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REVIEW

# Structure and function of the synaptonemal complex

Brenda I. Cesar[1] and Yumi Kim[1]

**A defining feature of meiosis is the synaptonemal complex (SC), a zipper-like protein structure that forms between homologous chromosomes to regulate their recombination and segregation. Historically viewed as an enigmatic electron-dense scaffold, the SC is now recognized as a dynamic signaling platform that coordinates key meiotic processes. Here, we review recent advances in understanding SC structure and function. We describe diverse complementary approaches that have expanded the catalog of SC components and their network of interactions within this architecture. We highlight striking conservation in structural organization and ancient molecular modules that couple SC structure to crossover regulation and further discuss how the SC implements feedback mechanisms controlling meiotic DNA break formation and repair capacity to ensure faithful chromosome segregation across generations.**

## Introduction

Sexual reproduction in eukaryotes depends on meiosis, a specialized cell division that produces haploid gametes from a diploid precursor. Unique to meiosis is its prolonged prophase I, during which homologous chromosomes pair, synapse, and exchange genetic material through crossover formation. These crossovers, together with sister chromatid cohesion, create the physical linkages needed for proper homolog alignment and segregation during meiosis I. Beyond their mechanical role, crossovers also shuffle genetic information between maternal and paternal chromosomes, generating new allele combinations that enhance genetic diversity and drive eukaryotic evolution.

In most eukaryotes, homologous chromosome synapsis is reinforced by the assembly of the synaptonemal complex (SC). First discovered over 70 years ago by electron microscopy (Fawcett, 1956; Moses, 1956), the SC is a ladder-like protein structure that forms between homologous chromosomes. Despite its absence in some protists and fungi, the SC displays remarkable conservation across diverse organisms, maintaining a characteristic tripartite architecture comprising two parallel lateral elements and a central region that bridges the two chromosome axes in a zipper-like fashion (Page and Hawley, 2004). The central region is subdivided into transverse filaments that span the width of the SC and central elements that form the midline of the complex (Fig. 1 A).

Initial insights into SC structure and function came from electron microscopy observations. The zipper-like appearance of the SC and the strong correlation between chromosome synapsis and crossover frequency suggested that this structure functions to align homologous chromosomes and promote crossover formation (Maguire, 1965). Moreover, recombination nodules, electron-dense ellipsoidal structures thought to represent protein complexes at sites of ongoing recombination, were observed in association with the SC in *Drosophila melanogaster* females, including early recombination nodules that appear concurrent with SC assembly during zygotene and late nodules whose number and distribution closely matched those of chiasmata (Carpenter, 1975; Carpenter, 1979). Similar structures were subsequently reported in several other species (Anderson et al., 2001), establishing a direct link between the SC and recombination sites. Notably, *Drosophila* males lack both SC and meiotic recombination, further supporting this correlation (Rasmussen, 1973).

While these correlations between the presence of the SC and crossover formation seemed compelling, molecular identification of SC components and mutant analyses have substantially revised our understanding of its function. Contrary to early models that the SC creates preconditions for crossover formation by bridging homologs into close apposition (von Wettstein et al., 1984), SC assembly in most eukaryotes, including the budding yeast *Saccharomyces cerevisiae*, plants, and mammals, depends on the initiation of meiotic recombination through programmed DNA double-strand breaks (DSBs) (Alani et al., 1990; Padmore et al., 1991; Baudat et al., 2000; Romanienko and Camerini-Otero, 2000; Grelon et al., 2001). However, this requirement is not universal. In *Drosophila* females and *Caenorhabditis elegans*, the SC forms independently of DSB formation (Dernburg et al., 1998; McKim et al., 1998), yet crossovers strictly depend on SC assembly (Page and Hawley, 2001; MacQueen et al., 2002).

The relationship between the SC and crossover formation becomes even more complex when examining organisms with reduced or absent SC. In most organisms, crossovers exhibit interference, a phenomenon in which the presence of a crossover reduces the probability of additional crossovers nearby, thereby distributing crossovers more evenly along chromosomes

[1]Department of Biology, Johns Hopkins University, Baltimore, MD, USA.

Correspondence to Yumi Kim: yumi.kim@jhu.edu.







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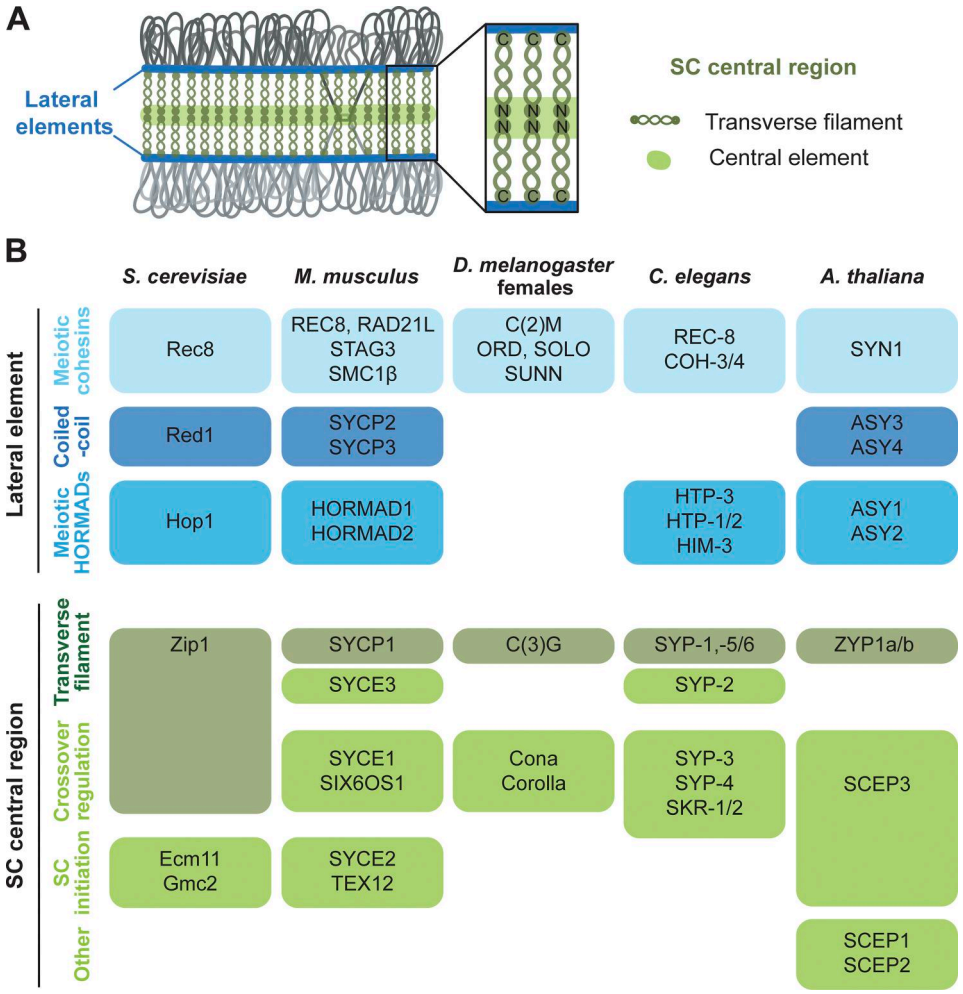


Figure 1. **SC structure and protein components across model organisms. (A)** Schematic of the SC architecture showing the lateral elements (blue), which associate with chromatin (gray), connected by the SC central region comprising transverse filaments (dark green) and central element proteins (light green). **(B)** A current compilation of known SC subunits. Proteins are organized by their localization, interaction, and functions within the SC. For axis-associated cohesins, only the meiosis-specific cohesin subunits are shown. SYCE3 and SYP-2 are grouped with transverse filament components because of their direct interactions.

(Muller, 1916). The fission yeast *Schizosaccharomyces pombe* lacks a canonical SC structure and forms crossovers with little or no interference (Olson et al., 1978; Bähler et al., 1993). *Aspergillus* species lack SC entirely yet still form crossovers, with *Aspergillus fumigatus* producing up to 30 per chromosome pair, the highest known in any eukaryote (Egel-Mitani et al., 1982; Auxier et al., 2023). Strikingly, disrupting SC assembly in the model plant *Arabidopsis thaliana* increases crossover numbers while abolishing interference (Capilla-Pérez et al., 2021; France et al., 2021). These findings reveal a complex, species-specific relationship between SC assembly and crossover formation, suggesting that the SC may primarily function to limit crossover numbers and impose interference rather than to promote crossover formation.

How can we reconcile this paradox? Recent advances have provided key insights into SC architecture and function. Continued genetic studies and biochemical purification, complemented by AlphaFold-based structural predictions revealing protein–protein interactions, have identified previously missing subunits across model organisms (Collins et al., 2014; Gómez-H et al., 2016; Hurlock et al., 2020; Zhang et al., 2020; Vrielynck et al., 2023; Feng et al., 2025) (Fig. 1 B). Super-resolution and expansion microscopy, together with quantitative live imaging, have revealed the molecular organization and biophysical properties of the SC (Schücker et al., 2015; Cahoon et al., 2017; Rog et al., 2017; Wang et al., 2018; Xu et al., 2019; Zwettler et al., 2020; Köhler et al., 2025). In parallel, progress in biochemical reconstitution and structural biology has begun to map protein interfaces within the SC (Dunce et al., 2018; Dunce et al., 2021; Blundon et al., 2024), advancing toward in vitro reconstitution of the entire complex. Here, we provide an updated overview of the SC structure and function, beginning with the chromosome axes that form the structural foundation for SC assembly. We focus particularly on how conserved molecular modules within the SC regulate crossover formation and implement feedback mechanisms to ensure the obligate crossover essential for accurate homolog segregation.

## Chromosome axis assembly

Axis assembly is one of the earliest events in meiotic prophase and is essential for all subsequent processes, including meiotic

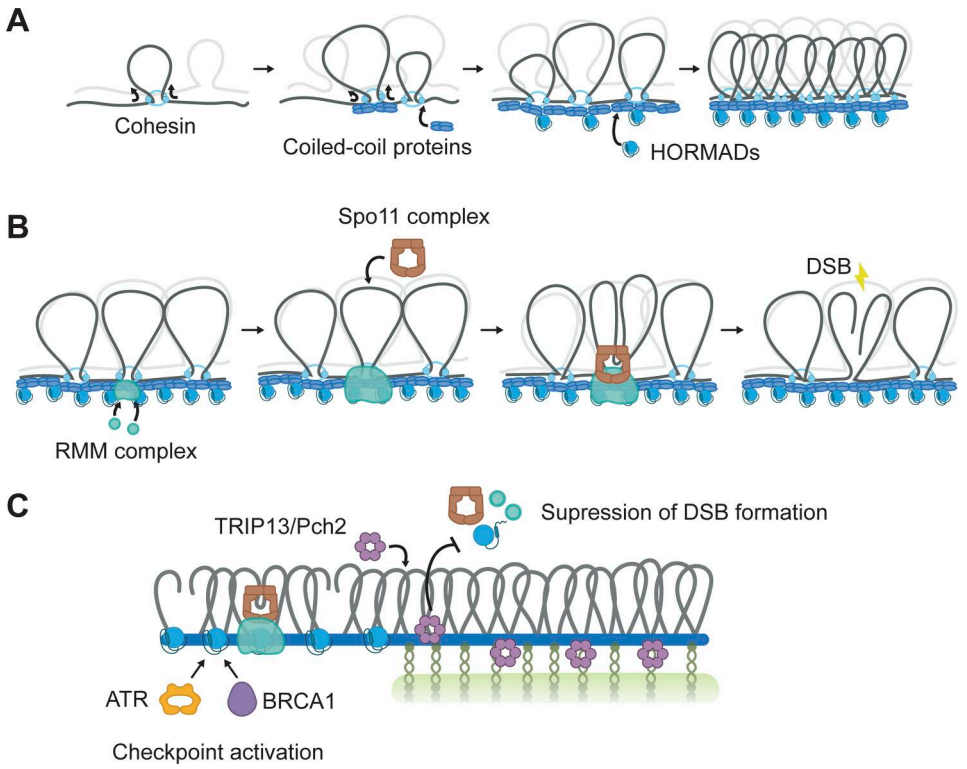


Figure 2. **Meiotic chromosome axis assembly and recombination control. (A)** Assembly of the meiotic chromosome axis. Meiosis-specific cohesin complexes (light blue rings) extrude chromatin into loops and provide the structural foundation for recruiting coiled-coil proteins and meiotic HORMADs. **(B)** Rec114–Mei4–Mer2 (RMM) complexes are recruited to the chromosome axis by HORMADs and form nucleoprotein condensates, recruiting the Spo11 complex and inducing meiotic DSBs. **(C)** Upon synapsis, HORMADs are actively removed from chromosome axes by TRIP13/Pch2, thereby dismantling the DSB-forming machinery and preventing further DSB formation. Unsynapsed chromosome axes retain HORMAD proteins, which recruit ATR kinase and BRCA to activate checkpoint signaling.

DSB formation, homolog pairing, and SC assembly (Ur and Corbett, 2021). Once homologs synapse, these axes (also called axial elements) become the lateral elements of the SC, which are then connected by the transverse filaments that span the ~100 nm distance between paired chromosomes (Fig. 1 A). Axis formation begins when meiosis-specific cohesin complexes containing the kleisin subunit Rec8 establish sister chromatid cohesion and organize chromatin into arrays of loops anchored around a central proteinaceous core (Schalbetter et al., 2019). This cohesin-based scaffold provides a structural framework for the recruitment of conserved coiled-coil proteins, which assemble into tetrameric complexes that further oligomerize into filamentous structures (West et al., 2019) (Fig. 2 A). These include Red1 in budding yeast (Smith and Roeder, 1997), SYCP2/SYCP3 in mammals (Lammers et al., 1994; Offenberg et al., 1998), and ASY3/ASY4 in plants (Ferdous et al., 2012; Chambon et al., 2018) (Fig. 1 B). Although these proteins show little sequence homology across species, they act as functional homologs through shared closure motifs that recruit meiotic HORMADs, named after their conserved HORMA (Hop1, Rev7, and Mad2) domains, to the chromosome axes.

While chromosome axis components are broadly conserved across eukaryotes, some species have evolved distinct mechanisms for axis assembly. In *Drosophila*, meiotic HORMADs and Red1 homologs are absent (Tromer et al., 2021). Instead, specialized cohesin-related proteins (including C(2)M, ORD, SOLO, and SUNN) mediate sister chromatid cohesion and organize chromosome axes (Webber et al., 2004; Yan and McKee, 2013; Krishnan et al., 2014; Gyuricza et al., 2016). In contrast, *C. elegans* encodes four meiotic HORMADs (HIM-3, HTP-1, HTP-2, and HTP-3) that assemble hierarchically to form the chromosome axis but lacks Red1 homologs (Zetka et al., 1999; Couteau and Zetka, 2005; Martinez-Perez and Villeneuve, 2005; Kim et al., 2014; West et al., 2019). Despite these differences in composition, axis formation is universally required for interhomolog recombination, a role mediated in large part by meiotic HORMADs.

## HORMAD proteins promote DSB formation and interhomolog recombination

Once recruited to chromosome axes, HORMADs play essential roles in meiotic recombination (Gu et al., 2022). First, they promote DSB formation by recruiting the conserved Rec114–Mei4–Mer2 complex (known in mammals as REC114–MEI4–IHO1) to chromosome axes through direct interaction with Mer2/IHO1 (Panizza et al., 2011; Stanzione et al., 2016; Rousová et al., 2021; Laroussi et al., 2023). Recent studies further show that the Rec114–Mei4 complex and Mer2 independently form DNA-driven nucleoprotein phase-separated condensates in vitro, which may help recruit the Spo11 holoenzyme to chromatin loops tethered to the axis (Claeys Bouuaert et al., 2021) (Fig. 2 B). Interestingly, *C. elegans* lacks obvious Mer2/IHO1 homologs, while

duplicated REC114 orthologs DSB-1 and DSB-2 form complexes with the MEI4 ortholog DSB-3 that load onto chromatin without clear axis enrichment (Rosu et al., 2013; Stamper et al., 2013; Hinman et al., 2021). Nevertheless, HTP-3 is essential for DSB formation through association with MRE-11/RAD-50 (Goodyer et al., 2008).

Following DSB formation, HORMADs also help establish interhomolog bias, ensuring that recombination occurs preferentially between homologous chromosomes rather than sister chromatids. Rec8-containing cohesin creates a default sister bias by holding sister chromatids together, and genetic assays in budding yeast suggest that intersister repair accounts for up to one-third of meiotic recombination events (Goldfarb and Lichten, 2010; Kim et al., 2010). In response to meiotic DSBs, Mec1 and Tel1 (the yeast homologs of ATR and ATM kinases) phosphorylate Hop1, which in turn recruits and activates the meiosis-specific kinase Mek1 to chromosome axes (Carballo et al., 2008). Mek1 then phosphorylates Rad51 regulators, including Rad54 and Hed1, which together suppress Rad51-mediated strand invasion between sister chromatids (Niu et al., 2009; Callender et al., 2016). By inhibiting Rad51 activity through this mechanism, the meiosis-specific recombinase Dmc1 becomes the primary mediator of strand invasion, favoring the use of homologous chromosomes as templates (Schwacha and Kleckner, 1997; Lao et al., 2013). Together, axis components and Dmc1 counteract the intrinsic sister preference by Rec8 cohesin to generate strong interhomolog bias (Kim et al., 2010; Hong et al., 2013).

In mouse oocytes deficient for HORMAD1 or HORMAD2, irradiation-induced DSBs are rapidly repaired through intersister pathways (Shin et al., 2013; Rinaldi et al., 2017), suggesting that mammals also use HORMAD-dependent mechanisms to establish interhomolog bias. Meiotic HORMADs preferentially accumulate on unsynapsed chromosome axes and are actively removed from synapsed regions by the AAA+ ATPase TRIP13 (Wojtasz et al., 2009) (Fig. 2 C). Thus, their removal upon synapsis is thought to relieve the HORMAD-dependent barrier that prevents intersister repair. HORMAD2 recruits ATR to unsynapsed axes, where ATR signals through its effector kinase CHK1 to promote the loading of RAD51 and DMC1 recombinases onto resected DSBs, thereby facilitating interhomolog strand invasion and SC elongation (Pacheco et al., 2018; Widger et al., 2018). Although HORMAD1 and HORMAD2 themselves undergo ATR-dependent phosphorylation (Fukuda et al., 2012; Royo et al., 2013), it remains unknown whether this modification directly contributes to recombinase recruitment.

Plant meiosis employs similar axis-dependent mechanisms to promote interhomolog recombination, though with distinct regulatory features. In *Arabidopsis*, the HORMAD protein ASY1 is dispensable for meiotic DSB formation but is crucial for sustaining DMC1 activity and promoting interhomolog recombination (Sanchez-Moran et al., 2007). In the absence of DMC1 and/or ASY1, DSBs are efficiently repaired, likely using sister chromatids without resulting in chromosome fragmentation (Sanchez-Moran et al., 2007). Interhomolog bias therefore emerges from ASY1-mediated suppression of intersister repair rather than being an intrinsic property of the recombinase (Kurzbauer et al., 2012). ASY1 achieves this by counteracting FIGL1, an AAA-ATPase that limits RAD51/DMC1-mediated interhomolog repair (Emmenecker et al., 2024). Thus, while the basic logic of axis proteins working with DMC1 to direct repair toward homologs is conserved, plants appear to rely on a balance between ASY1 and FIGL1 rather than phosphorylation cascades that suppress RAD51.

*C. elegans*, which lacks DMC1, provides another variation. RAD-51 foci form and disappear without delay in *him-3* and *htp-1* mutants, even though homologs are unavailable, suggesting that these HORMAD proteins promote interhomolog repair by creating a barrier between sister chromatids (Couteau et al., 2004; Martinez-Perez and Villeneuve, 2005). These evolutionary variations highlight that while the requirement for interhomolog recombination during meiosis is universal, the molecular strategies to achieve this outcome differ considerably across lineages.

## Identification of SC central region components

Compared with chromosome axis components, defining the molecular composition of the SC central region has been challenging because of the rapid sequence divergence of its proteins (Hemmer and Blumenstiel, 2016). Below, we outline the complementary approaches that have enabled the identification of transverse filament proteins and, more recently, central element components.

### Transverse filament proteins

The first transverse filament protein characterized at the molecular level was rat SYCP1 (formally known as SCP1), identified through screening of cDNA libraries with antibodies generated from purified SCs (Meuwissen et al., 1992). SYCP1 has predicted coiled-coil domains that span the width of the SC, bridging the lateral elements. Shortly thereafter, budding yeast Zip1, discovered in forward genetic screens, was shown to form the transverse filaments of the SC, sharing structural organization with SYCP1 despite limited sequence homology (Sym et al., 1993).

Transverse filament proteins in other model organisms were subsequently identified through various experimental approaches. In *Drosophila*, the *c(3)G* gene, long known from mutants lacking both SC and meiotic crossovers (Hall, 1972), was later identified as the transverse filament component (Page and Hawley, 2001). In *C. elegans*, SYP-1 was discovered through forward genetic screens (MacQueen et al., 2002), while two paralogs, SYP-5 and SYP-6, were identified recently as additional transverse filament proteins through biochemical purification (Hurlock et al., 2020; Zhang et al., 2020). In *Arabidopsis*, ZYP1a and ZYP1b were found through bioinformatic searches for proteins with predicted coiled-coil domains flanked by globular domains (Higgins et al., 2005).

### Central element proteins

Central element proteins have been discovered more recently, using increasingly diverse strategies. Expression profiling and

localization studies identified the first mammalian central element proteins, SYCE1 and SYCE2 (Costa et al., 2005), followed by TEX12, which interacts with SYCE2 (Hamer et al., 2006). SYCE3 was later shown to be required for the loading of other central element proteins onto chromosomes (Schramm et al., 2011). SIX6OS1 was discovered through a human genome-wide association study that linked a nonsynonymous variant to an elevated female recombination rate (Kong et al., 2014). Subsequent functional analyses confirmed that SIX6OS1 encodes a component of the SC central element (Gómez-H et al., 2016), illustrating how population genetics can uncover novel constituents of the SC.

Beyond mammals, a combination of forward genetic screens, RNA interference screens, yeast two-hybrid assays, and computational approaches has expanded the repertoire of central element proteins across model organisms. Early examples include Ecm11 and Gmc2 in budding yeast (Humphryes et al., 2013); Cona and Corolla in *Drosophila* (Page et al., 2008; Collins et al., 2014); and SYP-2, SYP-3, and SYP-4 in *C. elegans* (Colaiácovo et al., 2003; Smolikov et al., 2007; Smolikov et al., 2009). Biochemical purification coupled with mass spectrometry has proven powerful for identifying previously missing SC components, including paralogs with partially redundant functions and moonlighting proteins with canonical roles outside meiosis. This approach identified two paralogous Skp1-related proteins, SKR-1 and SKR-2, as structural subunits of the SC in *C. elegans* (Blundon et al., 2024). Remarkably, six *C. elegans* SC subunits form a long-sought soluble protein complex in vitro, suggesting that the entire set of SC subunits is now known in this organism (Blundon et al., 2024). Complementary approaches, including transcriptomics-based candidate screening and proximity labeling, have further expanded the inventory of central element proteins, leading to the discovery of SCEP1, SCEP2, and SCEP3 in *A. thaliana* (Vrielynck et al., 2023; Feng et al., 2025).

A current compilation of known SC subunits across model organisms is shown in Fig. 1 B. These findings underscore that our knowledge of the molecular composition of the SC remains incomplete, even in well-studied model organisms. Nevertheless, as the catalog of SC components and their interaction networks have expanded, conserved structural and functional features have begun to emerge from comparative analyses across species.

## Molecular features that govern SC assembly

### Structural organization of transverse filaments

One of the most conserved structural features of the SC is its ~100 nm width (von Wettstein et al., 1984), which is defined by the length of the coiled-coil domains of transverse filament proteins (Sym and Roeder, 1995; Ollinger et al., 2005; Dunce et al., 2018). Across diverse organisms, these proteins assemble in a head-to-head configuration with their N termini at the midline and their C termini oriented toward the chromosome axes (Liu et al., 1996; Dong and Roeder, 2000; Anderson et al., 2005; Schild-Prüfert et al., 2011; Hurlock et al., 2020; Billmyre et al., 2023) (Fig. 1 A). When overexpressed in yeast or somatic cells, transverse filament proteins form higher-order structures known as polycomplexes that recapitulate ultrastructural features of the SC, indicating an inherent propensity for self-assembly (Sym and Roeder, 1995; Ollinger et al., 2005). Biochemical analyses have further revealed that SYCP1 forms a tetramer through N-terminal interactions in vitro, forming the interface for head-to-head assembly that subsequently polymerizes into a zipper-like lattice (Dunce et al., 2018). The functional importance of this interface was recently validated as mutations that disrupt SYCP1 head-to-head assembly completely abolish synapsis in mouse spermatocytes (Billmyre et al., 2023). Similarly, studies in *Drosophila* have demonstrated that the N terminus of C(3)G is essential for SC assembly, while the C-terminal region mediates its interaction with the lateral elements (Jeffress et al., 2007). In *C. elegans*, the N- terminus of SYP-1 is acetylated in a NatB-dependent manner (Gao et al., 2016), likely co-translationally, a modification that may license folding or interactions required for SC assembly.

Despite these conserved structural principles, transverse filament proteins vary considerably across lineages. In the cnidarian *Hydra*, SYCP1 retains short sequence motifs with sufficient similarity to mammalian SYCP1, allowing it to cluster together in phylogenetic analyses (Fraune et al., 2012). However, other lineages show extensive sequence divergence while preserving the characteristic length and coiled-coil organization (Kursel et al., 2021). Interestingly, *C. elegans* uses two shorter transverse filament proteins, SYP-1 and SYP-5/6, each roughly half the length of transverse filament proteins in other species (MacQueen et al., 2002; Hurlock et al., 2020; Zhang et al., 2020). These proteins work together to span the SC width, demonstrating how divergent molecular mechanisms can generate a structurally conserved SC.

### The conserved module linking SC initiation to meiotic recombination

In most eukaryotes, synapsis initiation is tightly coupled to DSB repair, ensuring that SC assembly occurs specifically between homologous chromosomes. In budding yeast and mammals, this coupling relies on a conserved central element module that initiates SC assembly from recombination sites through its interaction with Zip4, a scaffolding subunit of the meiosis-specific Zip2–Zip4–Spo16 (ZZS) complex that is essential for crossover formation (De Muyt et al., 2018). In budding yeast, the central element proteins Ecm11 and Gmc2 are recruited to DSB repair sites independently of Zip1, where they nucleate SC assembly (Humphryes et al., 2013). Recent work shows that this recruitment requires a direct interaction between Ecm11 and Zip4 (Pyatnitskaya et al., 2022). Intriguingly, Ecm11 and Gmc2 are predicted to share structural similarities with mammalian TEX12 and SYCE2 (Pyatnitskaya et al., 2022). Moreover, TEX12 interacts with TEX11, the mammalian homolog of Zip4, reinforcing the idea that the mechanism linking SC initiation to crossover recombination is conserved in mammals. Together, these findings illustrate how central element proteins, despite extensive sequence divergence, retain structural features and interactions that enable synapsis initiation at recombination intermediates.

An analogous mechanism has recently been described in plants, where the central element component SCEP3 loads independently of ZYP1 and helps coordinate SC assembly with crossover formation (Feng et al., 2025; Seear et al., 2025). However, SC assembly proceeds normally in mutants lacking ZIP4, even though it is essential for crossover formation (Chelysheva et al., 2007). These observations suggest that plants may initiate SC assembly through a pathway distinct from budding yeast and mammals. By contrast, the absence of ZZS components in *Drosophila* and *C. elegans* correlates with their recombination-independent mode of SC assembly, suggesting the lack of selective pressure for coupling synapsis initiation to crossover designation.

### Molecular interfaces required for SC elongation across diverse species

Once nucleated at initial sites of homolog interaction, the SC central region rapidly extends along chromosome lengths through its inherent self-assembly properties and affinity for chromosome axes. This elongation mechanism varies across organisms, with a detailed understanding in yeast, mammals, and *C. elegans*, but significant gaps remain in other model organisms.

In budding yeast, SC elongation occurs as Zip1 is recruited to recombination intermediates through the Ecm11–Gmc2 complex (Humphryes et al., 2013). The C terminus of Zip1 interacts with the chromosome axis protein Red1, and this interface formation requires small ubiquitin-like modifier (SUMO ) and SUMO-interacting motifs on both proteins (Cheng et al., 2006; Hooker and Roeder, 2006; Eichinger and Jentsch, 2010). Ecm11 also undergoes SUMOylation in a Gmc2 and Zip1 N terminus–dependent manner, and this modification is essential for Zip1 polymerization along chromosomes (Humphryes et al., 2013; Leung et al., 2015). Therefore, SUMOylation is expected to increase as Zip1 assembly proceeds, creating a positive feedback loop that promotes robust SC elongation (Leung et al., 2015).

By contrast, mammalian SC elongation relies on a hierarchical assembly process driven by the intrinsic self-assembly properties of its components, which has been primarily defined in vitro by biochemical and structural analyses. SYCP1 provides the structural foundation for this process and is recruited to chromosomes via its C-terminal interaction with chromosome axes (Winkel et al., 2009). SYCE3 then binds to the tetrameric SYCP1 core and remodels its interface into 2:1 heterotrimers (Crichton et al., 2023), generating an integrated SYCP1-SYCE3 lattice that serves as a platform for recruiting SYCE2–TEX12 and SYCE1–SIX6OS1 subcomplexes (Hamer et al., 2006; Schramm et al., 2011; Gómez-H et al., 2016; Sánchez-Sáez et al., 2020).

Once assembled on the SYCP1-SYCE3 scaffold, these additional central element complexes drive SC elongation through their polymerization. In vitro, SYCE2 and TEX12 form a 2:2 complex that self-assembles into filamentous structures (Davies et al., 2012; Dunce et al., 2021). Through these properties, SYCE2–TEX12 complexes can convert local synapsis initiation sites into extended synapsis along chromosome lengths (Bolcun-Filas et al., 2007; Hamer et al., 2008). Meanwhile, SYCE1 and SIX6OS1 form a 1:1 complex through two essential binding interfaces and provide structural stability for the SC (Gómez-H et al., 2016; Dunne and Davies, 2019; Sánchez-Sáez et al., 2020). Together, SYCP1 and SYCE3 form a bilayered central structure at the SC midline, with the other central element proteins positioned between the layers (Hernández-Hernández et al., 2016). Through these coordinated activities, the central element proteins convert the initial SYCP1 lattice into a mature SC extended along the entire chromosome length (Fig. 3 A).

Unlike the hierarchical assembly of the SC in yeast and mammals, SC formation in *C. elegans* relies on the mutual interdependence among all SC subunits for both stability and chromosomal loading (Fig. 3 B). SC proteins are expressed before meiotic entry and assemble into polycomplexes, which adopt spherical shapes and fuse upon contact, exhibiting liquid-like properties (Rog et al., 2017). Although the molecular basis for the condensation of SC materials remains unknown, these polycomplexes serve as a reservoir for chromosomal loading and SC elongation. Synapsis initiates at special chromosomal regions called pairing centers, which serve as signaling hubs to mediate homology recognition and SC elongation (MacQueen et al., 2005). Extension of the SC central region between chromosome axes requires electrostatic interactions between the meiotic HORMAD protein HIM-3 and the acidic disordered C-terminal tails of SYP-5/6 (Gold et al., 2025; Gordon et al., 2025). Recent work has further demonstrated that SKR-1 and SKR-2, best known for their role in the Skp1-Cul1-F-box (SCF) ubiquitin ligase, moonlight as structural components of the SC via their SCF-forming interfaces (Blundon et al., 2024). This finding illustrates how a conserved cell cycle regulator is co-opted to interact with SC components and become an integral part of the SC.

While studies in *C. elegans* have provided insight into material properties of the SC, the mechanisms of SC elongation in *Drosophila* and plants still remain unclear. In *Drosophila*, SC assembly initiates at centromeres enriched for meiosis-specific cohesin complexes, where SC proteins are first recruited (Takeo et al., 2011; Tanneti et al., 2011). Although Cona and Corolla interact to promote C(3)G polymerization (Page et al., 2008; Collins et al., 2014), the molecular interfaces within the *Drosophila* SC remain largely uncharacterized. Super-resolution microscopy shows that the *Drosophila* SC adopts a bilayered architecture similar to that of mammals, with Cona and Corolla forming parallel tracks along chromosomes (Cahoon et al., 2017).

In *A. thaliana*, a hierarchical model of SC assembly is emerging. SCEP3 acts at the top of this hierarchy, recruiting other SC subunits and initiating SC formation (Feng et al., 2025; Seear et al., 2025). SCEP1 and SCEP2 interact with each other and are required for ZYP1 loading (Vrielynck et al., 2023). Despite these advances, elucidating the mechanisms of SC elongation will likely require identifying additional SC subunits and mapping their interaction networks and assembly dependencies.

## The role of the SC in crossover regulation

Early cytological studies initially portrayed the SC as a passive structural scaffold for meiotic recombination. However, the SC

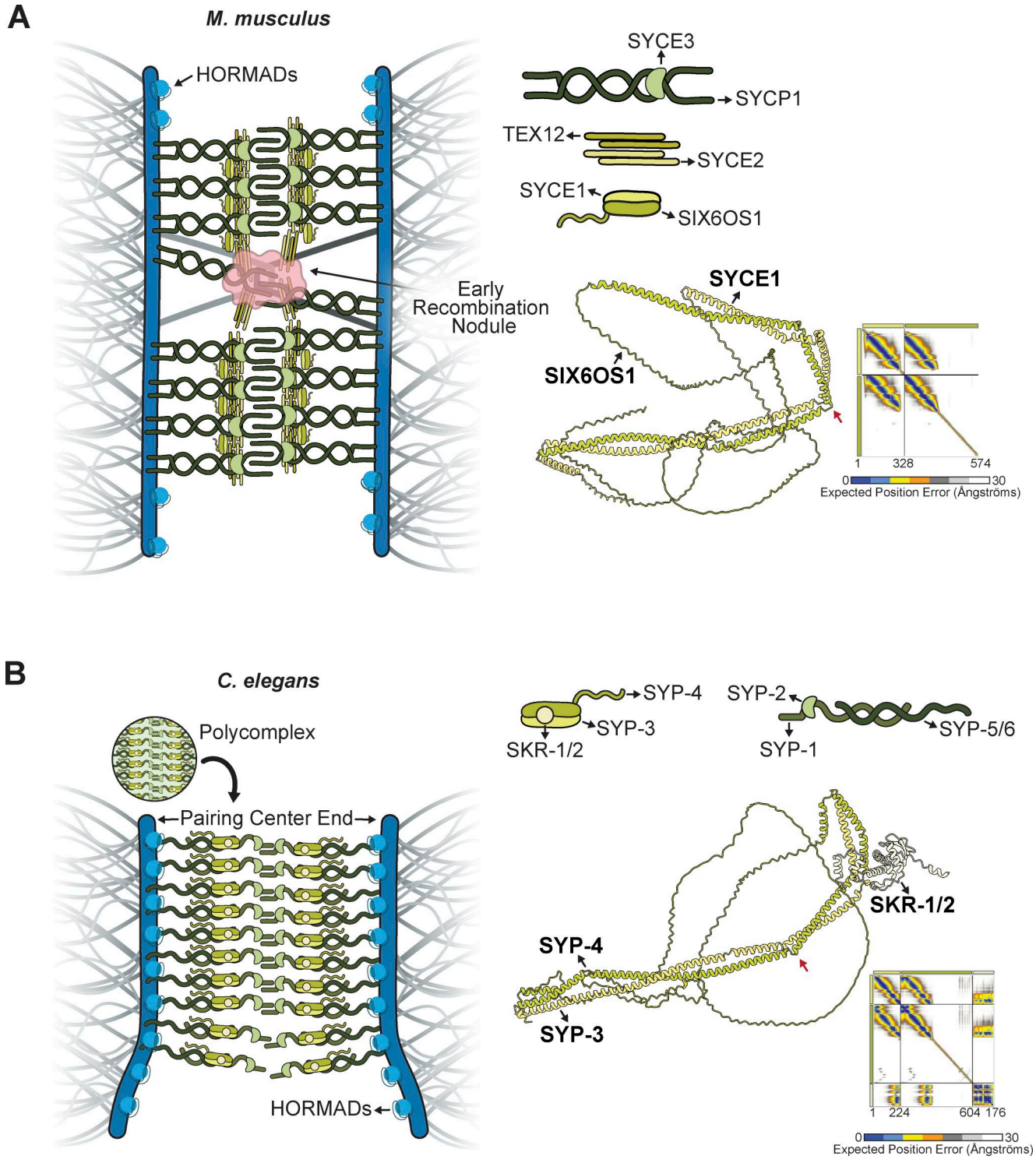


Figure 3. **SC architecture in mouse and *C. elegans*. (A)** Schematic representation of the mouse SC region. The molecular organization of SC central region components and AlphaFold 3–predicted structure of the SYCE–SIX6OS1 complex are shown on the right. The predicted aligned error (PAE) plot is also shown. **(B)** Schematic representation of the *C. elegans* SC central region. Right panel shows the molecular organization of SC central region components and AlphaFold 3–predicted structure of the SYP-3/SYP-4/SKR-1 complex with corresponding PAE plot. Red arrows indicate kinks that disrupt coiled-coils in both models.

is now recognized to play complex and seemingly contradictory roles in both promoting and limiting crossover formation. Here, we synthesize recent evidence to provide an updated overview of how the SC regulates crossover number and distribution.

## The SC promotes the formation of class I crossovers

The pro-crossover function of the SC was first established by pioneering genetic studies in *D. melanogaster*. Mutations in *c(3)G* result in virtually no crossing-over, demonstrating an absolute

requirement for the SC (Hall, 1972). In budding yeast, however, *zip1* mutants retain some crossovers but show delayed crossover maturation and loss of crossover interference (Sym and Roeder, 1994; Storlazzi et al., 1996). The remaining crossovers in *zip1* mutants depend on structure-specific endonucleases Mus81-Mms4 (de los Santos et al., 2003), indicating that the SC is not absolutely required for all crossovers.

These findings reveal two mechanistically distinct crossover pathways. The class I pathway generates 80–90% of crossovers in most species and depends on the SC and a set of conserved ZMM proteins (named after budding yeast Zip, Mer, and Msh proteins) that stabilize crossover-specific recombination intermediates and produce crossovers exhibiting interference (Pyatnitskaya et al., 2019). In contrast, the class II pathway produces crossovers independently of the SC and lacks interference (Börner et al., 2004). Class II crossovers often increase when the class I pathway is compromised, providing a backup mechanism that helps generate chiasmata to ensure faithful chromosome segregation (Anderson et al., 2014).

How does the SC promote crossovers? Key steps in the class I pathway, including the formation of single-end invasion intermediates and double Holliday junctions (dHJs), occur in tight temporal coordination with SC morphogenesis (Börner et al., 2004) (Fig. 4, A and B). By sequestering and organizing ZMM proteins, the SC creates protective microenvironments around crossover-designated sites as recombination progresses. Super-resolution imaging in *C. elegans* shows that these sites become encased by SC central region proteins in late pachytene, forming specialized compartments that shield recombination intermediates from premature dismantling (Woglar and Villeneuve, 2018). Consistent with this protective role, recent work in budding yeast reveals a reciprocal feedback mechanism in which Zip1 stabilizes dHJ-associated ZMM complexes, which in turn reinforce the local SC central region (Henggeler et al., 2025; Tang et al., 2025). This aligns with evidence that the SC is a dynamic structure with continuous turnover and incorporation of its subunits, which modulate SC stability in response to recombination events (Voelkel-Meiman et al., 2012; Nadarajan et al., 2017; Pattabiraman et al., 2017). Importantly, this dHJ-stabilizing function of the SC does not require a fully continuous tripartite structure. Instead, local ensembles of Zip1 and ZMM proteins are sufficient to protect dHJs until they are resolved into crossovers (Voelkel-Meiman et al., 2016; Tang et al., 2025), consistent with an SC-independent role of Zip1 in meiotic recombination (Storlazzi et al., 1996). Moreover, SC disassembly is tightly coupled to dHJ resolution, ensuring that these compartments persist throughout crossover maturation (Henggeler et al., 2025). These findings suggest that the SC actively orchestrates multiple steps in crossover recombination, extending far beyond merely juxtaposing homologous chromosomes.

### An ancient module linking the SC central region to RING-domain E3 ligases

A key mechanism by which the SC promotes crossover formation is through the recruitment of the Zip3 RING-domain E3 ligase family, which is essential for class I crossover formation across nearly all eukaryotes. These conserved ligases (Zip3 in yeast; HEI10, RNF212, and RNF212B in mammals; Vilya in *Drosophila*; ZHP-1/2 and ZHP-3/4 in *C. elegans*; and HEI10 in plants) localize to discrete foci along the SC, accumulating at sites designated for crossover formation (Agarwal and Roeder, 2000; Jantsch et al., 2004; Chelysheva et al., 2012; Reynolds et al., 2013; Qiao et al., 2014; Lake et al., 2015; Zhang et al., 2018; Condezo et al., 2024; Ito et al., 2025). A growing body of work suggests that the SC interacts with these RING ligases through unexpectedly conserved molecular mechanisms. In budding yeast, the Zip1 N terminus, which includes conserved phenylalanine residues, is required for Zip3 recruitment to the SC polycomplex and recombination initiation sites (Voelkel-Meiman et al., 2019). However, Zip3 forms discrete foci along chromosomes without Zip1 (Agarwal and Roeder, 2000), suggesting that the Zip1 N terminus might stabilize Zip3 at crossover-designated sites rather than mediating its initial chromosomal loading.

This mechanism appears to be conserved, as phenylalanine-rich motifs are also present in SC central region proteins across taxa. In *C. elegans*, phenylalanine residues in the C-terminal tail of SYP-4 are required for recruitment of the ZHP-3/ZHP-4 complex to the SC, which is essential for crossover regulation but dispensable for SC assembly (Neves et al., 2025). Similar motifs are present in the C-terminal tail of mammalian SIX6OS1 and in *Drosophila* Corolla. Based on their shared functions and conserved motifs, SYP-4, SIX6OS1, and Corolla have recently been proposed as homologs (Neves et al., 2025; Williams et al., 2025), a hypothesis supported by AlphaFold structural predictions that reveal similarities in their overall coiled-coil organization and the positioning of kinks that disrupt coiled-coils (Fig. 3). While a direct interaction between Zip1 and Zip3 has recently been demonstrated in budding yeast (Sharmin et al., 2025, *Preprint*), experimental validation in other organisms remains an important future direction.

Remarkably, this ancient module extends to plants. In *Arabidopsis*, SCEP3 contains conserved phenylalanine repeats within its N-terminal disordered region and plays analogous roles in recruiting SC proteins to the recombination sites and initiating SC elongation (Feng et al., 2025; Seear et al., 2025). SCEP3 first localizes to recombination sites along chromosome axes and later relocalizes to the SC central region as synapsis proceeds (Seear et al., 2025). Interestingly, SCEP3 does not appear to interact directly with HEI10, leaving unresolved how it interfaces with crossover-promoting factors. Nevertheless, the striking conservation of this molecular module across eukaryotic lineages suggests that coupling between the SC central region and RING-domain E3 ligases is a fundamental feature of meiosis.

### The role of the SC in crossover patterning

Studies across model organisms show that mutations disrupting SC assembly or integrity severely impair crossover interference, resulting in more randomly distributed crossovers (Sym and Roeder, 1994; Libuda et al., 2013; Capilla-Pérez et al., 2021; France et al., 2021). This evidence suggests that the SC acts as a structural scaffold or signaling conduit that transmits information about a designated crossover, thereby inhibiting the designation of additional crossovers nearby. However, the precise mechanism for this chromosome-wide signaling remains contentious.

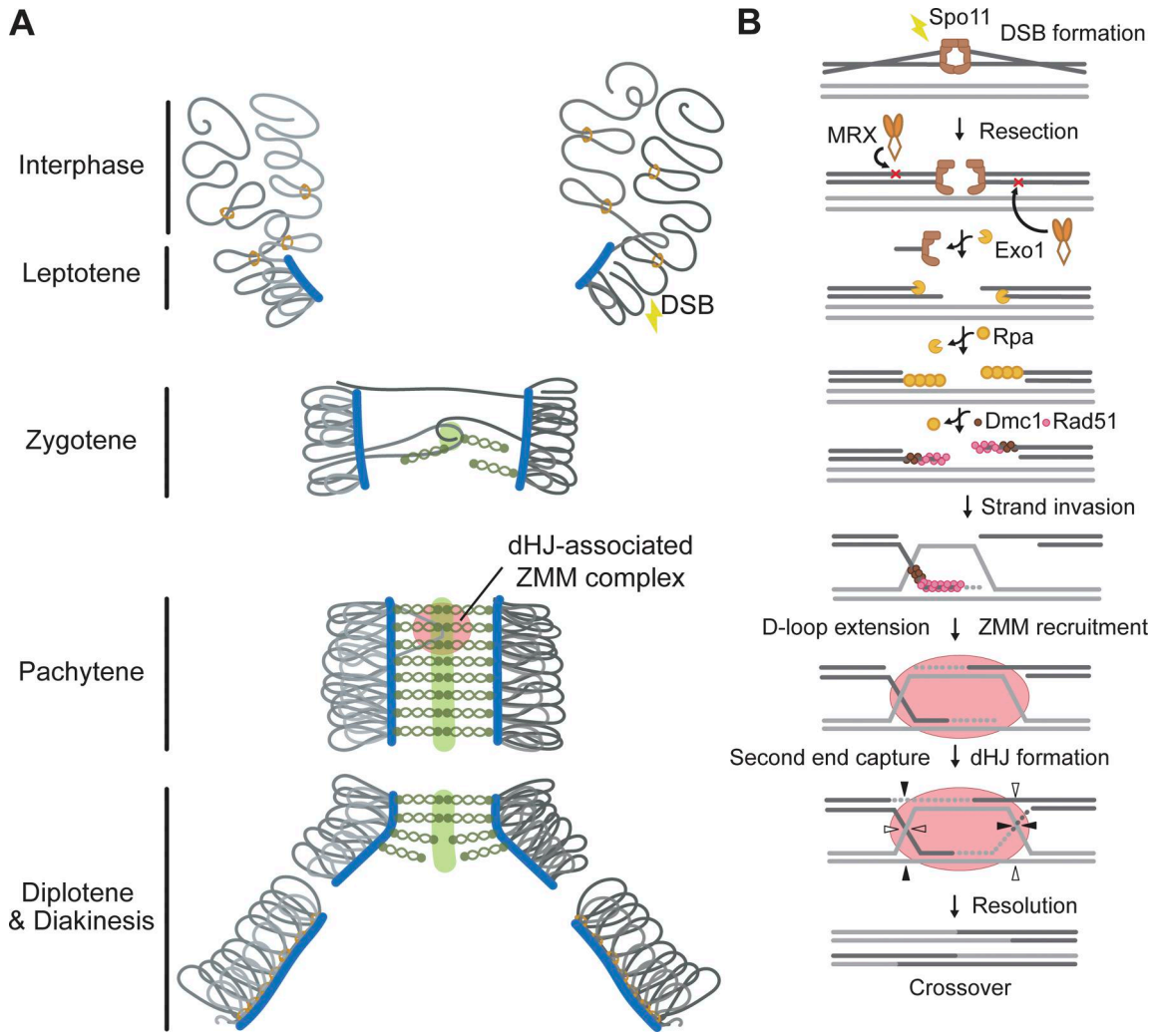


Figure 4. **SC morphogenesis is tightly linked to steps in homologous recombination. (A)** Temporal coordination of SC morphogenesis through meiotic prophase I. Meiosis-specific cohesins load in pre-meiotic S phase and organize chromatin into arrays of loops. In leptotene, chromosome axes begin to form, and DSBs are induced. During zygotene, homologous chromosomes begin to synapse at recombination sites. In pachytene, the full SC is assembled and protects crossover-specific recombination intermediates. **(B)** Molecular steps of the class I crossover pathway in budding yeast. Spo11 catalyzes DSB formation, followed by the Mre11–Rad50–Xrs2 (MRX) complex and Exo1-mediated resection. The resulting ssDNA is initially coated by RPA and subsequently replaced by Rad51 and Dmc1 to promote strand invasion. Formation and stabilization of HJs requires ZMM proteins (light red). The resolution of dHJ triggers SC disassembly.

Recent quantitative imaging and mathematical modeling in *Arabidopsis* have led to a diffusion-based coarsening model for crossover interference (Morgan et al., 2021). In this model, the SC harbors a constrained, diffusible pool of HEI10, which initially appears as numerous small foci at early recombination nodules. According to this model, these foci undergo coarsening, analogous to Ostwald ripening in phase-separated systems, where larger, evenly dispersed foci grow at the expense of smaller ones through diffusion along the SC (Fig. 5 A). The redistribution dynamics of HEI10 is thus proposed as the primary driver of both crossover designation and interference. This framework accurately predicts crossover numbers and spacing and explains the sensitivity of crossover number to HEI10 dosage (Ziolkowski et al., 2017; Morgan et al., 2021).

This view is further supported by work in *C. elegans* showing that the ZHP-3/4 complex forms biomolecular condensates that diffuse along the SC (Zhang et al., 2025). The SC thus serves as a one-dimensional track that compartmentalizes diffusion, allowing each chromosome pair to undergo independent coarsening and, thereby, establish its own crossover pattern (Zhang et al., 2018). Intriguingly, modeling in *Arabidopsis zyp1* mutants suggests that the coarsening process can still occur in the nucleoplasm, with competition for HEI10 across chromosomes rather than being strictly limited to individual bivalents (Durand et al., 2022; Fozard et al., 2023). This implies that crossover patterning can emerge from generic coarsening dynamics of HEI10 condensates and does not intrinsically require an SC scaffold. Together, these findings suggest that the SC functions primarily as a spatial constraint that compartmentalizes HEI10 diffusion to individual chromosome pairs, rather than being essential for the coarsening process itself. While this model explains many aspects of crossover patterning, several observations across organisms suggest that additional mechanisms must be at play.

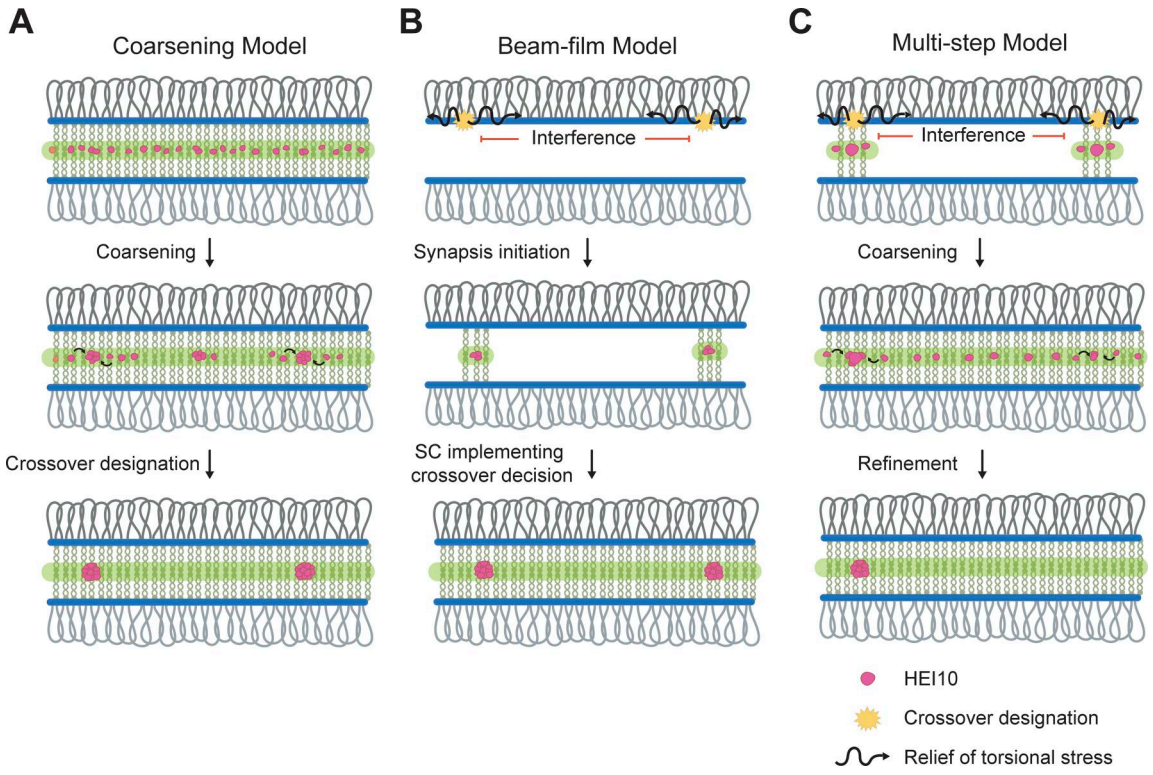


Figure 5. **Models of crossover patterning. (A)** Coarsening model. HEI10 (magenta) initially localizes uniformly along the SC. Through diffusion-mediated coarsening, HEI10 accumulates at a subset of sites at the expense of neighboring foci, driving crossover designation and interference. **(B)** Beam-film model. Chromosome axes act as elastic beams that store mechanical stress. Crossover designation (yellow star) generates local "cracks" that relieve tension; this relief propagates bidirectionally (black arrows), preventing nearly precursors from reaching the stress threshold required for crossover designation. Synapsis initiates from crossover designated sites, and these initiation sites themselves exhibit interference. **(C)** Multistep model. This model integrates coarsening and beam-film frameworks. Stress-mediated, axis-based processes establish an initial crossover pattern, while diffusion-mediated coarsening along the SC subsequently refines and stabilizes designated sites.

If diffusion-based coarsening were the primary mechanism for crossover designation and patterning, a fully continuous SC would be required to propagate inhibitory signals along chromosomes at the time of designation. However, in budding yeast, crossover designation is established early, even before the completion of SC assembly (Allers and Lichten, 2001; Börner et al., 2004; Fung et al., 2004). These observations directly challenge a strictly SC-dependent interference mechanism and support alternative models. One such framework, the beam-film model, posits that mechanical stress along chromosome axes distributes crossovers by locally relieving tension after each crossover event (Kleckner et al., 2004), thereby providing an early, SC-independent mechanism for crossover patterning (Fig. 5 B).

Providing molecular support for this model, topoisomerase II (Top2) has been identified as a key mediator of crossover interference in budding yeast (Zhang et al., 2014b). Interference strength inversely correlates with negative supercoils (Tan et al., 2022), and Top2 degradation by the ubiquitin ligase Ufd2 modulates interference strength by tuning DNA supercoiling (Tan et al., 2026). Because this torsional stress mechanism operates along the chromosome axis rather than the SC, these findings support that the role of the SC is in implementing crossover patterning decisions that were established earlier (Börner et al., 2004). Consistent with this view, SC nucleation sites in *Sordaria* are themselves evenly spaced by an interference-like mechanism (Zhang et al., 2014a). Furthermore, crossover frequencies covary with axis length across chromosomes within individual nuclei (Wang et al., 2019), linking patterning outcomes to the physical properties of the axis rather than the SC. Together, these observations suggest that the SC functions downstream of crossover designation, stabilizing committed sites rather than generating the pattern de novo.

Additional challenges to a simple coarsening model come from mammals, where evidence points to more complex spatiotemporal dynamics among the three RING-domain ligases. In mouse spermatocytes, RNF212B and RNF212 mark early recombination intermediates, while HEI10 appears later at maturing crossovers (Reynolds et al., 2013; Qiao et al., 2014; Condezo et al., 2024; Ito et al., 2025). However, in oocytes, RNF212 and RNF212B foci remain abundant throughout pachytene, challenging the underlying assumption that successful crossover designation relies on their depletion from noncrossover sites (Ito et al., 2025).

Recent super-resolution microscopy and real-time imaging of recombination factors in *C. elegans* indicate that crossover patterning arises from a dynamic, multilayered regulation process rather than a single decision point (Čavka et al., 2025, *Preprint*).

An initial selection process appears to occur shortly after DSB formation and restricts crossovers to a small subset of DSB sites that already exhibit interference, likely through axis-based cues such as mechanical stress. This early patterning is then followed by a refinement phase that coincides with the first signs of ZHP-3 coarsening along the SC. This multistep model reconciles the timing paradox of crossover designation: axis-based mechanisms establish the initial pattern, while SC-dependent diffusion-based processes subsequently refine and stabilize early-designated sites (Fig. 5 C). Together, these findings highlight that crossover designation involves multilayered regulatory inputs acting at distinct stages, with different organisms potentially weighing these mechanisms to varying degrees.

## The SC coordinates feedback control of DSB formation and quality surveillance

The assembly status of the SC is closely monitored by cells to assess homolog engagement and coordinate meiotic progression. Mutants defective in SC formation exhibit elevated DSB levels, indicating that the SC provides negative feedback to limit further DSB formation (Kauppi et al., 2013; Thacker et al., 2014; Lee et al., 2021). This feedback operates in a chromosome-autonomous manner, with each chromosome pair sensing its own homolog engagement status and independently down-regulating DSB formation (Mu et al., 2020). The molecular basis of this feedback control has been well elucidated in yeast and mammals. As described earlier, axis-associated HORMADs are actively removed from synapsed chromosomes by TRIP13 (Pch2 in budding yeast) (Joshi et al., 2009; Wojtasz et al., 2009). Because HORMADs provide an axial platform for recruiting the SPO11 machinery via the REC114–MEI4–IHO1 complex in mammals (Rec114–Mei4–Mer2 complex in budding yeast) (Panizza et al., 2011; Stanzione et al., 2016; Rousová et al., 2021; Laroussi et al., 2023), their removal from synapsed regions dismantles the DSB-forming machinery, rendering synapsed regions incompetent for further DSB formation (Fig. 2 C). Through this feedback, HORMAD dynamics prevents excessive DSB formation and ensures that crossover formation proceeds appropriately for accurate chromosome segregation.

In mammals, HORMADs are also essential for recruiting ATR and BRCA1 to unsynapsed chromatin (Fig. 2 C), where ATR phosphorylates histone H2AX and activates checkpoint responses that ultimately eliminate oocytes with persistent asynapsis or recombination defects (Kouznetsova et al., 2009; Shin et al., 2010; Daniel et al., 2011; Wojtasz et al., 2012; Cloutier et al., 2015; Jiao et al., 2025). Additionally, ATR regulates HORMAD1/2 phosphorylation and is required for proper localization of BRCA1 and ATR cofactors to unsynapsed axes, contributing to meiotic silencing of unsynapsed chromatin (Royo et al., 2013). Thus, HORMADs function as sensors of synapsis status, linking SC assembly to both suppression of DSB formation and activation of surveillance pathways that safeguard genome integrity and prevent aneuploidy in gametes.

A distinct feedback mechanism operates in *C. elegans*, where DSBs occur in the context of a fully assembled SC and HORMADs remain axis-associated even after synapsis, inverting the logic seen in yeast and mammals. Here, the meiotic kinase CHK-2 serves as the master regulator whose activity sustains DSB competence by maintaining chromatin association of DSB proteins and is prolonged by HORMADs when synapsis or crossover formation fails (Rosu et al., 2013; Stamper et al., 2013; Kim et al., 2015; Hinman et al., 2021). Crossover designation stabilizes the SC central region by recruiting the Polo-like kinase PLK-2, which attenuates further DSB formation through phosphorylation of SYP-4 (Nadarajan et al., 2017; Pattabiraman et al., 2017). Chromosomes that fail to designate crossovers do not recruit PLK-2 and undergo desynapsis (Machovina et al., 2016), maintaining them in a DSB-competent state. Importantly, removing SC components from nuclei with designated crossovers reactivates CHK-2 and resumes DSB formation, demonstrating continuous surveillance (Castellano-Pozo et al., 2020). Moreover, nuclei with persistent unsynapsed chromosomes are ultimately eliminated by apoptosis, providing a final failsafe (Bhalla and Dernburg, 2005). Thus, while the molecular players differ, *C. elegans* shares with yeast and mammals the fundamental principle of using SC-associated signals to coordinate DSB formation with crossover status and eliminate defective meiocytes.

## Concluding remarks

Once viewed as an enigmatic electron-dense scaffold, the SC is now recognized as a dynamic regulatory platform that coordinates multiple essential meiotic processes. In most eukaryotes, SC assembly is coupled with meiotic recombination, positioning it as a signaling hub for self-reinforcing feedback loops. The SC recruits and organizes ZMM proteins to stabilize crossover-specific recombination intermediates, which in turn reinforce the SC structure. Additionally, the SC provides negative feedback that suppresses additional DSB formation on synapsed chromosomes, preventing excess DSB formation and enabling quality control. Together, these features illustrate how a supramolecular chromosome structure integrates its assembly with sophisticated DNA metabolism.

Studies across diverse model organisms reveal several recurring themes. Despite extensive sequence divergence among SC components, the fundamental architectural principles and core regulatory modules of the SC are far more conserved than previously appreciated. Features such as the ∼100 nm SC width, head-to-head assembly of transverse filaments, and the coupling between the SC central region and ZMM proteins highlight how divergent strategies achieve similar structural and functional outcomes. A particularly striking example is the conserved interface of the SC with the Zip3 family RING-domain E3 ligases (Neves et al., 2025; Williams et al., 2025; Seear et al., 2025). This ancient module suggests that the regulatory link between the SC and the class I crossover pathway is under strong evolutionary constraint.

Central to the regulatory mechanisms of the SC are the HORMAD proteins, which couple homolog synapsis to recombination control and quality surveillance. Prior to SC assembly, HORMADs on chromosome axes establish platforms for DSB formation and enforce interhomolog bias. Upon synapsis, their

removal by TRIP13/Pch2 dismantles the DSB-forming machinery and relieves the barrier to intersister repair. HORMADs that persist on asynaptic chromosomes trigger checkpoint responses that arrest or eliminate defective meiocytes, thereby preventing the production of aneuploid gametes (Wojtasz et al., 2009; Rinaldi et al., 2017; Jiao et al., 2025). These interconnected mechanisms create a robust system that balances DSB formation with the capacity for DNA repair.

Despite substantial progress, fundamental questions about the SC remain. How complete is the SC parts list, and what components are still missing? Why do the primary sequences of SC components change so rapidly on evolutionary timescales? How are individual SC subunits produced in the correct stoichiometry and coordinated to form functional complexes? What molecular mechanisms drive SC polymerization and its dynamic remodeling during recombination? Developing in vitro reconstitution systems for SC assembly will be crucial for answering these questions. The recent discovery of Skp1 proteins as SC subunits in *C. elegans* further raises intriguing questions about the prevalence and functional significance of such co-option. Resolving these questions will advance our understanding of how the SC integrates structural organization, crossover recombination, and quality control to safeguard genome integrity across generations.

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