), and, as described below, proteins specifically required for the formation of crossovers localize to the AAs, as observed by immunostaining foci. Third, mutants in the yeast *sgs1* gene, which encodes a member of the RecQ family of DNA helicases, increase both the number of AAs and the level of meiotic crossing over (although not to the same extent), without affecting the frequency of gene conversion events (Rockmill et al. 2003). Finally, similar to meiotic crossovers, AAs display interference (Fung et al. 2004).

Axial associations serve as sites for the assembly of a complex of proteins that are referred to as synapsis initiation complexes (SICs) (Fung et al. 2004). These complexes are composed of a group of proteins (including Zip1p, Zip2p, Zip3p, and Msh4p) that play critical roles in establishing meiotic synapsis and in the process of maturing DSBs into meiotic crossovers (see below). In *zip2* mutants, the AEs of the homologous chromosomes pair (and are connected by AAs), but synapsis does not occur, and the transverse filament protein Zip1p fails to localize properly to the meiotic chromosomes (Chua & Roeder 1998). As noted by Chua & Roeder (1998), "These results imply that Zip2p must be present on chromosomes before Zip1p can stably localize, as expected of a protein involved in synapsis."

Indeed, Agarwal & Roeder (2000) presented strong evidence in support of a model in which the binding of Zip3p to the AAs recruits Zip2p, and both Zip2p and Zip3p recruit Zip1p. The binding of Zip1p to the AAs then catalyzes the assembly of the full-length SC, which spans the regions between the AA/SIC nodes and allows the completion of synapsis.

The ability of AAs to play critical roles in synaptic initiation is likely intertwined with their central role in crossover maturation. Indeed, several lines of evidence suggest SICs correspond to cytologically identified structures known as late recombination nodules that appear to mediate the maturation of DSBs into meiotic crossover events. First, the timing of the appearance and disappearance of SICs parallels that of late recombination nodules, and both are Spo11p dependent (Agarwal & Roeder 2000). Second, mutations in any of the genes whose proteins make up this structure specifically reduce the frequency of crossing over without affecting the frequency of gene conversion (Sym et al. 1993, Chua & Roeder 1998, Agarwal & Roeder 2000), and genetic analyses performed to date suggest that all these mutants lie in the same recombination epistasis group, which suggests that they function in the same pathway. Third, as noted above, *sgs1* mutants increase both the number of AAs/SICs and the level of meiotic crossing over without affecting the frequency of conversion events (Rockmill et al. 2003).

A recent model (Börner et al. 2004) proposes that Zip1p, Zip2p, Zip3p, Msh5p, and Mer3p, designated as ZMM proteins, promote the crossover-specific processing of a DSB. This proposal is based on observations of yeast cells lacking any one of the Zip1p, Zip2p, Zip3p, or Msh5p proteins under conditions (e.g., high temperatures) that arrest the cell cycle and block progression of crossover-designated DSBs. Under these conditions, absence of any one of the Zip1p, Zip2p, Zip3p, or Msh5p proteins specifically prevents the conversion of DSBs into meiotic crossovers at the first step along the crossover-specific pathway (i.e., the production of SEIs). However, *zip1*, *zip2*, *zip3*, or *msh5* mutants do not inhibit the normal recovery of noncrossover products of DSB repair (i.e., gene conversion without associated crossing over). These data are consistent with a view in which DSBs are differentiated into pathways that yield crossover and noncrossover (gene conversion) products (Börner et al. 2004). Such differentiation may take place either before, or coincident with, creation of DSBs, before the onset of stable strand exchange, and certainly before, and independently of, the establishment of the SC. Thus ZMM/SIC sites may mark the sites of those DSBs that will mature into reciprocal exchanges.

The relationship between DSB differentiation (to crossover or noncrossover events), AA formation, and the formation of ZMM/SIC foci can be explained by a recent model of crossover maturation and synaptic association (Börner et al. 2004). During early-mid-leptotene, the interaction of DSBs with matching sequences on the homologous chromosome creates the interaxis bridges (Albini & Jones 1987, Tesse et al. 2003) described above. Consistent with roles in early recombination events, these interaxis associations display RecA homolog-containing recombination complexes across their lengths (Franklin et al. 1999, Tarsounas et al. 1999).

Indeed, as suggested by Hunter & Kleckner (2001), they likely contain a DSB already engaged in a nascent interaction with its partner DNA. Börner et al. (2004) propose that an unknown mechanism commits a small fraction of these interaxis bridges to become future crossovers in a process in which crossover interference acts. These crossover-designated DSBs then progress to SEIs in a ZMM-dependent fashion. The nucleation of the SC is coupled to the onset of SEI formation at the crossover-designated sites. (It is also possible that such ZMM assemblies facilitate the later transition of SEIs to dHJs.)

This model also proposes an active buckling of the chromosome axes at the sites of interaxis bridges, which then determines the sites to be designated as crossover. Those sites at which such changes in the axes occur will create AAs, upon which ZMM/SIC foci can be assembled. In this view, DSB sites (or interaxis bridges) where such active buckling does not occur are proposed to result in the disappearance of the interaxis bridges without resulting in axial discontinuities. Such sites may be sites of noncrossover recombination (gene conversion without associated crossing over).

Although attractive, this model does not explain the process of SC assembly in *Drosophila* females and in *C. elegans*, where DSB formation is not required for SC formation and where DSBs do not normally occur until after the completion of the SC (Colaiácovo et al. 2003, Jang et al. 2003). Perhaps in these organisms the alignment of axial cores, and thus LEs, occurs by methods other than early recombinational interactions, and these interactions alone are sufficient to allow the polymerization of the transverse filaments.

THE ASSEMBLY AND STRUCTURE OF LATERAL ELEMENTS

The Role of Cohesin Proteins in Formation of Lateral Elements

Mounting evidence suggests that meiosis exploits proteins involved in mitotic chromosome structure for use in SC morphogenesis. The condensin and cohesin protein complexes were named for their mitotic functions in chromosome condensation and sister chromatid cohesion, respectively (Haering & Nasmyth 2003). In mitotic cells, cohesin is required to establish cohesion between sister chromatids during DNA replication. The mitotic cohesin complex consists of two structural maintenance chromosome (SMC) proteins, SMC1 and SMC3, and two non-SMC components called SCC1 and SCC3 (Hirano 2002, Haering & Nasmyth 2003). Cohesin is also present in meiotic cells, but certain members of the complex have been replaced by meiosis-specific paralogs. SCC1 is replaced in most meiotic systems by a similar protein known variously as REC8 (Klein et al. 1999, Watanabe & Nurse 1999, Pasierbek et al. 2001, Eijpe et al. 2003, Lee et al. 2003), C(2)M (Manheim & McKim 2003, Schleiffer et al. 2003), or SYN1 (Cai et al. 2003). Additionally, SCC3 is replaced by STAG3 in mammals and by Rec11p in fission yeast (Pezzi et al. 2000, Molnar et al. 2003), and SMC1β replaces mitotic SMC1 in many mammalian meiotic cohesin complexes (Revenkova et al. 2001).

The cohesin complex assembles along the axial chromosomal cores during meiotic prophase. The replacement of mitotic SCC1 by REC8 occurs during premeiotic S phase (Klein et al. 1999, Watanabe & Nurse 1999, Pasierbek et al. 2001, Eijpe et al. 2003, Manheim & McKim 2003, Cai et al. 2003). Eijpe and colleagues (2003) found that REC8 is initially present on short axial structures in the absence of other cohesin components. During leptotene, the remaining cohesin components, SMC1β, SMC3, and STAG3, associate with the REC8-containing axial element fragments (Eijpe et al. 2000, 2003; Pezzi et al. 2000; Prieto et al. 2001; Pelttari et al. 2001; Revenkova et al. 2001). These cohesin-associated AE fragments are thought to form part of the SC because they coalesce to eventually colocalize with SC components along the entire length of the chromosomes at pachytene. Similarly, evidence in both yeast and *Drosophila* indicates that cohesin components are associated with SCs during pachytene (Klein et al. 1999; R.S. Khetani, S.L. Page & S.E. Bickel, personal communication).

Recent experimental evidence supports the hypothesis that REC8 and the rest of the cohesin complex function in LE formation by forming an axial chromosome core on which LE proteins bind and assemble. In *rec8* and *smc3* mutants in *S. cerevisiae*, formation of the SC or AE fragments is abolished (Klein et al. 1999). Members of the cohesin complex can be detected in SCs isolated by subcellular fractionation (Eijpe et al. 2000), and the LE protein SCP3 co-immunoprecipitates with REC8, SMC1, and SMC3 from mammalian testis nuclear extracts, indicating the tight association of cohesin and LE proteins (Eijpe et al. 2000, Lee et al. 2003).

Cohesin is clearly important for the localization of LE-associated proteins in many species. Yeast Rec8p is required for normal localization of the LE protein Red1p to chromosomes (Klein et al. 1999). In *C. elegans*, the SC-associated protein HIM-3 fails to localize correctly in REC-8-depleted cells (Pasierbek et al. 2001) and REC-8 localization is defective in meiotic cells depleted of SCC-3 (Wang et al. 2003, Pasierbek et al. 2003). In mammals, LE proteins SCP2 and SCP3 are first detected on chromosomes at the same time that SMC1β and SMC3 appear, after the appearance of REC8 (Eijpe et al. 2003). However, SCP2 and SCP3 are dispensable for cohesin localization because the cohesins SMC1, SMC3, and STAG3 all localize normally in the absence of SCP3 (Pelttari et al. 2001).

The Role of Condensins in Assembly of the Lateral Elements

Condensin is a complex composed of two SMC proteins, SMC2/CAP-E and SMC4/CAP-C, and three non-SMC subunits, CAP-D2/Ycs4p, CAP-G/Ycs5p/Ycg1p, and CAP-H/Brn1p, all of which have roles in the condensation of mitotic chromosomes (Hirano 2002). Condensin proteins are necessary for axial length compaction and chromosome individualization (longitudinal compaction) during meiotic prophase (Yu & Koshland 2003), similar to their effects on mitotic chromosome condensation (Hirano & Mitchison 1994; Saka et al. 1994; Strunnikov et al. 1995; Ouspenski et al. 2000; Lavoie et al. 2000, 2002; Bhalla et al. 2002).

The cohesin component Rec8p localizes normally in the absence of condensin, a finding that suggests a chromosome axis does form in the absence of condensin and shows that cohesin binds to meiotic chromosomes independently of condensin.

Recent work by Yu & Koshland (2003) has demonstrated several meiosis-specific roles for members of the condensin complex. The specificity of these defects to meiosis was demonstrated by the isolation of a meiosis-specific allele of *ycs4* that was competent for chromosome condensation in mitosis and meiosis, but was defective in recruiting SC proteins, chromosome pairing, and Dmc1p-dependent DSB repair. In both conditional and meiosis-specific condensin mutants, the SC proteins Red1p, Hop1p, and Zip1p fail to localize properly to the chromosomes (Yu & Koshland 2003). Interestingly, cohesin is also necessary for the normal assembly of Red1p and Zip1p on chromosomes during meiotic prophase (Klein et al. 1999), indicating that although cohesin and condensin associate with chromosomes independently, both are required for forming the SC. Additionally, condensin mutants failed to process DSBs through a Dmc1p-dependent pathway and were somewhat impaired for homolog pairing (Yu & Koshland 2003).

Non-Cohesin Components of the Lateral Elements

SCP2 AND SCP3 IN MAMMALIAN LEs Synaptonemal complex proteins (SCP) SCP2 and SCP3 were first identified as antigens bound by monoclonal antibodies raised against isolated rat SCs (Heyting et al. 1985, 1987, 1989; Offenberg et al. 1991). SCP3 (known as COR1 in hamster) is a 30-kDa protein with a possible nucleotide-binding motif and stretches of predicted coiled coils in its C-terminal half (Dobson et al. 1994, Lammers et al. 1994). SCP2 is a 173-kDa putative DNA-binding protein with a short predicted coiled coil region near the C terminus (Offenberg et al. 1998, Schalk et al. 1999).

Several lines of evidence indicate that these proteins are structural constituents of the LEs. SCP2 and SCP3 first localize to unsynapsed AEs during leptotene and remain associated with chromosomes and SCs until most arm staining is lost at metaphase I. By immunoelectron microscopy, SCP2 and SCP3 localize to LEs (Dobson et al. 1994, Lammers et al. 1994, Offenberg et al. 1998, Schalk et al. 1998). When expressed in cultured mammalian cells, SCP3 forms transversely striated fibrous structures in the nucleus and cytoplasm (Yuan et al. 1998). The formation of higher-order structures by SCP3 is consistent with data suggesting that SCP3 molecules interact with each other through the C-terminal coiled coil domain (Tarsounas et al. 1997, Yuan et al. 1998).

SCP2 and SCP3 also colocalize in wild-type SCs and when coexpressed in mammalian cells (Schalk et al. 1998, Pelttari et al. 2001). When coexpressed, SCP2 and SCP3 colocalize on short, stubby fibrous structures that are distinct from SCP3 fibers (Pelttari et al. 2001). In vivo, SCP3 is required for normal binding of SCP2 to the AE/LEs (Pelttari et al. 2001). However, it is now apparent that SCP2 can localize to telomeres via an SCP3-independent mechanism (Yuan et al. 2002, Liebe et al. 2004).

SCP3 is essential for the formation of LEs. In male mice lacking SCP3, spermatogenesis arrests at the zygotene stage of meiosis without the development of AE/LE structures (Yuan et al. 2000). In contrast, although female mice lacking SCP3 also lack AE/LEs, meiosis can be completed (Yuan et al. 2002). However, the frequencies of achiasmate univalents among mutant oocytes and of aneuploidy in zygotes are increased, which results in embryonic lethality in utero (Yuan et al. 2002). Despite the absence of LEs, the transverse filament protein SCP1 still localizes to linear structures that appear to be synapsed regions of bivalents, although fewer synapsed regions occur in males lacking SCP3 relative to females lacking SCP3. The localization of SCP2 and SCP3, the dynamics of their appearance and disappearance from chromosomes during meiosis, and their importance for LE formation suggest that SCP2 and SCP3 are structural elements of the LE.

Hop1 AND Red1 IN YEAST AE/LEs In *S. cerevisiae*, Hop1p and Red1p are meiosis-specific proteins that are constituents of the LE (Hollingsworth et al. 1990, Smith & Roeder 1997). These proteins play important roles in axial/lateral element formation. Electron microscopy of mutants in *hop1* and *red1* revealed that a normal SC does not form (Hollingsworth & Byers 1989, Rockmill & Roeder 1990, Loidl et al. 1994). Although *hop1* mutants can form fragments of AEs, AEs are completely absent from mutants in *red1* (Rockmill & Roeder 1990, Loidl et al. 1994).

Hop1p is a member of a family of proteins that all localize along meiotic chromosome axes during prophase I. This family includes Hop1p in yeast (Hollingsworth et al. 1990), HIM-3 in *C. elegans* (Zetka et al. 1999), and Asy1 in plants such as *Arabidopsis* (Armstrong et al. 2002). These proteins share a region of amino acid sequence similarity known as the HORMA domain, which is predicted to form a globular structure that may be involved in sensing specialized chromatin states, such as those associated with DSBs or other DNA damage (Aravind & Koonin 1998). Hop1p has a nonspecific DNA-binding activity with a strong preference for binding guanine-rich sequences that may be mediated by a zinc finger domain (Kironmai et al. 1998, Muniyappa et al. 2000), although both HIM-3 and Asy1 lack a zinc finger (Zetka et al. 1999, Caryl et al. 2000).

The *S. cerevisiae RED1* gene encodes a 95.5-kDa protein with little sequence similarity to other known proteins (Thompson & Roeder 1989). Although Red1p remains associated with bivalents through pachytene, most Hop1 protein dissociates from chromosomes as they synapse. Red1 protein associates with chromosomes in a *hop1* mutant, but Hop1p requires Red1p for chromosomal localization (Smith & Roeder 1997).

The function of a complex containing Red1p and Hop1p is essential for synapsis in yeast (Woltering et al. 2000). Red1p forms homo-oligomers and physically interacts with Hop1p (Hollingsworth & Ponte 1997, de los Santos & Hollingsworth 1999, Woltering et al. 2000). Red1p also shows a direct physical interaction with Mek1p, a kinase whose activity is required for normal synapsis (Rockmill & Roeder 1991, Bailis & Roeder 1998, de los Santos & Hollingsworth 1999). Mek1p colocalizes with Red1p extensively from zygotene through pachytene, although it

remains on chromosomes after Red1p dissociates. Mek1p chromosomal localization requires both Red1p and Hop1p (Bailis & Roeder 1998). Hollingsworth and colleagues proposed a model for Hop1p/Red1p/Mek1p function in which Hop1p binds to chromosomes at sites of DSB formation, which recruits phosphorylated Red1p. Mek1p then binds to Red1p, and phosphorylation by an unknown kinase activates the Mek1p kinase activity. Mek1p then phosphorylates substrates that are involved in DSB repair pathways (Wan et al. 2004).

Hop1-LIKE PROTEINS IN OTHER ORGANISMS The HORMA domain proteins HIM-3 in *C. elegans* and Asy1 in plant species show similarities to Hop1p in both sequence and function (Zetka et al. 1999, Caryl et al. 2000, Armstrong et al. 2002). Despite this conservation, additional homologs with a meiotic function in other model organisms have yet to be identified.

HIM-3 protein is first observed associating with early prophase chromosomes as speckles that coalesce to become linear along the chromosomes through pachytene until it disassociates at the metaphase I to anaphase I transition (Zetka et al. 1999). HIM-3 localizes to the axial cores of both synapsed and unsynapsed chromosomes; hence it is likely a component of AE/LEs. Analysis of HIM-3 mutant and RNAi phenotypes indicate that the protein plays important roles in chromosome pairing, synapsis, and the regulation of DSB repair (Zetka et al. 1999, Colaiácovo et al. 2003, Couteau et al. 2004).

Asy1 is specifically expressed in cells corresponding to meiotic prophase in *Arabidopsis* and *Brassica* (Caryl et al. 2000, Armstrong et al. 2002). On chromosome spreads, Asy1 is first seen as punctate dots at premeiotic interphase that extend into continuous signals along the chromosomal AEs, but not the chromatin loops, and become associated with the entire LEs. It is maintained through pachytene and disappears as homologs desynapse at diplotene. Asy1 is required for normal synapsis in both male and female *Arabidopsis*, although bivalents are observed at a low frequency at metaphase I (Ross et al. 1997, Caryl et al. 2000).

THE ROLE OF ORD IN *DROSOPHILA* LE FORMATION AND SC MAINTENANCE The *Drosophila* ORD protein plays a key role in sister chromatid cohesion and SC morphogenesis. In *ord* mutants, sister chromatids separate precociously prior to the first meiotic division in both sexes, and meiotic recombination is reduced (Mason 1976, Miyazaki & Orr-Weaver 1992). The morphology and maintenance of the SC are also abnormal in *ord* mutants (Webber et al. 2004). Webber et al. (2004) detected GFP-ORD staining within all 16 nuclei of early prophase cysts. Linear stretches of ORD became pronounced within pro-oocyte nuclei as they began to assemble the SC protein C(3)G. ORD colocalized extensively with C(3)G and was enriched in regions of centromeric heterochromatin. Further studies have implicated ORD in the regulation of cohesin binding to chromosomes during meiosis, which in turn affects the ability of the SC to assemble (R.S. Khetani, S.L. Page & S.E. Bickel, personal communication), and in the regulation of partner choice during meiotic DSB repair (Webber et al. 2004).

FUNCTIONS OF THE AXIAL/LATERAL ELEMENTS

Chromosome Condensation

One function of the AE/LEs may be to promote chromosome compaction during meiotic prophase. Meiotic chromosomes fail to individualize normally in *S. cerevisiae* condensin, *red1* and *hop1* mutants, although condensin is required for axial length compaction (Yu & Koshland 2003). In addition, absence of SCP3 in mouse results in a twofold increase in chromosome length in males and females, indicating an impairment of chromosome condensation in meiosis (Yuan et al. 2002, Liebe et al. 2004). In contrast, depletion of HIM-3 by RNAi or mutation of the *him-3* locus results in a failure to synapse and form chiasmata (Zetka et al. 1999, Couteau et al. 2004). Thus, some, but not all, LE proteins may be required for proper chromosome condensation during meiosis.

Pairing

The alignment of AEs of homologs during early prophase has long suggested a role for AE/LEs in chromosome pairing. In yeast, deficiency of either Red1p or Hop1p results in decreased levels of homolog pairing, whereas condensin mutants show a weaker defect in pairing (Loidl et al. 1994, Nag et al. 1995, Yu & Koshland 2003). Sister chromatid cohesion and the normal pairing of homologs at pachytene is similarly disrupted by depletion of HIM-3, REC-8, or SCC-3 in *C. elegans* and mutation of the *Arabidopsis Rec8* homolog *SYN1* (Peirson et al. 1997; Bai et al. 1999; Zetka et al. 1999; Pasierbek et al. 2001, 2003; Wang et al. 2003; Couteau et al. 2004). Similarly, in mouse spermatocytes lacking SCP3, homolog pairing is delayed and never reaches wild-type levels (Liebe et al. 2004).

Regulation of the Mode in which Double-Strand Breaks Are Repaired to Crossover or Noncrossover Products

Lateral element proteins may regulate the DSB repair pathways in the context of the SC. The interaction of mutants in the *Drosophila c(3)G* and *c(2)M* genes suggests that one function of the C(2)M protein is to regulate the decision for DSB repair to proceed along a C(3)G-dependent pathway that yields mature crossovers (Manheim & McKim 2003). Mutants in the *c(2)M* gene do not appear to completely eliminate meiotic exchange, as do *c(3)G* mutants, but rather reduce the frequency of crossing over to approximately 10% of normal. However, *c(2)M*; *c(3)G* double mutants exhibit crossing over at levels intermediate between the two single mutants. One reasonable interpretation of these data is that the C(2)M protein directs the initial repair of DSBs along a pathway that requires the SC, or at least C(3)G. In the absence of functional C(2)M protein, DSBs could be repaired by mechanisms analogous to mitotic recombination pathways that do not depend on SC function (Manheim & McKim 2003).

The LEs may also promote interhomolog repair of meiotic DSBs and prevent sister chromatid exchanges. In *Drosophila ord* mutants, the frequency and timing of DSBs and their repair does not appear to be altered, although the frequency of interhomolog crossovers is reduced (Webber et al. 2004). Webber et al. (2004) found evidence that sister chromatid exchange is greatly elevated in *ord* null oocytes compared with that in wild-type. This supports the model that sister chromatid cohesion or SC formation mediated by ORD activity is required to suppress sister chromatid exchange and promote recombination between homologs in *Drosophila* oocytes (Webber et al. 2004). Similarly, one function of HIM-3 in *C. elegans* may be to prevent the use of sister chromatids for the repair of DSBs during meiosis (Couteau et al. 2004). Analysis of RAD-51 foci suggested that DSBs form and initiate recombination normally in the absence of HIM-3. The RAD-51 foci disappear from a *him-3* mutant with kinetics similar to that of wild-type, indicating that the DSBs are repaired despite a lack of pairing, synapsis, and interhomolog exchange (Couteau et al. 2004).

Control of Crossover Distribution (Interference)

As noted below, crossover formation must include a break and exchange of chromosome axes (Blat et al. 2002). It seems likely that one level of control over this process may reflect the structure and function of the axial elements. In a view that has been most clearly defined by Kleckner and colleagues (Blat et al. 2002, Kleckner et al. 2003, Börner et al. 2004), interference results from the ability of a stress-related signal to be transmitted along an axial core such that a break or discontinuity in that axial core will reduce stress locally. The presence of such a crossover-inducing axial disruption would thus diminish the local stress and reduce the likelihood of other such disruptions, thereby diminishing the probability that other DSBs in that vicinity will become differentiated to be crossovers. One observation that fits well with this model is the noted covariation within an organism between crossover number and total SC length for a given chromosome (Quevedo et al. 1997, Lynn et al. 2002; for discussion see Kleckner et al. 2003).

Assembly of the Transverse Filaments to Form a Mature Synaptonemal Complex

The conventional view of SC assembly states that the EM-defined axial elements mediate the assembly of the transverse filaments within the central region between them. In contrast to this view, recent work suggests that a feature of meiotic chromosome structure other than the AE is sufficient for transverse filament assembly.

The mammalian LE proteins SCP2 and SCP3 are not absolutely required for synapsis. The transverse filament protein SCP1 localizes to short, fragmented fibers in mouse spermatocytes lacking SCP3, and these are often associated with paired homologous sequences (Yuan et al. 2000, Pelttari et al. 2001, Liebe et al. 2004). In SCP3-deficient female meiosis, SCP1 localized to even longer fibers,

although these also had axial gaps (Yuan et al. 2002). Electron microscopy of spermatocyte nuclei showed SC-like structures that have a central element and transverse filament but no AE/LEs (Yuan et al. 2000, Liebe et al. 2004). These findings indicate that SCP3 is required for AE/LE formation but that AEs are not required for central element/transverse filament assembly.

Construction of SC-like structures in the absence of LEs has also been observed in *Drosophila*. In wild-type, the cohesin subunits SMC1 and SMC3 colocalize with ORD protein along the entire length of meiotic chromosomes in female germ cells that assemble the SC (R.S. Khetani, S.L. Page & S.E. Bickel, personal communication). In flies lacking ORD activity, both cohesin and the transverse filament protein C(3)G prematurely dissociate from the meiotic chromosomes. A transient SC-like structure consisting of a central element and transverse filaments is able to form in meiotic cells lacking ORD, but distinct LEs are not detectable (Webber et al. 2004). Analysis of the progressive loss of cohesin proteins from meiotic chromosomes showed that the dissociation of SMC1 and SMC3 is quickly followed by the loss of C(3)G, suggesting that the maintenance of C(3)G requires the presence of cohesin along chromosome arms (R.S. Khetani, S.L. Page & S.E. Bickel, personal communication). Similarly, excessive C(3)G accumulates when the *Drosophila* Rec8p homolog C(2)M is overexpressed (Manheim & McKim 2003). These results indicate that the presence of cohesin along chromosome arms may allow the assembly of transverse filaments and a central element in the absence of a defined LE.

Analyses of mutant phenotypes further suggest that cohesin and condensin are required for transverse filament protein localization. In *S. cerevisiae*, the transverse filament protein Zip1p fails to localize properly to the chromosomes in the absence of condensin or cohesin (Klein et al. 1999, Yu & Koshland 2003). Likewise, localization of C(3)G is disrupted in mutants for cohesin components SMC1 and C(2)M, but C(2)M localizes normally in a C(3)G mutant (Manheim & McKim 2003; S.L. Page, B.K. Singh & R.S. Hawley, unpublished data).

The failure in transverse filament assembly could result from the lack of a proper cohesin/condensin-based chromosomal axis or from the failure of other proteins to bind to the chromosome axis. Proteins containing the HORMA domain, such as Hop1p and HIM-3, are prime candidates for such a role (Hollingsworth et al. 1990, Zetka et al. 1999). In yeast, Hop1p, along with Red1p, are mislocalized in condensin and cohesin mutants (Klein et al. 1999, Yu & Koshland 2003). Hop1p physically interacts with Red1p on the LE, and both proteins are necessary for proper Zip1p assembly (Hollingsworth et al. 1990, Sym & Roeder 1995, Smith & Roeder 1997, Hollingsworth & Ponte 1997, de los Santos & Hollingsworth 1999). HIM-3 may play a similar role in *C. elegans*. HIM-3 requires the cohesin protein REC-8 to localize properly (Pasierbek et al. 2001). Although meiotic chromosomes are able to load REC-8 onto chromosome cores in the absence of HIM-3, the transverse filament/central element proteins SYP-1 and SYP-2 do not assemble. When present in HIM-3-deficient meiosis, SYP-1 and SYP-2 often localize between nonhomologous chromosomes (Colaiácovo et al. 2003, Couteau et al.

2004), indicating that HIM-3 is important for proper transverse filament/central element formation.

THE ASSEMBLY AND STRUCTURE OF TRANSVERSE FILAMENTS

Proteins that form the transverse filaments, which stretch between LEs, have been identified in several species. These include Zip1p in *S. cerevisiae* (Sym et al. 1993), SCP1 in mammalian species (Meuwissen et al. 1992), C(3)G in *Drosophila melanogaster* (Page & Hawley 2001), and SYP-1 and SYP-2 in *C. elegans* (MacQueen et al. 2002, Colaiácovo et al. 2003). Although their primary amino acid sequences differ greatly, these proteins all possess an extended coiled coil–rich segment located in the center of the protein, flanked by largely globular domains (Figure 3). Immunolocalization of SCP1 and Zip1p by EM elucidated the organization of these proteins within the SC (Dobson et al. 1994, Liu et al. 1996, Schmekel et al. 1996, Dong & Roeder 2000). These results suggest that the proteins form parallel dimers through their coiled coil regions and then align between the chromosomes with the C termini along the lateral elements and with the N-termini from opposing dimers interacting in an antiparallel fashion across the center of the SC to form the transverse filaments (Figure 2).

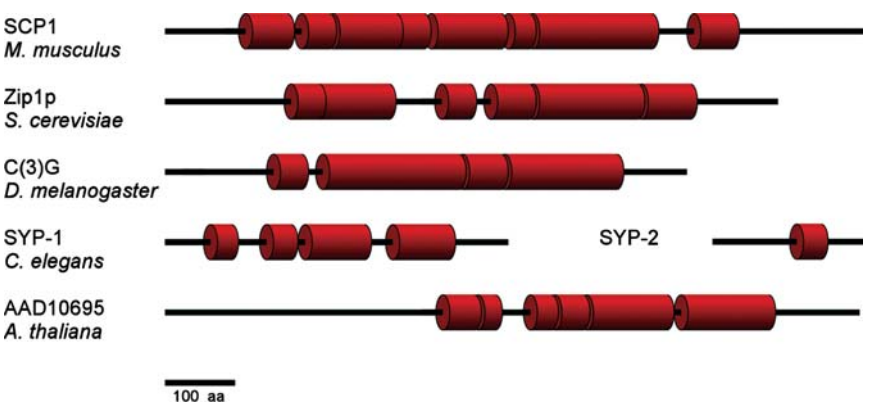

Figure 3 Diagram of known transverse filament proteins. Transverse filament proteins share a common predicted secondary structure that includes a central domain in which coiled coils predominate. Shown is the arrangement of predicted coiled coils (*red cylinders*) (Lupas et al. 1991) and noncoiled coil regions within the transverse filament proteins SCP1 (Sage et al. 1997), Zip1p (Sym et al. 1993), C(3)G (Page & Hawley 2001), SYP-1 (MacQueen et al. 2002), and SYP-2 (Colaiácovo et al. 2003). The *Arabidopsis thaliana* predicted protein AAD10695 has also been proposed to be a component of transverse filaments (Bogdanov et al. 2003).

Structure-function studies on the Zip1p transverse filament protein in budding yeast performed by Roeder and colleagues support a model in which the antiparallel dimers of Zip1p are connected to each other by interactions between the N-terminal portion of the coiled coil domain, and the C-terminal regions of Zip1p connect the transverse filaments to the LEs (Dong & Roeder 2000). These authors have suggested that the N-terminal globular domain of Zip1p makes up the central element of the SC.

PRE-SYNAPTONEMAL COMPLEX FUNCTIONS OF THE TRANSVERSE FILAMENTS

Commitment of Double-Strand Breaks to a Crossover-Specific Recombination Pathway

Although the transverse filament proteins are not required for the formation of the DSBs in yeast, *C. elegans*, or *Drosophila* (Sym et al. 1993, Nag et al. 1995, McKim et al. 1998, MacQueen et al. 2002, Colaiácovo et al. 2003, Börner et al. 2004), they are required for the maturation of most (yeast) or all (*C. elegans* and *Drosophila*) crossover events (Hunter & Kleckner 2001, Page & Hawley 2001, MacQueen et al. 2002, Colaiácovo et al. 2003, Börner et al. 2004). It is likely that the role of transverse filaments in crossover maturation is functionally and temporally separate from its role as a building block of the full length SC. Indeed, several lines of evidence support a model in which the transverse filament proteins act very early at the sites of those DSBs that will mature into crossover events (and indeed play a role in committing those DSBs to a crossover fate) and then act later to fill in the gaps between these sites to allow the completion of the mature SC (Hunter 2003).

THE GENETICS OF TRANSVERSE FILAMENT PROTEINS

The Yeast Zip1 Protein

The yeast *ZIP1* gene encodes a 875 amino acid (aa) protein that is a component of the central region of the SC (Sym et al. 1993). Zip1p localizes to synapsed pairs of homologs but does not localize to asynapsed AEs. Null mutants in *ZIP1* display four meiotic defects: (*a*) Homologous chromosomes pairs and apparently normal AEs are joined by axial associations, but they do not synapse (Sym et al. 1993, Rockmill et al. 1995). (*b*) In some strains, *zip1*-null mutations induce a *SPO11*-dependent meiotic arrest (Sym & Roeder 1994), and the process of crossover production is blocked prior to the creation of SEIs (Börner et al. 2004). (*c*) In those strains with more relaxed controls of meiotic progress (i.e., those in which *zip1*-null mutants do not block sporulation and in which crossover maturation is allowed), the frequency of crossing over is substantially reduced, and dHJs persist

longer than in wild-type (Sym & Roeder 1994, Storlazzi et al. 1996). (*d*) Crossover interference is completely eliminated in *zip1*-null mutant strains (Sym & Roeder 1994, Tung & Roeder 1998).

On the basis of their analysis of the *zip1* recombination defect in a *red1* background, Storlazzi et al. (1996) argued that the role of Zip1p in recombination is independent of its role in formation of the complete SC. The *RED1* gene encodes a component of the AE, mutants in *red1* fail to form SC, and crossovers occur at reduced levels (Rockmill & Roeder 1990, Smith & Roeder 1997). If Zip1p acted only as a component of the full-length SC, then one might expect that the absence of Zip1p in a *red1* background would confer no further defect in crossing over than is observed in the presence of the *red1* single mutant. However, a *zip1, red1* double mutant displays a recombination defect that approximates the sum of the two mutant phenotypes, suggesting that Zip1p acts to promote recombination in a pathway that is independent of full-length SC formation (Storlazzi et al. 1996). On the basis of these data, Storlazzi et al. (1996) proposed that, "Perhaps some Zip1 molecules act first in or around the sites of recombinational initiation to influence the recombination process and hence nucleate SC formation."

Indeed, Smith & Roeder (1997) note that "there is some Zip1 protein associated with the spread meiotic chromosomes from a *red1* null mutant." Although this staining is often punctate and discontinuous, occasional long stretches of continuous staining are observed. If residual Zip1p is required for crossover formation, then one would expect a level of exchange suppression similar to that observed in the double mutant. Moreover, as noted above, Börner et al. (2004) have demonstrated that Zip1p does act early, prior to SC formation, to mediate the earliest steps in crossover maturation.

Given that Zip1 proteins colocalize with SIC/ZMM proteins in early zygotene and that SICs likely mark the sites of the majority of meiotic crossover events, Zip1p may act at the SIC to promote crossover maturation and subsequently polymerize along the lengths of the chromosome arms to facilitate full assembly of the SC. One such role is suggested by the observation that Zip1p (along with Zip2p) is required to recruit Msh4p, a protein specifically required for the formation of meiotic crossovers, to the SIC (Novak et al. 2001).

One can imagine two mechanisms by which Zip1p would play such a dual function. According to the first model, Zip1p performs the same function (bridging the two homologs) at two different times, once early in the process of maturing recombinational intermediates and again in the assembly of mature SC. This model of Zip1p function is supported by the observation that the large number of partial loss-of-function *zip1* alleles studied show remarkable consistency with respect to their effects on synapsis and exchange (Tung & Roeder 1998). Alternatively, one could imagine that Zip1p plays different biochemical roles in crossover differentiation of DSBs and SC assembly. The identification of an allele of the *Drosophila* Zip1p functional homolog [C(3)G, see below] that appears to separate these two functions (near normal exchange with severely defective SC formation) supports this view (Page & Hawley 2001).

Finally, the observation that crossover interference is abolished in *zip1* mutants can also be understood in light of an early function of Zip1p that is required for crossover maturation (Börner et al. 2004). The finding that SICs also display crossover interference (Fung et al. 2004) demonstrates that such interference occurs prior to SC nucleation or assembly and indicates that whatever mechanism establishes interference must act prior to, and independently of, the formation of the SC. Moreover, the observation that *zip1* mutants do not alter the interference observed at the level of ZMM/SIC foci indicates that the process of interference itself is Zip1p independent (Fung et al. 2004). The effect of *zip1* mutants on interference may reflect the drastic reduction of crossovers arising via the major pathway in the presence of residual crossovers produced by secondary recombination pathways that are SIC independent and do not display interference, such as the Mus81p/Mms4p recombination pathway defined by de los Santos et al. (2003).

THE REGIONS OF Zip1p THAT ARE ESSENTIAL FOR MEIOTIC RECOMBINATION There is a good, but not perfect, correlation between the ability of various in-frame deletion constructs to form SCs and their ability to complete recombination and sporulate (Tung & Roeder 1998). The first exceptions to this generalization are the Zip1-M2p and Zip1-MC1p deletion constructs, which do not allow sporulation in sensitive backgrounds, even though they allow synapsis. Indeed, in the presence of these deletion constructs, the SC persists even after 42 h in sporulation media. Thus the regions deleted in these constructs may define sites that are required to influence the recombination process but are not required for full SC formation. In another example of discordance between the effects on recombinational maturation and synapsis, delayed sporulation is allowed in the presence of the Zip1-M1p despite an absence of synapsis.

THE REGIONS OF Zip1p THAT ARE ESSENTIAL FOR SYNAPSIS The defect in synapsis observed in *zip1*-null mutants may reflect the role of the Zip1p proteins in bridging the lateral elements of the SC. Mutations that increase the length of the Zip1p coiled coil domain increase the width of the SC (Sym & Roeder 1995), and deletions within the C-terminal end of the Zip1p coiled coil domain can decrease the width of the SC (Tung & Roeder 1998). Tung & Roeder (1998) have also used deletion analysis to demonstrate that the protein product of an in-frame deletion (*zip1-M1*) that deletes the N-terminal half of the coiled coil domain prevents synapsis, suggesting that this region is required for synapsis. Similarly sized deletions that remove the C-terminal half of the coiled coil domain or the N-terminal globular domain of Zip1p do not impair synapsis. These data are consistent with a model in which the antiparallel association of Zip1p dimers in the N-terminal region of the coiled coil domain is essential to form transverse filaments.

A deletion that removes only 34 aa (791–824) within the C-terminal globular domain (*zip1-C1*) fully prevents the formation of the SC (Tung & Roeder 1998).

Moreover, the deleted Zip1-C1p does not assemble onto the chromosome, but rather assembles in aggregates that are not associated with chromosomes (polycomplexes). These data suggest that C-terminal amino acids 791–824 are critical for the binding of Zip1p to the chromosomes and thus define a site required for Zip1p to attach to other SC components (perhaps the LEs).

The *Drosophila* C(3)G Protein

C(3)G is a 744 aa protein predicted to contain a central coiled coil–rich region flanked by globular domains at the N and C termini (Page & Hawley 2001). As shown in Figure 4, immunolocalization of the C(3)G protein, as well as the analysis of a C(3)G-GFP expression construct, reveal that C(3)G is present in a thread-like pattern along the lengths of chromosomes in meiotic prophase, consistent with a role as a SC protein present on meiotic bivalents. Moreover, L. Anderson (unpublished data) recently demonstrated by immuno-gold EM that C(3)G localizes to the central region of the SC, as expected for a transverse filament protein. In addition, the C terminus of the C(3)G protein is located adjacent to the LEs, as predicted by the model of SC organization shown in Figure 2 (L. Anderson, S.L. Page & R.S. Hawley, unpublished data). Electron microscopy studies of ovaries from *c(3)G* mutant females revealed no evidence of SC formation (Meyer 1964, Smith & King 1968, Rasmussen 1975).

Although null mutants of *c(3)G* do not eliminate, and may not even diminish DSB formation (Jang et al. 2003, Webber et al. 2004), they do completely

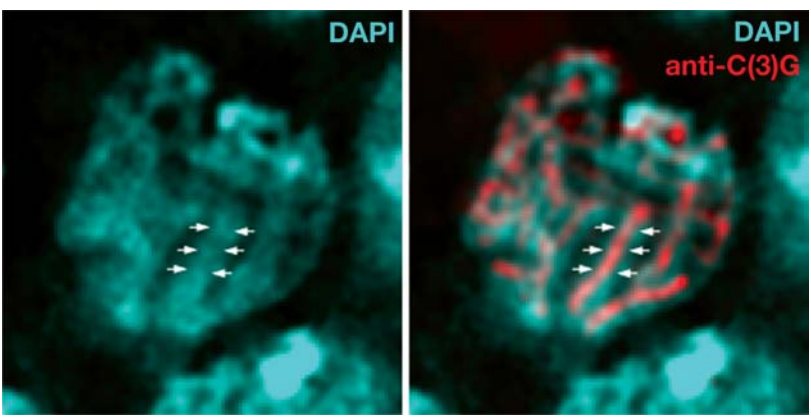

Figure 4 A deconvolved optical section of a *Drosophila melanogaster* pro-oocyte nucleus stained with DAPI and anti-C(3)G. (*Left*) DAPI staining in the pro-oocyte nucleus. Arrows indicate part of a meiotic bivalent. (*Right*) Merged image of overlapping DAPI (*cyan*) and anti-C(3)G (*red*) immunofluorescence. Note the thread-like morphology of the anti-C(3)G immunofluoresence associated with the center of the DAPI-stained meiotic chromosomes (*arrows*).

eliminate meiotic crossing over (Gowen & Gowen 1922, Gowen 1933, Hall 1972, Page & Hawley 2001). This suggests that in *Drosophila* the maturation of DSBs into meiotic exchanges is transverse filament dependent. It is not clear whether *c(3)G* mutants abolish gene conversion. There is but one report of this experiment (Carlson 1972), and although this report states that no convertants were recovered among the progeny of *c(3)G* females, no value of N is reported.

Page & Hawley (2001) characterized a deletion mutant construct of the *c(3)G* gene [denoted $c(3)G^{X204}$] that appears to partially separate the roles of C(3)G in mediating crossover maturation and complete synapsis. This deletion construct is expected to produce a protein in which amino acids 340 to 552 are removed in-frame from within the coiled coil region. Females carrying the $c(3)G^{X204}$ allele as their only functional *c(3)G* gene displayed high levels of recombination (60% of normal) and high levels of unsynapsed or partially synapsed bivalents (Page & Hawley 2001). Rather than localizing to three long contiguous threads, the internally deleted $C(3)G^{X204}$ protein was found in an increased number of long linear arrays (a number of shorter lines are also visible). These results are most easily explained by a failure to initiate or maintain synapsis and by the localization of the mutant protein to unsynapsed or partially synapsed chromosomes. Thus the deleted $c(3)G^{X204}$ construct was sufficient to provide the exchange functions of C(3)G in the majority of meioses but was not capable of providing the functions required for proper synapsis. Perhaps the deleted protein was sufficient to maintain local synapsis at the few sites of crossing over. Alternatively, the deleted construct may be able to provide the early exchange functions suggested for such proteins (Hunter 2003) but not able to maintain synapsis.

The SYP-1 and SYP-2 Proteins in *C. elegans*

Caenorhabditis elegans possesses two coiled coil Zip1/SCP1-like proteins, a 484 aa protein, SYP-1 (MacQueen et al. 2002), and a 213 aa protein, SYP-2 (Colaiácovo et al. 2003), both of which localize to the interface between synapsed chromosomes (Figure 3). Their localization to the chromosomes is interdependent because neither protein is detected on the chromosomes in the absence of the other. Indeed, Colaiácovo et al. (2003) propose that "SYP-2 and SYP-1 together constitute the structural module used to construct the central element of the *C. elegans* SC." The ability of both proteins to assemble on the chromosomes appears to require components of the AEs. A comparison of the timing of AE protein HIM-3 and SYP-1 localization suggests that SYP-1 loads onto the chromosomes following the morphogenesis of the chromosome axes (MacQueen et al. 2002). Similarly, mutants in either the *him-3* or *rec-8* genes (both of which encode axis-associated proteins), prevent the assembly of SYP-1 and SYP-2 proteins onto the chromosomes (Colaiácovo et al. 2003, Couteau et al. 2004).

In *syp-1* and *syp-2* mutants, chromosomes initially pair. However, the chromosomes desynapse by pachytene and no SC is present. For both mutants, the initiation of recombination and the loading of strand-exchange proteins appear

to occur normally, and are thus independent of SC formation. However, meiotic crossovers are not produced, and progression beyond early recombination intermediates (as evidenced by the SPO-11-dependent triggering of a pachytene arrest for both *syp-1* and *syp-2* mutants and the persistence of RAD-51 foci in *syp-2* mutants) is inhibited (MacQueen et al. 2002, Colaiácovo et al. 2003).

FUNCTIONS OF THE MATURE SC

The mature SC plays a role in the maturation of recombination intermediates to crossover events. The maturation of SEIs to dHJs occurs in the context of the SC (i.e., during pachytene) and the final maturation of dHJs to crossovers occurs at the end of pachytene, concordant with the breakdown of the SC (Börner et al. 2004). Moreover, this process of DNA recombination must be coupled to the processes that mediate the interchange of chromosomal axes to produce two mature crossover products (Blat et al. 2002). Börner et al. (2004) proposed a model in which the full-length SC provides the torsional constraints on axes required to mediate axial interchange. Specifically, these authors suggest that "SC twisting could coordinately mediate local changes between DNA (the SEI-dHJ transition) and between chromosome axes."

Finally, at least in *C. elegans*, the mature SC appears to be required to maintain and/or stabilize pairing associations as meiosis progresses. In the absence of a SC in *C. elegans*, the initial pairings dissolve as the cell enters pachytene (MacQueen et al. 2002, Colaiácovo et al. 2003). In the following section we consider cases where SC modification alone (in the absence of recombination) is sufficient to maintain pairing and ensure segregation. Thus the SC may function to stabilize meiotic pairing in those organisms as well.

MODIFICATIONS OF THE SYNAPTONEMAL COMPLEX ALONE CAN ENSURE SEGREGATION

A number of organisms are known in which the segregation of achiasmate homologs is ensured by the retention of a modified form of the SC, which appears to hold homologs together until their separation at anaphase I (reviewed by Zickler & Kleckner 1999). A well-studied example of such a case is the achiasmate meiosis of *Bombyx mori* females in which the synaptonemal complex is maintained in an elaborated form until homolog separation at anaphase I (Rasmussen 1977).

More recently, Page et al. (2003) documented a similar role of axial element modification in mediating the segregation of achiasmate sex chromosomes in the meiosis of the marsupial species *Thylamys elegans*. In this case, the modification of axial core proteins of meiotic chromosomes creates a dense plate that supercedes the need for the exchange to hold homologs together. Finally, Harris et al. (2003) speculated that heterochromatic pairings that ensure the segregation of achiasmate homologs in *Drosophila melanogaster* females may reflect some type of

modification of the heterochromatic SC that conjoined those chromosomes during meiotic prophase.

MEIOTIC SYSTEMS THAT LACK A SYNAPTONEMAL COMPLEX

Although the SC is often regarded as a universal feature of meiosis, it is absent from meiosis in several organisms, including *Schizosaccharomyces pombe*, *Aspergillus nidulans*, and *Drosophila melanogaster* males (Olson et al. 1978, Egel-Mitani et al. 1982, Meyer 1960, Rasmussen 1973). In these organisms, homologous chromosomes pair efficiently without a typical SC, suggesting that any role the SC normally plays in homolog interactions was discarded in evolution and, perhaps, replaced by other structures or strategies to ensure proper chromosome segregation.

In organisms such as *S. pombe*, the familiar SC structure is not observed, but in its place along paired homologs are a series of discontinuous structures called linear elements (Olson et al. 1978, Bähler et al. 1993). Cytologically, linear elements resemble the AEs of early prophase chromosomes and were proposed to represent these structures (Bähler et al. 1993). In support of this hypothesis, Scherthan et al. (1994) found that linear elements appear during the period in which the alignment of interstitial regions of homologous chromosomes takes place, similar to the timing of AE/LE formation. Furthermore, proteins that are found along AE/LEs of budding yeast are necessary for the formation of linear elements in *S. pombe*. Analysis of mutants for the meiotic cohesins *rec8* and *rec11* revealed severe impairments in the formation of linear elements and defects in chromosome pairing (Molnar et al. 1995, 2003). Thus linear elements bear striking similarities to AE/LEs in SC-bearing organisms and act to promote homologous chromosome pairing in asynaptic meiosis.

In contrast to *Drosophila melanogaster* females, males of the species do not form SCs (Meyer 1960, Rasmussen 1973) and do not undergo meiotic recombination (Morgan 1912). In the absence of both a SC and chiasmata, *Drosophila* males must apply different means to achieve homolog pairing. At least some of the chromosomes depend on the interaction of specific sites in order to find their partner (Merrill et al. 1992; McKee et al. 1992, 1993). A recent cytological analysis in living spermatocytes suggested a three-phase model for pairing in *Drosophila* male meiosis (Vazquez et al. 2002). First, chromosomes enter meiosis with extensive alignment of homologous euchromatic regions already established from previous mitotic divisions. Second, chromosome pairs are separated into distinct territories within the nucleus, which are thought to discourage interactions between nonhomologous chromosomes. During the third stage, proximity within the nucleus is maintained, but homologs and sister chromatids show extensive separations (Vazquez et al. 2002). These examples show that whereas synapsis may be the most common mechanism, it is by no means the only mechanism by which meiosis may proceed.

SYNAPTONEMAL COMPLEX MIS-ASSEMBLY AND HUMAN INFERTILITY

At least three cases of human male infertility have recently been attributed to a failure to properly assemble the SC (Miyamoto et al. 2003, Judis et al. 2004). Two of these patients were heterozygous for a frameshift mutation in the human SCP3 gene. The frameshift results in a truncated protein product that can interfere with the production of SCP3-containing fibers when co-expressed with full-length SCP3 in cell culture, suggesting that it could disrupt SC assembly in a dominant fashion (Miyamoto et al. 2003). In the third patient, SCP3 localization and DSB formation appeared to occur normally in the spermatocytes, but there was no evidence of normal pairing and synapsis (Judis et al. 2004). These findings indicate that disruptions in the structure and function of the SC may be a factor in human infertility.

ACKNOWLEDGMENTS

We thank Beth Rockmill, Nancy Hollingsworth, Anne Villeneuve, Lorinda Anderson, Nancy Kleckner, Jennifer Gerton, Tomomi Tsubouchi, Neil Hunter, and Valentin Börner for helpful discussions and/or for comments on various parts of the manuscript. We also thank Lorinda Anderson and Sharon Bickel for sharing unpublished data and Jennifer Gerton for a critical reading of the entire manuscript. Finally, we thank Nina Kolich for help with manuscript preparation. We apologize to those researchers whose work we did not have space to include. The authors were supported by funds from the National Institutes of Health (RO1 GM051444) and the Stowers Institute for Medical Research.

The *Annual Review of Cell and Developmental Biology* is online at http://cellbio.annualreviews.org

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NOTE ADDED IN PROOF

Recently published work has shed additional light on synaptonemal complex formation. Through an analysis of *spo11* mutants, Henderson & Keeney (2004) have correlated DSB formation with SC initiation in yeast, which supports the model for SC initiation at sites of crossover-designated recombination intermediates. White et al. (2004) analyzed SC assembly in live yeast cells and showed that SCs localize first at the nuclear periphery then later become redistributed throughout the nucleus. Disruption of the gene encoding murine SMC1β by Revenkova et al. (2004) resulted in shortened AEs, incomplete synapsis, and impaired recombination and sister chromatid cohesion in meiosis.

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