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INVITED REVIEW

Sperm Biology

The organization, regulation, and biological functions of the synaptonemal complex

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The synaptonemal complex (SC) is a meiosis-specific proteinaceous macromolecular structure that assembles between paired homologous chromosomes during meiosis in various eukaryotes. The SC has a highly conserved ultrastructure and plays critical roles in controlling multiple steps in meiotic recombination and crossover formation, ensuring accurate meiotic chromosome segregation. Recent studies in different organisms, facilitated by advances in super-resolution microscopy, have provided insights into the macromolecular structure of the SC, including the internal organization of the meiotic chromosome axis and SC central region, the regulatory pathways that control SC assembly and dynamics, and the biological functions exerted by the SC and its substructures. This review summarizes recent discoveries about how the SC is organized and regulated that help to explain the biological functions associated with this meiosis-specific structure.

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INTRODUCTION

Meiotic cell division is required by all sexually reproducing organisms. Unlike mitotic cell division, where identical sets of chromosomes are created and transmitted to daughter cells, meiosis divides diploid germ cells into haploid gametes, halving the chromosome number and exchanging genetic information happen between homologous chromosomes. Halving of the genome is achieved during meiosis by sequential segregation of homologous chromosomes (meiosis I division) and sister chromatids (meiosis II division) after a single round of DNA replication. A pronounced feature of meiosis is its prolonged prophase, during which a series of meiosis-specific events take place. According to the chromosome morphology and nuclear organization, meiotic prophase can be divided into five substages: leptotene, zygotene, pachytene, diplotene, and diakinesis. During leptotene, the replicated sister chromatids are closely apposed by cohesin complexes, and meiotic chromosome axes start to assemble, forming loop-axis meiotic chromosome structures. During zygotene, programmed double-strand break (DSB) formation initiates meiotic recombination, and homologous chromosomes pair and align. A zipper-like proteinaceous structure known as the synaptonemal complex (SC) starts to assemble between the homologous chromosome axes, which are referred to as lateral elements after SC assembly. Chromosomes preferentially cluster and polarize in the nucleus. During pachytene, the SC assembles along the entire length of the paired homologs, and chromosomes are dispersed throughout the nuclear periphery. A subset of DSBs are then repaired through interhomologous recombination to form crossovers (CO), resulting in the exchange of chromosome regions between homologs. During diplotene, the SC starts to disassemble unevenly, and regions of homologous chromosomes desynapse. At diakinesis, chromosomes undergo remodeling and condensation, and homologs are mainly held together by chiasmata (the cytological correlates of COs) and centromere pairing. These stable associations are critical for metaphase alignments, where homologous chromosomes are bi-oriented and pulled toward different poles by spindle microtubules. Finally, two waves of separase-mediated cohesin cleavage sequentially release attachments between homologs and sister chromatids during anaphase of meiosis I and meiosis II. The completion of the meiosis-specific events during prophase is critical for accurate chromosome segregation, and mutations in SC genes are associated with human infertility.

The ultrastructure of the SC is highly conserved and consists of two lateral elements and a central region (**Figure 1**). Studies in different organisms have revealed the conserved features of the SC,[1–3] some of which are highlighted below. First, the width of the SC is similar (90–150 nm) between species regardless of their genome size (*e.g.*, approximately 12 Mb in yeast and approximately 3000 Mb in mammals). Second, although SC components do not show obvious sequence similarity between organisms, the organization of central region components is conserved. In most organisms, the central region comprises transverse filaments and central elements. The transverse filaments are organized in a head-to-head manner, with their N-terminal domains located at the middle of the central region and their C-terminal tails facing the chromosome axis. The central element proteins overlap with the N-terminal domain of the

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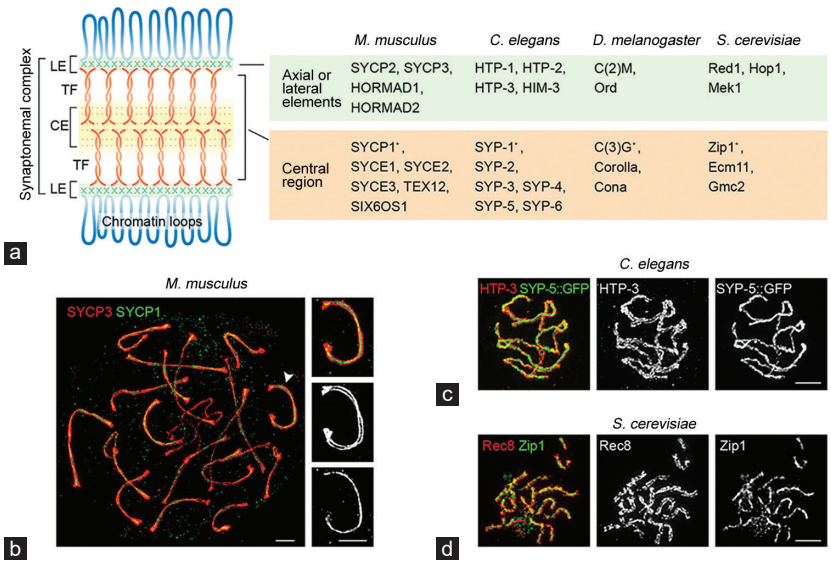

Figure 1: SC structure and components in different organisms. (**a**) Diagram of the SC structure and components in the indicated organisms. Transverse filament proteins are indicated by asterisks. (**b**) Structured illumination microscopy (SIM) analysis of SYCP3 (red) and SYCP1 (green) localization in mouse spermatocytes (image provided by Yong-Liang Shang from the lab of Liang-Ran Zhang). The SC stretch indicated by a white arrowhead is shown at a higher magnification on the right. Scale bars=2 μm. (**c**) SIM analysis of HTP-3 (red) and SYP-5 (GFP-tagged, green) localization in *C. elegans* germline. Scale bar=2 μm. (**d**) SIM analysis of Rec8 (red) and Zip1 (green) localization in *S. cerevisiae* pachytene cells (image provided by Mei-Hui Song from the lab of Liang-Ran Zhang). Scale bar=2 μm. SC: synaptonemal complex; GFP: green fluorescent protein; CE: central elements; LE: lateral elements; TF: transverse filament; *C. elegans*: *Caenorhabditis elegans*; *S. cerevisiae*: *Saccharomyces cerevisiae*; *M. musculus*: *Mus musculus*; *D. melanogaster*: *Drosophila melanogaster*.

transverse filaments at the middle of the central region, stabilizing the SC structure. Moreover, most of the known central region proteins in various organisms contain coiled-coil domains, and coiled-coil domains in transverse filaments can mediate their homo-dimerization. These conserved features might be critical for the biological functions of the SC, although the underlying mechanisms are still unclear.

Over the last few years, with the development of super-resolution microscopy, advanced structural analyses and *in vivo* functional studies have provided profound insights into the internal three-dimensional (3D) organization of SC substructures, the regulatory pathways controlling SC formation and dynamics, and the integrated functions of the SC during meiotic progression. Due to space constraints, here we review this progress from the perspective of a few model organisms but refer interested readers to our previous review and other excellent reviews on the topic.[1–4]

MEIOTIC CHROMOSOME AXIS ASSEMBLY

Meiotic chromosomes are organized as loop-axis structures upon meiotic entry, and this organization is mediated by cohesin complexes and meiosis-specific proteins. Integrated Hi-C analysis and simulations suggest that meiotic chromosome assembly is controlled by loop extrusion with growth limited by barriers.[5] Super-resolution microscopy has allowed the investigation of the internal organization of the axis in worms (*Caenorhabditis elegans* [*C. elegans*]) and mice (*Mus musculus* [*M. musculus*]). In *C. elegans*, meiosis-specific Hop1, Rev7, and Mad2 (HORMA) domain proteins (HORMADs) span a gap between cohesin complexes and the central region of the SC, forming a layered organization and consistent with their essential roles in SC assembly (**Figure 2a**).[6] By combining expansion microscopy with super-resolution microscopy, meiotic chromosome axis organization was examined in mouse spermatocytes. The coiled-coil filaments of synaptonemal complex protein 3 (SYCP3) and the SYCP2 C-terminus (SYCP3/SYCP2-C) form an axis core, around which cohesin complexes, HORMADs, and the N-terminus of SYCP2 (SYCP-N) array, forming a

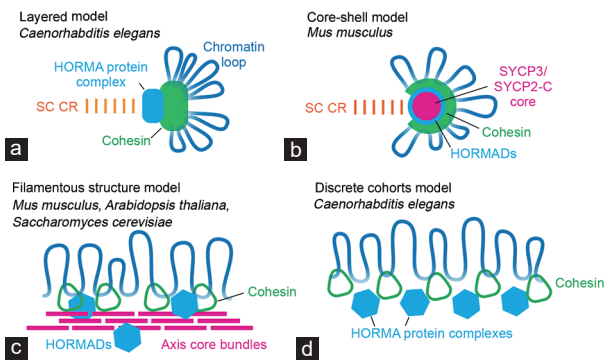

Figure 2: Models for meiotic chromosome axis organization in different organisms. (**a**) Cross-sectional view of meiotic chromosome axis organization in worms. (**b**) Cross-sectional view of meiotic chromosome axis organization in mouse, which represents a core-shell-like structure. (**c**) Model for the longitudinal organization of the meiotic chromosome axis in fungi, plants, and mammals. (**d**) Model for the longitudinal organization of meiotic chromosome axis organization in worms. CR: central region; SC: synaptonemal complex; HORMAD: Hop1, Rev7, and Mad2 (HORMA) domain protein; SYCP: synaptonemal complex protein.

core-shell organization (**Figure 2b**). SYCP2-N may serve to link other proteins or chromatin to the SYCP3/SYCP2-C core.[7] Although the proposed organization models show differences between organisms, cohesin complexes are consistently distant from the SC central region, supporting the idea that interactions with SC central region are mediated by meiosis-specific complexes on the axis.

The molecular interactions between meiosis-specific axial proteins have been investigated both biochemically and structurally. In *C. elegans*, HORMAD proteins form hierarchical complexes through binding of their HORMA domains to cognate peptides within the C-termini of their partners, resembling the "safety belt" binding mechanism of yeast mitotic arrest deficient 2 (Mad2).[8] Structural analysis of axis core proteins in budding yeast (reductional division protein 1 [Red1] in

Saccharomyces cerevisiae [*S. cerevisiae*]), mammals (SYCP2/SYPC3 in *M. musculus*), and plants (ASYNAPTIC 3/ASYNAPTIC 4 [ASY3/ASY4] in *Arabidopsis thaliana*) has revealed conserved axis assembly features (**Figure 2c**). All these complexes contain closure motifs that recruit meiotic HORMAD proteins, the critical regulator of meiotic recombination. Moreover, axis core proteins form homotetrameric (in yeast) or heterotetrameric (in mammals and plants) complexes through their coiled-coil domains. Oligomerization of the assemblies can further form micron-length filamentous structures.[9] Human SYCP3 also self-assembles into regular filamentous structures that resemble SC lateral elements *in vitro*.[10] These observed properties are consistent with the morphological features of the lateral elements *in vivo*, where occasional splitting into two or more sublateral elements (subLEs) was observed by super-resolution microscopy or electron microscopy.[11,12]

However, there appear to be distinct models for axis assembly in different organisms. Quantitative cytogenetics has revealed that meiosis-specific HORMAD proteins assemble into cohorts in defined numbers and co-organize the axis together with distinct cohesin complexes with defined stoichiometry. The chromosomal axis is resolved as individual HORMAD foci arranged like pearls on a string instead of a continuous linear structure (**Figure 2d**).[13] Exactly how distinct mechanisms of axis assembly support many conserved functions across species still needs to be determined.

ORGANIZATION OF THE SC CENTRAL REGION

It is well established that the SC transverse filaments are organized with their N-termini locating in the middle of the SC and C-termini facing toward the lateral elements, a feature conserved across species. With electron microscopy and super-resolution analysis, the 3D organization of the SC central region has been investigated in different organisms. Super-resolution microscopy showed that the central element comprises two parallel cables approximately 100 nm apart, oriented perpendicular to the two parallel cables of the lateral element in mice.[14] Consistently, analysis of SC protein localization by immunoelectron microscopy in mouse spermatocytes has shown that the N-terminal region of SYCP1 and synaptonemal complex central element protein 3 (SYCE3) form a joint bilayered central structure and that SYCE1 and SYCE2 localize in between the two layers.[15] Moreover, the SC structure in *Drosophila* revealed by expansion microscopy coupled with structured illumination microscopy (SIM) also appears to form two mirrored layers.[16] Thus, these studies suggest a bilayered organization of the SC central region (**Figure 3a**).

However, analysis of SC organization with different technologies suggests that SC central element proteins might not be unambiguously organized into two layers (**Figure 3b**). For example, a 3D mouse SC model generated by electron tomography and manual feature extraction did not support a bilayered organization, instead suggesting unstructured organization of the SC transverse filaments.[17] Consistent with this, expansion microscopy coupled with SIM showed that the SYCP1 N-terminus and SYCE3 have a monomodal distribution, again suggesting unstructured organization of the transverse filaments.[12] This distinct organization observed in different analyses may be due to different epitope accessibility through preexpansion or postexpansion labeling.[12] It remains to be determined whether the SC central region is organized consistently throughout the chromosomes and whether 3D regulation can be regulated by specific meiotic events.

SC central region proteins are largely alpha-helical, coiled-coil proteins undergoing heterotypic interactions, and they usually self-assemble *in vitro*. Human SYCP1 has an obligate tetrameric structure in which an N-terminal four-helical bundle bifurcates into two elongated C-terminal dimeric coiled coils. This building block further assembles into a zipper-like structure through self-assembly sites at the N-terminus and C-terminus.[18] The N-terminus half of SYCE1 mediates dimerization and forms an alpha-helical core, while the C-terminus adopts an extended conformation that may tether other components.[19] Human SYCE3 was found to adopt a dimeric four-helical bundle structure that can further self-assemble into a series of discrete higher-order oligomers.[20] Despite these self-interacting properties, *in vivo* interactions, are more complex and might result in distinct properties when specific binding partners are present. For example, SYCE1 and six6 opposite strand transcript 1 (SIX6OS1) undergo multivalent interactions, and the SIX6OS1 N-terminus can disrupt SYCE1 self-dimerization and form 1:1 complexes. Mutations that disrupt the interfaces are associated with nonobstructive azoospermia and premature ovarian failure.[21]

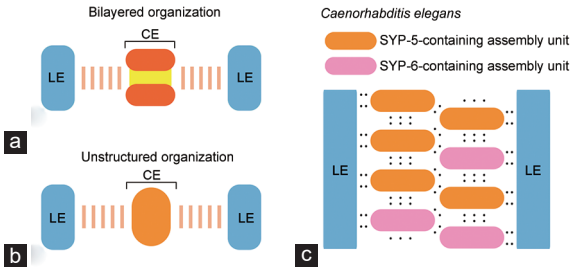

Figure 3: Models for SC central region organization. (**a**) Model for the bilayered organization of the SC (axial view). Central elements and N-termini of SC transverse filaments are organized into distinct layers at the central region. (**b**) Model for unstructured organization of the SC (axial view). Central elements and N-termini of SC transverse filaments are not organized into distinct layers. (**c**) Model for SC assembly in *C. elegans*. SYP proteins form assembly units through stable interactions, and SYP-5 and SYP-6 belong to distinct SC assembly units. Multi-directional weak interactions (indicated by black dots) between assembly units drive SC formation. CE: central elements; SC: synaptonemal complex; *C. elegans*: *Caenorhabditis elegans*; LE: lateral elements; SYP: synapsis in meiosis abnormal.

Synapsis in meiosis abnormal 5 (SYP-5) and SYP-6, recently identified SC components in *C. elegans*, are paralogs that play redundant roles in SC assembly during early prophase and CO formation.[22,23] Interestingly, immunoprecipitation and proteomic analyses have revealed that SYP-5 and SYP-6 belong to distinct SC assembly units that are assembled through coiled-coil-mediated stable interactions, with multivalent weak interactions between assembly units driving SC formation (**Figure 3c**).[23] Hydrophobic and charge-mediated interactions are likely to promote multi-directional assembly of the SC.[23–26] These findings are consistent with the observation that the SC has liquid crystalline properties in different organisms.[24] Notably, such properties appear to be critical for the compartmentalized signal transduction for CO control and asymmetric SC disassembly during pachytene exit in *C. elegans*.[23,27] Furthermore, normal properties of the SC are also critical for CO control at elevated temperatures, promoting meiotic thermotolerance.[28]

REGULATORY PATHWAYS CONTROLLING SC ASSEMBLY AND DISASSEMBLY

Phosphorylation regulation

Studies in various organisms suggest that SC phosphorylation and dephosphorylation during meiotic prophase play critical roles in regulating SC assembly, dynamics, and late prophase disassembly. Studies in yeast have shown that molecular zipper 1 (Zip1) phosphorylation and dephosphorylation, which are mediated by

mitosis entry checkpoint protein 1 (Mec1) kinase ATR and protein phosphatase 4 (PP4), respectively, control the dimerization of Zip1 N-termini to regulate centromere pairing.[29] In *C. elegans*, SYP-1 phosphorylation at its polo-box domain-binding motif also promotes timely synapsis and progression of meiotic prophase.[30] Moreover, CO designation triggers a switch in SC dynamics to a more stable state, and phosphorylation of SC components might be responsible for this switch.[31,32] SYP-1 can also be phosphorylated at its C-terminus by ataxia-telangiectasia mutated (ATM)-ATR kinases in response to excessive meiotic DSBs, and such phosphorylation safeguards the germline against persistent or excessive DSBs by channeling repair to the sister chromatid.[33]

SC lateral element phosphorylation is also implicated in meiotic progression. In *C. elegans*, axial HORMA protein him-three paralog 1 (HTP-1) can be phosphorylated at Ser325 by extracellular signal-regulated kinase (ERK), which in turn promotes SC extension and/or maintenance.[34] Another HORMA protein, high incidence of males 3 (HIM-3), can also be phosphorylated at its "closure motif" region, thereby mediating interactions with HTP-1 and HTP-2 in a critical step of chromosome remodeling during late prophase.[35] In *Arabidopsis*, the chromosome axis protein ASYNAPTIC 1 (ASY1), the *Arabidopsis* homolog of homolog pairing 1 (Hop1), can be phosphorylated by the cyclin-dependent kinase 1 (Cdk1) and Cdk2 homolog CDKA-1, and such phosphorylation is required for its recruitment to the chromosome axis.[36]

Phosphorylation not only regulates SC assembly but is also critical for SC disassembly during the late meiotic prophase. During budding yeast meiosis, increase in ploidy 1 (Ipl1)/Aurora B kinase coordinates SC disassembly with cell cycle progression and CO formation,[37] and the concerted action of cell cycle kinases (Dbf4-dependent Cdc7 kinase [DDK]), polo-like kinase, and CDK1 also promotes efficient SC destruction at the end of meiotic prophase I.[38] SC disassembly in mice also relies on multiple kinases. Polo-like kinase 1 (PLK1) can directly phosphorylate SC central region components SYCP1 and testis-expressed protein 12 (TEX12), thereby promoting central region disassembly.[39] An *in vitro* study also suggested that SC disassembly is regulated by cyclin-dependent kinases, but the mechanism remains unclear.[40] In mouse and human spermatocytes, inhibiting Aurora kinase B (AURKB) and Aurora kinase C (AURKC) kinase activity impairs the disassembly of SC lateral elements, and *Aurkb* and *Aurkc* double-knockout mouse spermatocytes show lateral element disassembly defects and chromosome missegregation.[41] In *C. elegans*, mitogen-activated protein kinase (MAPK) inactivation during late pachytene is critical for timely disassembly of the SC proteins from the long arms.[42] In *Drosophila*, overexpression of B regulatory subunits of protein phosphatase 2A (PP2A) Wrd/B56 results in delayed assembly and premature disassembly of the SC.[43] These observations suggest the critical role for phosphorylation in SC disassembly, but their regulatory mechanisms require further investigation.

Ubiquitination and proteasome pathways

The involvement of ubiquitination and proteasome regulation in SC formation and functions has been established in various organisms, suggesting a conserved regulation of the SC via these processes. In yeast, proteolytic core and regulatory proteasome particles were recruited to chromosomes by Zip3 (the ortholog of mammalian E3 ligase RNF212) and SC protein Zip1, and a functional proteasome was required for a coordinated transition that entails SC assembly between axes.[44] Depletion of cell division control protein 53 (Cdc53), a cullin in the Skp-Cullin-F-box (SCF) ubiquitin ligase family, results in SC polycomplex formation.[45] Moreover, SUMOylated SC components extracellular mutant protein 11 (Ecm11) and Zip1 can be recognized by heterodimeric Slx8p-Slx5p SUMO-targeted ubiquitin ligase (STUbL) complex and degraded.[46]

In *C. elegans*, cullin RING E3 ubiquitin ligase 4 (CRL4) components are also required for proper SC assembly, and their depletion results in polycomplex formation. However, SC components are not likely to be the direct targets of CRL4 ubiquitination.[47] Ubiquitination also mediates SC components degradation in mitotic germ cells before meiotic entry.[48] Mutations in constitutive photomorphogenesis 9 (COP9) signalosome (CSN) subunits lead to SC assembly defects and the formation of SC polycomplexes. This regulation at least partially relies on neddylation and might be associated with a ubiquitin degradation/proteasome pathway.[49] Interestingly, neddylation is also required for proper SC assembly and crossover localization in plants.[50]

In *Drosophila*, the E3 ubiquitin ligase seven in absentia (Sina) prevents the polymerization of SC components and lateral elements into polycomplexes. SC components are not likely to be direct substrates of Sina, which might block polycomplex formation by mediating the degradation of some unknown regulators.[51] Moreover, the SCF ubiquitin ligase is also important for assembly and maintenance of the SC in female meiosis in *Drosophila*, and this function is mediated by downregulating the phosphatase subunit PP2A-B56.[43]

In mice, SKP1, a core subunit of the SCF ubiquitin E3 ligase, localizes to the lateral elements of the SC in pachytene spermatocytes and is essential for viability and male meiosis. SKP1 loss leads to the accumulation of HORMAD proteins on the chromosome axis and causes precocious chromosomal desynapsis and pachytene exit.[52] Proteasome subunit beta type 8 (PSMA8), a testis-specific proteasomal subunit, is not required for normal synapsis but interacts with SC proteins and promotes axial protein SYCP3 degradation at meiosis II.[53] Although it is conserved for the requirements of ubiquitination in SC regulation, the specific substrates of these regulations are still largely unknown.

SUMOylation regulation

The requirement of SUMOylation in SC regulation is well described in yeast. In *S. cerevisiae*, the SC initiation protein Zip3 is a small ubiquitin-related modifier (SUMO) E3 ligase, and Zip1 interacts with SUMO-conjugated products.[54] Zip3 and proline isomerase formyl peptide receptor 3 (Fpr3) are required to prevent synapsis before the initiation of meiotic recombination.[55] SUMOylation of axial protein Red1 fosters interactions with Zip1, securing timely SC formation.[56] The SC central region protein Ecm11 can be SUMOylated in a grand meiotic recombination cluster protein 2 (Gmc2)-dependent manner, promoting SC assembly between homologous chromosomes.[57] Moreover, a polySUMOylation-driven feedback mechanism promotes SC elongation, in which Zip1 activates Ecm11 SUMOylation, which in turn facilitates more Zip1 recruitment.[58] In mice, the lateral element protein SYCP3 can also be SUMOylated,[59] and SUMO, ubiquitin, and proteasomes coordinate to regulate the major events of meiotic prophase.[60] SUMO, ubiquitin, and proteasomes show interdependent localization along chromosome axes, and chemical inhibition of SUMO conjugation, ubiquitin activation, or proteasomal degradation causes large extra-chromosomal aggregates of SYCP3 and SYCP2 and synapsis defects.[60] The requirement of SUMOylation for SC regulation in other organisms still needs to be investigated.

Regulation by nonstructural components

The conserved AAA+ ATPase thyroid receptor-interacting protein 13 (TRIP13)/pachytene checkpoint protein 2 (PCH2) remodeling proteins can be recruited to the SC and are well-known regulators of meiotic HORMADs for their chromosome association.[61] The HORMA domain consists of a core region and the C-terminal "safety belt" region, the latter packing against the core with different conformations, and meiotic axial HORMA proteins have been shown to be remodeled by TRIP13/PCH2 in yeast, mammals, and plants.[62–64] In *C. elegans*, loss of pch-2 accelerates synapsis.[65] In budding yeast, SC assembly defects caused by SCF component Cdc53 depletion can be suppressed in *pch2/cdc53* double mutants.[45] In the *Brassica rapa* plant, *pch2* mutants achieve only partial synapsis.[66] Similarly, *Trip13* mutation that severely impairs TRIP13 function causes synapsis defects in mice.[67] These observations suggest that TRIP13/PCH2 remodeling proteins may regulate SC assembly by affecting the axial HORMA proteins in various situations.

Moreover, several other proteins have also been found to regulate synapsis in mice. The SC-interacting protein, synaptonemal complex reinforcing element (SCRE), is required for homologous synapsis. SCRE may reinforce the integrity of the central elements, thereby stabilizing the SC for normal meiotic progression.[68] It remains to be established if SCRE has functional homologs outside mammals. Heat shock protein family A member 2 (HSPA2), a testis-enriched HSP70 family member, localizes to the SC and is required for proper SC disassembly and successful meiosis.[69,70] HSPA2 appears to be a molecular chaperone required for CDC2A (CDK1) activation, and it remains to be determined if HSPA2 may regulate SC independent of CDC2A.

BIOLOGICAL FUNCTIONS OF THE SC AND ITS SUBSTRUCTURES

Control of meiotic recombination initiation

The initiation of meiotic recombination is mediated by sporulation-specific protein 11 (SPO11) and its accessary proteins.[71] The chromosome axis is thought to serve as an evolutionarily conserved scaffold for meiotic DSB formation, and axis length affects recombination rates across mammalian species.[72–74] Many proteins involved in DSB formation and subsequent repair also localize on the chromosome axis in various organisms.[75–78] DSB formation is abolished or significantly impaired in mutants lacking some core axis components in different species.[79–82] In yeast, HORMA protein Hop1 stabilizes the interaction between proteins at meiotic DNA break hotspots and the chromosome axis to promote DSB formation.[83]

DSB formation is critical for successful meiosis but must be tightly controlled to prevent excessive DSB formation and genome instability. HORMADs have been shown to be involved in the feedback regulation of DSB formation in mice,[84] and the Zip-Mer-Msh (ZMM) proteins are involved in switching off further programmed DSB formation in yeast.[85] Moreover, a study in yeast showed that homolog engagement-defective chromosomes incurred more DSBs, concomitant with prolonged retention of the DSB-promoting protein Rec114, and that DSB number was regulated in a chromosome-autonomous fashion.[86] In *C. elegans*, removing SC proteins in pachytene cells functionally redeployed chromosome movement and the DSB machinery in a checkpoint kinase 2 (CHK-2)- and axial HORMA protein-dependent manner.[87] SC protein phosphorylation that is coupled with CO designation has also been revealed to regulate DSB formation in *C. elegans*.[32] These observations suggest that homolog engagement and CO designation have a feedback control of DSB numbers.

Control of DSB repair and CO formation

The SC controls DSB repair and CO formation at multiple steps, including the relocation of recombination intermediates from the axis to the SC, inhibition of DSB repair by inter-sister recombination during early meiotic prophase, CO designation, and inter-sister repair during later meiotic prophase.

The relocation of recombination complexes from on-axis association to the SC central region has been investigated in the fungus *Sordaria macrospora*, with Zip2-Zip4 playing a central role during this transition.[88] Yeast SC central region protein Zip1 plays a central role in coordinating SC assembly and CO recombination. Distinct N-terminal regions of Zip1 are differentially critical for crossing over and SC assembly, facilitating crosstalk between the two processes by bringing CO recombination and synapsis factors within proximity of one another.[89] In *C. elegans*, CO formation is tightly controlled within the context of the SC. Pro-CO factors are recruited by the SC central region proteins to control CO designation.[27,90] Super-resolution microscopy has revealed that CO-designated recombination intermediates are enveloped by SC central region proteins during late pachytene, which may protect CO intermediates from being dismantled inappropriately and promote CO maturation.[91] RAD51-associated intermediates do not frequently localize to the SC during late pachytene,[92] suggesting that only CO-designated intermediates may be selectively recruited to the SC. In mice, the meiotic chromosome axes are hubs for regulated proteolysis via SUMO-dependent control of the ubiquitin-proteasome system. CO recombination-promoting E3 ligases RING finger protein 212 (RNF212) and human enhancer of invasion 10 (HEI10) mediate the interdependent localization of SUMO, ubiquitin, and proteasomes along chromosome axes. It has been proposed that SUMO conjugation establishes a precondition for designating CO sites via selective protein stabilization.[60]

CO number and distribution on meiotic chromosomes are regulated by many factors.[93] Lateral elements and central region components are involved at different levels in the regulation of CO interference in different organisms.[94–96] In *C. elegans*, only one CO forms for each pair of homologous chromosomes in wild type, and the SC central region promotes the normal CO levels and shapes the CO landscape.[95,97] The SC exhibits liquid crystalline properties in *C. elegans*, and CO regulation is likely to operate separately in each compartment.[27,90] In yeast and plants, disruption of the SC does not result in a total loss of COs. *S. cerevisiae ZIP1* deletion mutants exhibit a modest reduction in CO formation and loss of CO interference.[98] In rice and *Arabidopsis*, null mutants of their transverse filament genes show increased COs and the absence of CO interference.[99–101] These observations suggest a conserved role of the SC central region in imposing CO interference.

The mechanism of how the SC structure inhibits the use of the sister chromatid as a template for repair during early prophase is still not clear. However, axis-recruited HORMA proteins are known to play critical roles in various species.[82,102–105] Meiotic DSBs generated in synapsis-defective *C. elegans* mutants cannot be repaired through inter-homologous recombination and persist until the barrier to sister chromatid repair is removed in late pachytene.[106] It is also unclear exactly how inter-sister repair is allowed during late pachytene. BRCA homolog 1 (BRC-1) and BARD homolog 1 (BRD-1), *C. elegans* orthologs of mammalian breast cancer susceptibility gene 1 (BRCA1) and binding partner BRCA1-associated RING domain protein 1 (BARD1), respectively, are involved in such repair, and they are also recruited to the SC after mid-pachytene.[107,108] Moreover, the SC central region can promote sister chromatid exchange when it mislocalizes

between sisters in the *rec-8* mutant background,[109] further suggesting the involvement of the SC in DSB repair.

Centromere pairing

Upon pachytene exit, paired homologous chromosomes desynapse and SC components start to dissociate from the chromosomes. The dissociation of SC components does not occur evenly throughout the chromosomes, with some components preferentially retained at centromeres and pericrossover regions and lost from the remainder of the chromosome arms during late meiotic prophase, a phenomenon conserved across species.[110–115] The biological significance of the persistence of SC components at centromeres is highlighted by their requirement for centrosome pairing, which promotes accurate meiotic chromosome segregation. In budding yeast, the transverse filament protein Zip1 and other ZMM/SIC components (Zip2, Zip3, Zip4, and Spo16) are critical for centromere pairing and localize to the paired centromeres on nonexchanging chromosome pairs during both pachytene and diplotene.[110,111] In *Drosophila* oocytes, centromeres cluster into one or a few clusters, and this clustering requires the SC transverse filament protein C(3)G and other proteins required for early prophase SC assembly.[116] In mouse spermatocytes, the centromeric SC represents a tripartite structure containing SYCP1 and lateral element SYCP3, and this structure persists until diplotene. However, at later stages, SYCP1 is lost from the chromosome, and only SYCP3 is retained at the centromeres, which persists until prometaphase I.[113,114] Moreover, shugoshin can promote meiotic centromere pairing by protecting centromeric SCs in mouse spermatocytes.[117]

Centromere pairing might promote disjunction by holding nonexchanged homologs together or facilitating kinetochore geometry to promote the bipolar attachment of microtubules. While SC proteins may be directly involved in centromere pairing in some cases, SYCP3 in mice for example,[113] the mechanisms are likely to be indirect in other cases. In flies and mice, centromeric tripartite SCs disassemble before nuclear envelope breakdown,[112–114] and SC structures are not likely to be directly involved in orienting homologous chromosomes. Moreover, it remains to be determined if SC components are required for centromere pairing and segregation of nonexchanged homologs in humans.

Chromosome remodeling

C. elegans does not have a defined single centromere on each chromosome, and the entire chromosome behaves as a centromere (holocentric chromosome). CO formation between homologs usually occurs at an off-center region separating the paired chromosomes into a long arm and a short arm. SC disassembly also takes place in an asymmetric manner in *C. elegans*, and the SC central region first disassembles on the long arms and is retained on the short arms.[118] SC disassembly is tightly coordinated with CO formation and is accompanied by chromosome remodeling, during which chromosome compaction and protein composition and localization along the chromosome arms change. While HORMA proteins HTP-3 and HIM-3 localize to both bivalent arms after chromosome remodeling, another two HORMA proteins HTP-1 and HTP-2 localize to only bivalent long arms.[119] SC central region proteins are lost from the bivalent during late diakinesis, and the HORMA proteins are retained until metaphase I. On the metaphase plate, the long arms of the bivalents point to distinct poles of the spindle, and cohesion between sister chromatids on the short arm is cleaved upon anaphase I.[120] Phosphorylation of central region protein SYP-1 and HORMA domain protein HIM-3 has been shown to be critical for the chromosome remodeling to establish distinct bivalent domains that mediate accurate chromosome segregation.[30,35] Moreover, in *C. elegans*, SYP-5 and SYP-6 play redundant roles in SC assembly and CO formation but exhibit distinct expression patterns.[22,23] Lack of SYP-5 does not significantly affect CO formation but causes premature SC disassembly, providing a tool to evaluate the biological functions of the SC during late prophase. Indeed, premature SC disassembly is associated with abnormal chromosome remodeling.[23]

Synapsis checkpoint and signal transduction

To avoid the formation of aneuploid gametes, meiotic progression is monitored, and the presence of unrepaired DSBs and incomplete synapsis can cause meiotic arrest. SC components are required for the meiotic checkpoint in various organisms. In mice, *Hormad1* is essential for the elimination of synapsis-defective oocytes. The SC and HORMAD1 are key components of a negative feedback loop that coordinates meiotic progression with homologous alignment.[82] In *C. elegans*, a PCH-2 dependent checkpoint monitors synapsis between homologous chromosomes, and oocytes with synapsis failure are removed by apoptosis.[121] Both SC central region and axial HORMA proteins are required for the functional synapsis checkpoint.[122] In budding yeast, the central element protein Zip1 is also required for Pch2-dependent pachytene checkpoint activation.[123] Moreover, RAS/ERK can phosphorylate meiotic chromosome axis protein HTP-1 at serine-325 to control chromosome dynamics and regulate oocyte number,[34] suggesting the involvement of the meiotic chromosome axis in signal transduction.

SC GENE MUTATIONS AND HUMAN INFERTILITY

Infertility is estimated to affect 8%–12% of reproductive-aged couples.[124] However, the cause of infertility remains largely unknown. Meiotic defects account for at least part of the human idiopathic infertility cases in males and females. With exome sequencing, mutations in several SC genes have been linked to human infertility, including *SYCP3*, *SYCP2*, *SYCE1*, and *C14ORF39/SIX6OS1*.

The first identified infertility-associated SC gene mutation is *SYCP3* with a 1-bp deletion that results in a premature stop codon and truncation of the C-terminal region of SYCP3.[125] This mutation was identified in azoospermic patients and had a dominant-negative effect on the function of the wildtype allele during meiosis. The mutant protein reduced interaction with the wild-type protein *in vitro* and interfered with SYCP3 filament formation in cultured cells. Later, heterozygous *SYCP3* mutations were found in two females with recurrent pregnancy loss of unknown cause.[126] These mutations affect normal splicing and possibly result in C-terminally mutated proteins, which may also have dominant-negative effects during meiosis and cause recurrent miscarriage. Recently, three heterozygous *SYCP2* frameshift variants were found in infertile males with cryptozoospermia and azoospermia.[127] These observations suggest that mutations in genes of SC axial components can cause human infertility in both genders. Moreover, SYCP2 overexpression resulted from enhancer adoption was found in a patient with severe oligozoospermia and chromosome rearrangement,[127] suggesting that dysregulation of SC gene expression can also cause human infertility.

Several studies have also linked human infertility with mutations in genes coding SC central region proteins. In female patients with primary ovarian insufficiency, a protein-truncating homozygous mutation in *SYCE1* was identified. The identified nonsense mutation accounts for the autosomal recessive primary ovarian insufficiency.[128] In another two unrelated studies, homozygous splicing mutations

in *SYCE1* were identified in male patients with autosomal recessive azoospermia. These mutations may cause the gain of premature stop codons or transcript degradation.[129,130] Moreover, three homozygous mutations in *C14orf39* were identified in infertile individuals, including males with azoospermia or meiotic arrest and a female with primary ovarian insufficiency.[131] These observations underscore the importance of SC central region proteins in the normal meiotic progression and fertility of males and females. It remains to be identified if mutations in other SC genes can also cause human infertility. Exome sequencing and creating mutant mouse models carrying analogous mutations will help to determine the genetic causes of infertility.

FUTURE PERSPECTIVES

The recent identification of novel SC components, nonstructural regulators, and posttranslational modifications, together with the employment of super-resolution microscopy and structural analyses, have significantly improved our understanding of how the SC is assembled and regulated in various organisms. However, there are still large knowledge gaps regarding the interactions and regulatory networks within the SC. It is still unclear how the SC structural components mediate interactions within the complex. For example, it is uncertain how cohesin complexes and meiosis-specific proteins interact to assemble the meiotic chromosome axis; it is also unknown exactly how SC transverse filament proteins or central region proteins mediate the interaction with lateral elements. Employing proteomic approaches to characterize the complete structural components and the recruited proteins will help to address these questions. Moreover, dissecting its internal organization through *in situ* cryo-electron microscopy is likely to provide further insights.

It is apparent that SC assembly and disassembly dynamics are tightly coordinated with meiotic recombination and that multiple pathways control SC dynamics. However, the interplay between SC structures and meiotic recombination is not well understood. Outstanding questions include how chromosome axis and the central region proteins respond to DSB formation and exert feedback to control DSBs; how CO designation triggers biochemical changes in SC components; and the exact molecular mechanisms underlying the asymmetric/uneven maintenance of SC components during late prophase. Exploring the dynamics of the localization and post-translational modification of SC components will help to address these questions.

It is well known that the SC controls CO formation; however, it is unclear exactly how the SC structure affects recombination outcomes. For example, how do axis-associated HORMA proteins inhibit inter-sister repair during early prophase? How is the barrier removed during the late prophase to allow inter-sister repair of persistent DSBs? In addition to the canonical functions during pachytene in regulating meiotic recombination, the SC and its components also have other functions. For example, SC components are required for centromere pairing and promote the segregation of nonexchanged homologs in various organisms. So is the SC also required for centromere pairing and segregation of nonexchanged homologs in humans? Moreover, there is increasing evidence that the chromosome axis might be involved in signal transduction, including synapsis checkpoint activation and other signaling pathways. It remains to be investigated which signaling pathways are affected and how they are controlled.

Mutations in multiple SC genes have now been linked to human reproductive diseases, paving the way for new diagnostics and preventative therapeutics for reproductive diseases. Although the role of the SC in controlling meiotic recombination is highly conserved, SC components are not highly conserved at the primary sequence level. Understanding the differences and common mechanisms regulating meiosis in various organisms will further shed light on the underlying mechanisms and benefit human reproductive health.

AUTHOR CONTRIBUTIONS

FGZ, RRZ, and JMG wrote the manuscript. JMG prepared the figures. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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