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Chromosome pairing and synapsis during *C. elegans* meiosis

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Abstract

Meiosis is the specialized cell division cycle that produces haploid gametes to enable sexual reproduction. Reduction of chromosome number by half requires elaborate chromosome dynamics that occur in meiotic prophase to establish physical linkages between each pair of homologous chromosomes. *C. elegans* has emerged as an excellent model organism for molecular studies of meiosis, enabling investigators to combine the power of molecular genetics, cytology, and live analysis. Here we focus on recent studies that have shed light on how chromosomes find and identify their homologous partners, and the structural changes that accompany and mediate these interactions.

Introduction

Meiosis involves several modifications of the mitotic cell cycle. Unlike mitosis, it is not cyclical – the reduction in chromosome number during meiosis yields haploid gametes, with diploidy restored only by fertilization. Haploidization is achieved by coupling two successive divisions to a single round of DNA replication. To accomplish reductional segregation, homologs (the 2 copies of each chromosome inherited from the parents) which are usually not associated with one another must first pair, or find and recognize each other. Pairing is required for crossover recombination, which results in chiasmata, linkages that persists through the process of congression and alignment on the meiotic spindle.

Molecular mechanisms of meiosis have been investigated in most genetically tractable model organisms. The nematode *Caenorhabditis elegans* combines the power of rapid molecular genetics with outstanding meiotic cytology. Because of these assets its role as a model meiotic system has expanded rapidly over the last two decades. The *XX/XO* sex determination system of *C. elegans* facilitates isolation of meiotic mutants, which often display a ‘High incidence of males’ (Him) phenotype due to elevated *X* chromosome missegregation [1]. Adult hermaphrodites continuously produce gametes in large syncytial gonads, in which all stages of meiosis are represented in a temporal gradient, making it straightforward to characterize genetic or other perturbations of meiotic progression. The

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size scale of the germline, and the organization of cells as a monolayer around a central rachis, enable imaging of many nuclei within a typical microscope field; while the dimensions of individual nuclei, $\sim 3.5\mu\text{m}$ in diameter, together with a simple karyotype ($2n=12$), make it possible to resolve subchromosomal features using conventional diffraction-limited light microscopy. The entire animal is transparent and small enough to be immobilized under a coverslip or in microfluidic devices, a feature that has recently been exploited to image meiotic dynamics in living animals [2, 3]. The development of RNAi and other reverse genetic tools has also accelerated discovery and analysis of meiotic mechanisms. Early efforts to express transgenes during meiosis were frustrated by germline silencing, but this has recently been mitigated through a better understanding of posttranscriptional regulation in the germline [4], combined with innovative transgenic methods [5].

Here we describe recent insights into chromosome dynamics during meiotic prophase in *C. elegans*, focusing on two related topics: the roles of specialized chromosome sites known as “Pairing Centers,” and the structural remodeling of chromosomes that accompanies homolog pairing and synapsis. Other important topics beyond the scope of this short review include homologous recombination mechanisms, meiotic checkpoints, and meiotic segregation.

Regulation of Meiotic Chromosome Dynamics at the Pairing Centers

A prerequisite for all crossovers (COs) in *C. elegans* is the process of homologous pairing and synapsis [6-8]. Within the first few hours of meiotic prophase, each chromosome normally finds its partner. Synapsis is defined as the assembly of the synaptonemal complex (SC), a structurally conserved protein polymer, which stabilizes pairing between homologs and results in close parallel alignment of each pair from end to end. In *C. elegans*, homolog pairing and synapsis occur normally even when programmed double-strand breaks (DSBs) [9] or other early steps in recombination [10-12] are blocked by mutations, while in many other species SC formation depends on DSBs and strand invasion enzymes. Notably, the molecular basis for homology recognition in any species remains unknown.

Genetic analysis of chromosome translocations, duplications, and deficiencies revealed a distinctive feature of *C. elegans*: each of the six chromosomes contains a region, located asymmetrically near one end, that plays a unique role in homologous chromosome segregation during meiosis [13, 14] (Figure 1a). These regions have been termed ‘Homolog Recognition Regions’ (HRRs) or ‘Pairing Centers’ (PCs). Cytological analysis revealed that chromosomes lacking these regions fail to pair and synapse with their homologs [13]. Conversely, chromosomes that share homologous PC regions, but are otherwise nonhomologous due to structural rearrangements, pair with each other and undergo synapsis along their lengths, indicating that homology within a limited region is sufficient for chromosomes to recognize each other as partners (Figure 2c). Because translocations abrogate synapsis between homologous regions attached to different PCs, such chromosomes are potent regional suppressors of meiotic recombination. Well-characterized translocations and other rearrangements are valuable as genetic “balancers” [15].

Insight into the molecular basis for PC function first emerged through analysis of *him-8* mutants, in which *X* chromosomes fail to pair and synapse [7]. HIM-8 contains two noncanonical zinc fingers (ZnFs) that target the protein to the *X* chromosome PC region. Three additional proteins, ZIM-1, -2 and -3 (for “zinc finger in meiosis”), are encoded within the same operon. Each of these four paralogs is required for PC activity on one or two pairs of chromosomes [16] (Figure 1a). A combination of *in vivo* analysis and *in vitro* SELEX experiments identified short ($\sim 12\text{bp}$) sequence motifs recognized by each of these proteins. Several hundred copies of each motif are distributed throughout the PC of each

chromosome, spanning regions of ~100 kb to more than a Mb [17]. Occasional instances of these motifs can be found outside the PC regions, sometimes in small clusters [17], and likely contribute weakly to homolog pairing [7, 18].

Recent work has illuminated how PCs contribute to pairing and synapsis. During early meiotic prophase, PCs interact with a pair of SUN/KASH domain proteins that span both membranes of the nuclear envelope (NE): SUN-1 and ZYG-12 [19-23] (Figure 1b). This SUN/KASH pair has been implicated in other functions, including anchoring of centrosomes to the NE, and nuclear positioning within the syncytial germline [24, 25]. In proliferating cells, these proteins are distributed throughout the NE. During early meiosis, SUN-1 and ZYG-12 are conscripted by PCs to aggregate into 'patches' that connect the PCs of each chromosome to cytoplasmic microtubules and dynein [19, 26] (Figure 1b). These connections result in rapid, processive movements along the NE that persist until synapsis is completed [2, 3] (Figure 1c). These saltatory motions carry PCs, either individually or in small clusters, along straight trajectories, likely along individual MTs or bundles that hug the nucleus. These movements are not directed, in that they do not move chromosomes closer to their partners or to a specific subnuclear location, but they do facilitate homolog pairing, most likely by accelerating the rate at which chromosomes explore the nuclear volume. In addition, PC activity promotes an elongated chromosome conformation, which likely contributes to homologous alignment [27].

These meiosis-specific chromosome motions require the activity of at least two kinases: CHK-2 and PLK-2. Worm CHK-2 appears to be a 'master regulator' of early meiotic events, in that it is also required for programmed DSB formation to initiate meiotic recombination [28], while PLK-2 is specifically involved in meiotic pairing and synapsis [26, 29]. At the onset of meiosis, PLK-2 localizes to PCs; this recruitment requires CHK-2 and the HIM-8/ZIM proteins. Polo-like kinases (PLKs) bind to phosphorylated S-pS/T-P motifs [30], and the ZnF proteins share a conserved motif matching this consensus. Mutation of the likely phosphothreonine residue in HIM-8 abrogates PLK-2 recruitment [26]. Localization of PLK-2 to the PCs leads to phosphorylation of a serine residue near the N-terminus of SUN-1 [26, 29] (Figure 1b). Together with other posttranslational modifications, this likely promotes aggregation of SUN-1/ZYG-12 to mediate chromosome movements. PLK-2 may also regulate SC assembly independent of its role in PC motion.

While PCs play essential roles in homolog pairing, the recognition of homology cannot be attributed to the ZnF proteins or their binding sites: e.g. ZIM-1 and ZIM-3 each mediate pairing and synapsis of two autosome pairs, yet the nonhomologous chromosomes that share the same ZnF protein do not pair with each other. Nevertheless, determinants of chromosome identity must reside within the PC region of the chromosome.

The dynamic linkages between PCs and the cytoskeleton not only facilitate homolog pairing, but also regulate synapsis [13]. Mutations in the SUN/KASH proteins, or loss of all four ZnF proteins, leads to promiscuous SC assembly between nonhomologous chromosomes or the arms of individual chromosomes that fold back into hairpin structures [19, 20, 26]. Conversely, disruption of dynein activity inhibits SC assembly between homologously paired PCs [19]. Taken together, these findings led us to posit the existence of a 'pairing checkpoint' that relies on force generated by dynein to assess whether chromosomes are properly paired, and to license SC loading once appropriate conditions – i.e., properly paired homologs – are met.

In other organisms, telomeres form analogous connections to cytoskeletal elements during meiotic prophase, resulting in chromosome motion [31]. Participation of SUN/KASH domain proteins in meiotic chromosome dynamics appears to be widely conserved.

However, while microtubules and dynein are important for meiotic chromosome dynamics in diverse organisms, in budding yeast the motion is driven by interaction of telomeres with actin cables in the cytoplasm [32, 33]. In the fission yeast *S. pombe*, telomeres associate with the NE and cluster at the spindle pole body (SPB). Large-scale oscillations of the SPB along the long axis of the cells are mediated by cortical dynein resulting in coordinated movement of all chromosomes and a ‘horsetail’ appearance of the nucleus. This movement promotes homologous interactions, disfavors ectopic interactions, and ensures subsequent function of the meiotic spindle [34-36].

While the dramatic nuclear movements in fission yeast may not be typical of other organisms, clustering of telomeres near the SPB/centrosome – the so-called “meiotic bouquet” – is a widespread feature of meiotic prophase [37]. In *C. elegans* oocytes, PCs do not form a prominent cluster, although they do interact with each other to form small, transient groups [2]. We have suggested that the lack of clustering reflects centrosome inactivation and the resulting lack of a cytoplasmic focus of microtubules [2]. The varying degree of telomere clustering seen across taxa has hinted that aggregation may not directly promote homolog pairing, but instead may reflect cytoskeletal organization. This hypothesis is supported by careful analysis of a spectrum of mutants in budding yeast, which revealed that pairing efficiency was better correlated with the rate of meiotic chromosome motion than the degree of telomere clustering [38].

It is clear that cytoskeletal-mediated chromosome motions play multiple roles to promote pairing and synapsis, and also that their importance varies among species. It remains mysterious why telomeres have ceded this function to PCs in *C. elegans*. We have speculated that the emergence of a unique site per chromosome may have accompanied the loss of a regional centromere during the emergence of holocentric chromosomes in this lineage [13].

Structure and Function of the Synaptonemal Complex

Throughout meiotic prophase chromosomes adopt an extended conformation and tend to be well separated from each other – this distinctive organization enabled early cytologists to trace individual chromosomes and to directly observe the process of pairing and synapsis [39]. Work in *C. elegans* has revealed that PC activity promotes this elongated chromosome conformation [27]. In addition, a major driver of chromosome remodeling at meiotic entry is the morphogenesis of a linear core of proteins, known as the axial element (AE) [40] (Figure 2a). Appearance of the AEs is a prerequisite for several key events of meiotic prophase, including homolog pairing, synapsis, and the formation of DSBs.

In most organisms, homolog pairing during meiosis culminates with SC assembly, which stabilizes pairing. Ultrastructural studies have shown that the SC resembles a ladder or zipper, with transverse filaments (TFs) that appear to bridge the AEs of paired chromosomes within the ‘central region’ of this structure [41] (Figure 2b). Axes assemble prior to and independently of homolog pairing [40], while central region proteins normally load only between properly paired homologs (Figure 2a).

AEs contain both canonical mitotic cohesins and additional complexes containing meiosis-specific subunits. They also contain meiosis-specific members of the “HORMA” domain protein family (named for three budding yeast proteins: AE component *Hop1*, translesion DNA synthesis factor *Rev7*, and the spindle-assembly checkpoint protein *Mad2*, which share this domain) [42]. Mammals express two meiotic paralogs (*Hormad1* and *Hormad2*) [43], and *C. elegans* has four such proteins (*HIM-3* and *HTP-1*, -2 and -3) [44, 45].

HTP-3 is required for loading of the other HORMA domain proteins and meiosis-specific cohesin complexes, placing it upstream in the axis assembly hierarchy [46, 47]. The *htp-3* mutant phenotype illuminates the diverse roles of AEs: homologs do not pair, central region proteins do not load, the nuclear reorganization that normally accompanies pairing and synapsis does not occur, and DSBs are either not initiated or greatly reduced [46, 47]. HTP-3 interacts with other AE components, with the DSB-promoting MRE-11/RAD-50 complex [46, 48], and the cohesin regulator LAB-1 [49], poising it to regulate and coordinate diverse functions. Loss of HIM-3 results in similar defects in pairing and synapsis, but HIM-3 is not required to initiate recombination [50]. Loss of HTP-1 results in aberrant loading of TFs between nonhomologous chromosomes. However, loss of both HTP-1 and -2 abrogates SC formation to the same degree as null mutations in *him-3*, suggesting that HTP-2 can partially support the same function(s) as HTP-1, consistent with their high degree of homology [44, 45]. Loss of HTP-2 alone does not markedly disrupt meiosis, but results in a slightly elevated rate of chromosome nondisjunction [51].

The molecular composition of the SC central region in some organisms is relatively simple – for example, only one component, Zip1, has been identified in budding yeast [52]. By contrast, *C. elegans* expresses 4 smaller proteins (SYP-1, -2, -3 and -4) that are mutually dependent for SC assembly [6, 8, 53-55]. TF proteins typically contain extensive coiled-coil domains, but otherwise SC components show evidence of rapid sequence divergence.

SC assembly usually requires two closely aligned axes (Figure 2a). Normally this “substrate” occurs only between paired homologous chromosomes, but under atypical conditions, SCs can form between axes in other configurations. For example, when all PC proteins are absent, chromosomes fail to pair but they undergo extensive “fold-back” synapsis, in which TFs assemble between the “arms” of individual chromosomes [26]. Super-resolution analysis of *hal-2* mutants indicated that TFs proteins load onto individual, unpaired axes [56]. Similar defects were also observed in animals with a small C-terminal truncation of the TF component SYP-3 [57]. Loss of the meiotic cohesin subunit REC-8 results in abnormal TF loading, likely between sisters ([49] & our unpublished observations), as seen in mice [58]. This likely reflects a defect in sister chromatid cohesion such that each chromatid forms a separate axis.

In *C. elegans*, COs occur only between synapsed homologous regions [8]. The SC holds homologous sequences in proximity to each other, but this is unlikely its only role in CO formation since homologous PCs remain associated for much of prophase even without synapsis, and other regions also undergo transient synapsis-independent homologous interactions, but these interactions do not yield COs [13, 27, 59]. The dependence of COs on synapsis, together with the assembly behavior of the SC in *C. elegans*, ensures that COs can only occur between homologous regions linked in *cis* to homologous PCs, minimizing the potential for chromosome rearrangements. These meiotic features have likely contributed to the extraordinary stability of the nematode karyotype during evolution: only a single translocation differentiates the karyotypes of *C. elegans* and *Pristionchus pacificus*, whose lineages diverged more than 200 million years ago [60].

Despite the near-ubiquity and structural conservation of the SC among eukaryotes (Figure 2b), little is known about the mechanism or dynamics of its assembly in any organism [41]. A combination of Y2H analysis and EM localization in *C. elegans* led to a proposed structure in which most of the ~100nm between the two AE axes is spanned by a head-to-head dimer of SYP-1, abutted on its sides by SYP-3 proteins [55]. However, it remains unclear how this structure assembles, and how it interacts with the axial components.

Some insight into SC assembly and function may be gleaned from the widespread phenomenon of synaptic adjustment, which in worms can be observed in animals carrying chromosomal rearrangements. In animals heterozygous for reciprocal translocations, synapsed chromosomes can differ in size by 20% or more, yet no overhanging regions of asynapsed AEs are observed at either end [13] (Figure 2c). This implies that their axes are differentially compacted so as to equalize their length. Similarly, in males carrying an *X;IV* chromosome fusion, the single fusion chromosome initially synapses with the normal copy of chromosome *IV*, but as meiosis progresses, the SC extends into the *X* chromosome (Figure 2d, left) [61]. These observations suggest that the building blocks of the SC are driven towards a configuration that minimizes the extent of asynapsed AEs, even at the cost of juxtaposing nonhomologous regions. They also suggest that the SC is not a static structure, but can be remodeled throughout prophase, as was recently documented in budding yeast [62]. These properties of the SC may underlie another enigmatic phenomenon: the regulation of CO number and distribution (see Box 1).

At the end of pachytene the SC disassembles, and the chromosomes undergo dramatic condensation in preparation for the first meiotic division [14]. The single CO acts as a focal point for these rearrangements, partitioning each chromosome into two domains: the short arm, where cohesion will be released at anaphase I, is eventually directed to the spindle I equator, and the long arm, along which chromatids remain associated until their separation in meiosis II. ZHP-3, a RING finger protein orthologous to budding yeast Zip3 and mammalian RNF212, and the recently identified COSA-1 protein, are important for this transition [63, 64]. SC components are asymmetrically distributed to these two domains: TF proteins and ZHP-3 become restricted to the short arms, while HTP-1/2, LAB-1, and REC-8-containing cohesins are maintained along the long arms [51, 63, 65]. Targeting of the Aurora B kinase AIR-2 to the short arm and GSP-1 and -2 (PP1 phosphatases that oppose AIR-2 activity) to the long arm depend on the activity of LAB-1 [49].

Here we have described many of the key players that remodel chromosomes during meiosis in *C. elegans* to achieve faithful segregation of homologous chromosomes. Most of these components have orthologs or functional counterparts in other eukaryotes, but interesting evolutionary variations, such as the emergence of PCs, have occurred within the nematode lineage. Most of the key building blocks of the SC have likely been identified, and a key area for future studies will be to understand how their interactions are regulated. It is certain that the dynamics of axis morphogenesis, SC assembly and disassembly, and the access of the meiotic recombination machinery to chromosomes are controlled through myriad posttranslational events. Progress in this area will be accelerated by new approaches, including refined methods for introducing transgenes into *C. elegans*, additional genome editing technologies, ultrastructural methods, and *in vivo* imaging.

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Box 1**Synaptonemal Complex and Crossover Interference**

In most species, each chromosome pair undergoes at least one meiotic CO – termed the “obligate crossover” – but the total number of COs is far too low to ensure one per chromosome by a Poisson process. When more than one CO occurs on a chromosome, they are spaced farther apart than would be expected based on independent occurrence. This phenomenon, termed ‘crossover interference,’ indicates that formation of a CO acts in *cis* to inhibit other COs, and is likely related to the mechanism ensuring an obligate crossover [66, 67]. In *C. elegans*, where there is normally only one CO per chromosome pair, the inhibitory effect acts robustly over the entire length of each chromosome [14, 68]. The SC was long considered a prime candidate to mediate CO interference, based on the absence of interference in some budding yeast mutants lacking SC [69], and on phylogenetic correlations: the fungi *A. nidulans* and *S. pombe* lack both SCs and CO interference [70, 71]. Evidence of non-random distribution of synapsis initiation sites in budding yeast mutants lacking SCs seems to negate this idea [72], but the debate about the role of the SC in crossover regulation is far from resolved [18]. One possibility is that the act of crossover commitment allows the SC to rapidly attain a ‘lower-energy’ state that is no longer compatible with crossover formation. However, it remains possible that the signal for interference is propagated through other chromosomal elements, rather than the SC [66].

Figure 1. PC dynamics

(a) The *C. elegans* karyotype (adapted from [16, 17]). PCs are marked in blue. PC proteins are indicated by colored spheres.

(b) PCs conscript the SUN/KASH bridge to initiate chromosome movements (adapted from [26]). (Top) Upon meiotic entry the PC proteins (dark yellow) recruit PLK-2 (magenta). The SUN/KASH proteins SUN-1 (orange) and ZYG-12 (green) are dispersed throughout the NE. (Bottom) PLK-2-dependent phosphorylation of SUN-1 and aggregation of the SUN/KASH bridge allows engagement of dynein (pink) and microtubules (red) to generate PC-led chromosome motions.

(c) Tracking PC motion in live cells (from [2]). Selected projections from a time-lapse movie showing a nucleus with six ZYG-12::GFP patches, which mark PCs (top), and overlays of the segmented patches (bottom). (Right) Colored tracks indicate all the steps for each patch over a 2-min time course.

Figure 2. SC structure and dynamics

(a) Diagram of structural changes occurring during synapsis. (Left) AEs (green) assemble independently on each homolog (chromatin loops shown in blue). (Right) TFs (red) assemble only between homologs.

(b) Transmission electron micrograph of SC from *C. elegans*. The ladder- or zipper-like structure of the central region is clearly visible (adapted from [6]).

(c) Synaptic adjustment of heterozygous translocations (adapted from [13]). (Top) In wild-type animals, the homologous copies of chromosome III (teal) synapse (PCs, yellow; SC, red). (Bottom) The translocation *eT1* attaches a large fragment of chromosome V (orange) to the non-PC end of chromosome III, resulting in a fusion chromosome >20% larger than chromosome III. Upon synapsis in animals heterozygous for *eT1* (right), asynapsed AE regions are not observed at the ends of the SCs.

(d) Synaptic adjustment in spermatocytes carrying *mnT12*, which fuses the X chromosome (purple) to chromosome IV (blue) (adapted from [61]). In early stages of synapsis, the SC spans chromosome IV (left), but during synaptic adjustment the SC extends into the X chromosome (right).