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Centromere pairing – tethering partner chromosomes in meiosis I

Emily L. Kurdzo and Dean S. Dawson

Program in Cell Cycle and Cancer Biology, Oklahoma Medical Research Foundation, and Department of Cell Biology, University of Oklahoma, Health Science Center, OK, USA

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Correspondence
D. S. Dawson, Program in Cell Cycle and Cancer Biology, Oklahoma Medical Research Foundation, and Department of Cell Biology, University of Oklahoma, Health Science Center, Oklahoma City, OK 73104, USA
Fax: +405-271-7312
Tel: +405-271-8192
E-mail: dawsond@omrf.org

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In meiosis, homologous chromosomes face the obstacle of finding, holding onto and segregating away from their partner chromosome. There is increasing evidence, in a diverse range of organisms, that centromere–centromere interactions that occur in late prophase are an important mechanism in ensuring segregation fidelity. Centromere pairing appears to initiate when homologous chromosomes synapse in meiotic prophase. Structural proteins of the synaptonemal complex have been shown to help mediate centromere pairing, but how the structure that maintains centromere pairing differs from the structure of the synaptonemal complex along the chromosomal arms remains unknown. When the synaptonemal complex proteins disassemble from the chromosome arms in late prophase, some of these synaptonemal complex components persist at the centromeres. In yeast and *Drosophila* these centromere-pairing behaviors promote the proper segregation of chromosome partners that have failed to become linked by chiasmata. Recent studies of mouse spermatocytes have described centromere pairing behaviors that are similar in several respects to what has been described in the fly and yeast systems. In humans, chromosomes that fail to experience crossovers in meiosis are error-prone and are a major source of aneuploidy. The finding that centromere pairing is a conserved phenomenon raises the possibility that it may play a role in promoting the segregation fidelity of non-exchange chromosome pairs in humans.

Introduction

In meiosis, diploid cells duplicate their DNA and then undergo two rounds of chromosome segregation. This results in the production of haploid meiotic products. In most organisms studied, proper movement of the chromosomes away from their partners at anaphase I is dependent on the homologs first becoming tethered to one another in meiotic prophase. Homologs can become tethered in a number of ways. In prophase of most organisms, each homolog pair becomes linked by one or more chiasmata, connections between the axes of the chromosomes that occur at sites of genetic exchange, or crossovers (see accompanying minireview by Sansam and Pezza [1]; reviewed in [2]) (Fig. 1).

The linkages provided by chiasmata are critical for the segregation of chromosomes in meiosis I for three reasons. First, the tethers provided by chiasmata in conjunction with sister chromatid cohesion help partners to remain associated from prophase I, when partners are identified, until the segregation process begins (see accompanying minireview by Rankin [3]). This is

Abbreviations
CEN–CEN, centromere–centromere; SC, synaptonemal complex; UFB, ultrafine anaphase bridges.

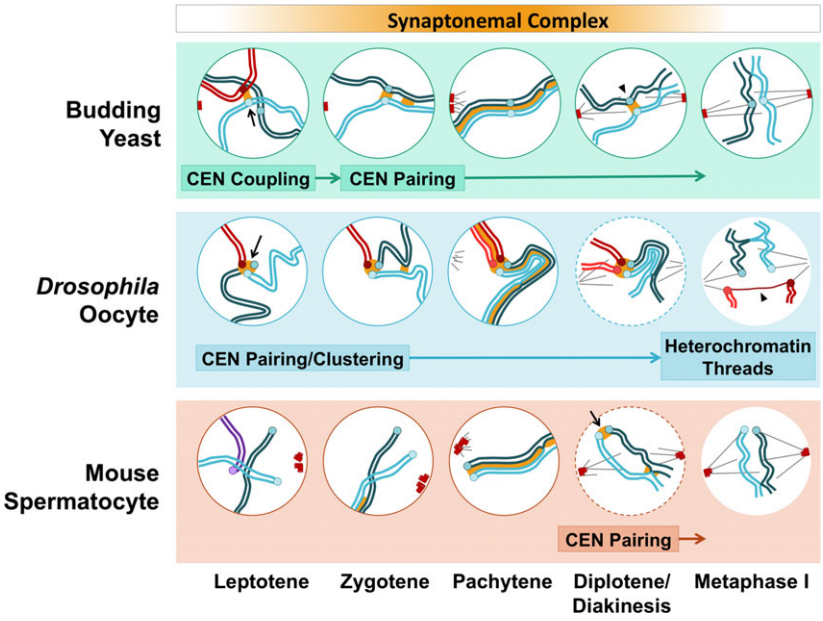

Fig. 1. Centromere behaviors in meiotic prophase in yeast, female *Drosophila* and male mouse. The synaptonemal complex (SC) proteins are implicated in the many interactions between centromeres; see text for details. The orange gradient at the top indicates the period through which SC proteins load onto and disassemble from the chromosomes, with exceptions noted in the text.

particularly important in mammalian oocytes in which the pairing (prophase) and segregation (anaphase) stages of meiosis I can be separated by years [4]. Second, tethers help prevent precocious sister chromatid separation. When there is no crossover, in fission yeast and mice oocytes, the cell reacts by splitting sister chromatids to presumably satisfy the spindle checkpoint in the absence of a partner chromosome [5–7] (see the accompanying minireview by Gorbsky [8]). Third, chiasmata contribute to the process by which the kinetochores attach to microtubules in such a way that the homologs will be pulled to the opposite rather than the same side of the spindle at anaphase I. Correct attachment of the homologous kinetochores to microtubules from opposite poles creates tension at the microtubule–kinetochore interface (Fig. 2), which in turn stabilizes the connections [9]. This tension is counteracted by the chiasmata.

These critical roles for chiasmata would predict dire consequences in meiosis for mutants that fail to form proper chiasmata. Indeed, in budding yeast and other fungi, nematodes, *Drosophila*, mice and *Arabidopsis* mutations that block the initiation of crossover formation result in sterility or greatly reduced fertility [10–20]. This infertility can be due either to the production of aneuploid gametes or to checkpoint mediated arrests in gametogenesis (see accompanying minireviews by Gorbsky [8] and Sansam and Pezza [1]).

Despite the clear importance of chiasmata in mediating pairing and segregation of homologous chromosomes in meiosis I, there are many recognized examples of organisms that partition achiasmate

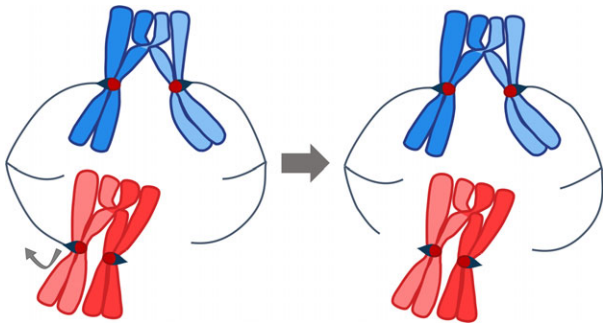

Fig. 2. Kinetochore–microtubule attachments. Bi-oriented attachment to the spindle creates tension at the kinetochore–microtubule interface and stabilizes the kinetochore–microtubule interaction (blue chromosomes). When chromosomes are only attached to one pole, or when both kinetochores are attached to the same pole (not shown), the kinetochore–microtubule attachments are not stabilized by tension. These attachments are released, which allows for a second try at bi-orientation (red chromosomes).

chromosome pairs in meiosis. How is this accomplished? In nearly all instances the achiasmate pair becomes tethered, but by a mechanism that does not involve conventional crossover and chiasma formation. There is emerging evidence (see below) that some of these mechanisms might work in conjunction with chiasma to accomplish high fidelity chromosome segregation.

Achiasmate mechanisms sometimes involve the entire chromosome set [21–23], while in some organisms only particular chromosome partners are achiasmate [24–32]. The tethering of achiasmate chromosomes can extend along entire chromosomes at designated pairing sites, as in male *Drosophila* [33], or

at unique sites on a chromosome [31,34,35]. The focus of this review is the pairing of chromosomes at their centromeres in ways that promote the segregation of achiasmate partners in meiosis I and could potentially act to improve the segregation of chiasmate chromosomes as well.

Early observations of CEN–CEN interactions

The initial observation that centromeres can actively become associated with one another was in cells at earlier stages of meiosis, before synapsis [36–45] (for review see [46,47]). Early meiotic centromere–centromere (CEN–CEN) associations were first documented in the onion *Allium fistulosum* using electron microscopy [36]. These CEN–CEN interactions were apparent to investigators because they were occurring in early stages of prophase before other types of chromosomal associations were evident. The studies showed that centromeres clustered in groups of two or a few centromeres prior to synapsis. In addition, it was found that these pairs and clusters included associations between non-homologous centromeres. Subsequent studies in wheat, yeast, rice, maize and mouse described similar associations of centromeres or associated heterochromatin [37–45]; however, in some of these organisms the CEN–CEN interactions appeared to be restricted to pairs rather than small groups. In most of these studies it was possible to determine whether the CEN–CEN interactions were between homologous partners; indeed, in every case that homology was tested, it appeared that pairing partner choice was homology independent.

The discovery of homology-independent interactions of early prophase in yeast [39] made it possible to more specifically probe the timing of CEN–CEN associations and identify pairing partners. CEN–CEN interactions were shown to occur in a homology-independent fashion that initiated in early prophase just after DNA replication (Fig. 1, budding yeast, arrow). These associations gave way to alignment of homologous centromeres later in prophase [39,40,48]. These early CEN–CEN associations, termed CEN-coupling, were found to be dependent on the synaptonemal complex (SC) protein Zip1 (Fig. 3), which was shown to localize to the coupled centromeres prior to SC assembly [39]. Hoffman, Hochwagen and colleagues have used a *zip1-S75E* coupling-deficient mutant to demonstrate that the formation of crossovers and synapsis do not depend on coupling [48]. While investigations of CEN-coupling have not revealed its function, they have demonstrated that there are mechanisms that allow the formation of persistent associations of centromeres. Furthermore, the fact that the associations are homology independent demonstrates that they depend upon centromeric chromatin rather than DNA.

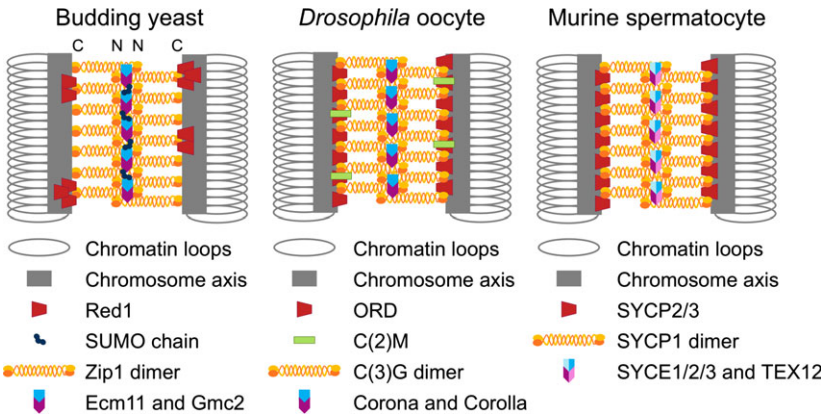

Fig. 3. Synaptonemal complex in yeast, *Drosophila* and mice. Models of budding yeast, *Drosophila* oocytes and murine spermatocyte synaptonemal complexes. The synaptonemal complex (SC) forms a bridge between the axes of the two homologous chromosomes (gray bars and loops). The lateral elements (LEs), containing the proteins indicated in red, extend along the chromosome axes (gray bars). Recent high resolution imaging suggests that in yeast Red1 is in distinct foci distributed along the axes [120]. In budding yeast SUMOylation of the Ecm11 central element protein appears to promote Zip1 assembly [68]. *Drosophila* oocyte LEs contain an additional protein, C(2)M (green), that is discontinuous along the SC. The transverse filament is depicted as an orange/yellow dimer in each species. It forms an anti-parallel tetramer zipper structure that bridges the two LEs (see N and C designation in the budding yeast diagram, indicating the N terminus and the C terminus). The central elements of each species are depicted in blue/purple. The transverse filament and central element, together, form the central region (CR). For a more detailed overview of SC structure see [63].

Discovery of CEN-pairing

A form of CEN–CEN association that occurs later in meiotic prophase, which we shall refer to as CEN-pairing, was identified by efforts to understand the basis of achiasmate chromosome segregation in *Drosophila* females. The evidence that, in an organism with meiotic crossing-over, individual chromosome pairs could be correctly segregated from one another without chiasmata was provided in 1936 from genetic studies of meiosis in *Drosophila* females [24]. This study found that in oocytes homologous X chromosomes often failed to recombine, but segregated well regardless. The same was found to be true for the fourth chromosome pair [26,27]. Nearly 50 years after the recognition of achiasmate segregation, a key genetic study suggested that the pairing of centromere proximal regions might direct the process [49]. Investigators tested the ability of an additional chromosome in the cell, a duplication chromosome composed of regions of chromosome 4, to disrupt the normally accurate segregation of the natural chromosome 4 pair. The ability of a duplication chromosome to interfere with the chromosome 4 pair correlated directly with whether it carried regions normally found in chromosome 4 pericentric heterochromatin. This and other experiments suggested to the authors that 'this chromatin may well be or contain a meiotic pairing site' [49]. This notion was confirmed by further work showing that a portion of centric heterochromatin, about 420 kb in length, conferred high fidelity segregation to mini-chromosomes [50,51]. Further, cytological experiments [34] demonstrated that achiasmate X and fourth chromosome pairs establish associations in prophase between large blocks of heterochromatin that extend outward from the centromeres. This heterochromatic pairing was shown to persist until metaphase when the chromosome pairs begin to attach to the meiotic spindle.

Studies in yeast and mice have suggested that CEN-pairing may be a conserved phenomenon. Work done in budding yeast demonstrated that chromosomes lacking chiasmata were still able to segregate away from each other in anaphase I, though not nearly with the fidelity of exchange partners or achiasmate partners in *Drosophila* females [28–30]. These studies used achiasmate centromere plasmids, homeologous chromosomes with a crossover frequency of 1 in 2500 meioses [52,53], artificial mini-chromosomes and natural non-homologous chromosome pairs to show unexpectedly high levels (~ 75–90%) of proper segregation [35,53–57]. Some of these studies went on to show that this pairing was mediated by a persistence of the SC (including Zip1) at the centromeres after SC disassembly, and this pairing was essential for achiasmate chromosomes to segregate properly [54,55]. It is important to note in the yeast experiments using *Saccharomyces carlsbergensis* or *Saccharomyces paradoxus* homeologous chromosomes that pairing partners were shown to be obligate non-exchange chromosomes; and, in fact, increasing the rate of crossovers by impairing the mismatch repair system actually increased segregation errors [52,53,56]. Whereas in *Drosophila* females the centromere pairing occurs preferentially between homologous blocks of peri-centric heterochromatin [49], in yeast CEN-pairing does not require homology of the underlying DNA sequences. Whether this difference between *Drosophila* and budding yeast reflects a mechanistic difference in the pairing mechanism is not clear at this point.

Studies with yeast have begun to explore the role of CEN-pairing in the segregation of exchange chromosomes. Zip1 persists at the centromeres of exchange chromosomes after SC disassembly and appears to mediate the pairing of homologous centromeres until prometaphase when chromosomes begin attaching to microtubules [54,55]. Elimination of Zip1 or the spindle checkpoint (*mad2*) led to modest levels of segregation errors for exchange chromosomes, but removal of both elements led to random segregation [54,55]. Although it should be noted that deletion of *ZIP1* also disrupts wild-type levels of recombination and chiasma formation [58], this result suggested that CEN-pairing may help chiasmate partners attach in a bi-oriented configuration to the spindle. By this model, in the presence of a functional spindle checkpoint, CEN-pairing might not be important as repeated cycles of attachment and detachment ultimately result in a correct attachment in most cases; but when the spindle checkpoint is non-functional, CEN-pairing is critical to promote bi-orientation. Analogous experiments with achiasmate partners suggest that Zip1 and a prophase delay caused by Mad3 act in parallel pathways to enhance the segregation of non-exchange chromosomes [54,55].

In mouse and human, centromere associations in the form of clustering were first described by Scherthan and colleagues [44]. Most of the associations described in this work appeared to be driven by attachment of the telomeres to the nuclear envelope and alignment of the chromosome arms. Subsequent studies revealed CEN-pairing in late prophase in mouse spermatocytes [59,60]. In these reports, systematic evaluation of the SC disassembly process using fluorescence microscopy revealed that after SC proteins were removed from the chromosome arms (in diplotene) they remained at the

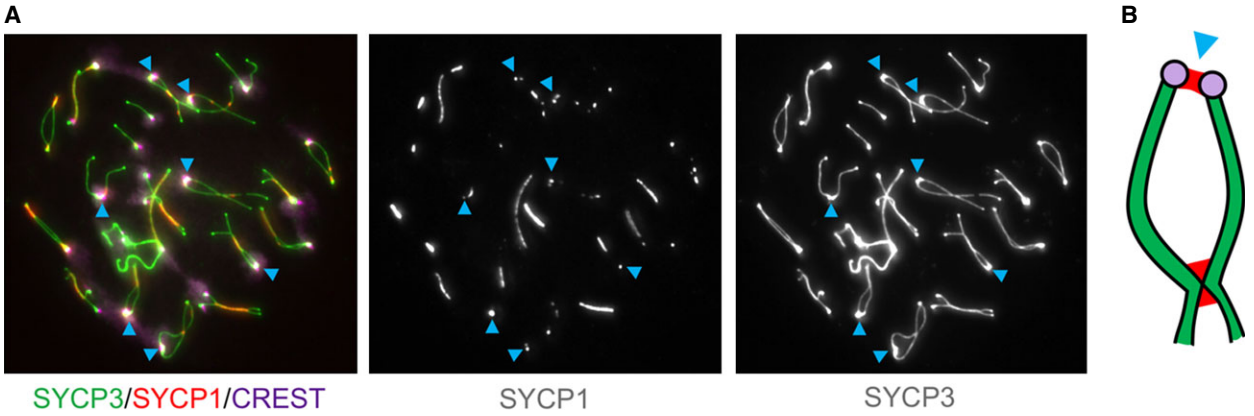

Fig. 4. CEN-pairing in mouse spermatocytes. (A) Chromosome spreads of wild-type mouse spermatocytes in the diplotene stage of meiotic prophase (see Fig. 1) (image provided by R. Pezza). SYCP3 antibody was used to label axial elements. CREST antibody was used to label centromeres. SYCP1 antibody was used to demonstrate its presence at the paired centromeres and sites of chiasmata during this stage of meiosis. Blue arrowheads indicate examples of paired centromeres on chromosomes that have disassembled most synaptonemal complex proteins from the chromosome arms. (B) A cartoon of two homologous chromosomes engaged in centromere pairing (blue arrowhead). Light purple circles represent centromeres. Green lines represent the lateral elements. Persisting SC proteins are indicated in red.

centromeres (Fig. 1, mouse, arrow, and Fig. 4). Further, the chromosomal arms could freely separate after SC removal, but the centromeres – with their associated SC proteins – remained paired. In these studies using mouse spermatocytes CEN-pairing was shown to be occurring between chiasmate chromosomes. Interestingly, studies in mouse oocytes show no detectable SC components (SYCP3) at the centromeres following exit from pachytene [61] whereas SYCP3 does persist at centromeres through meiosis I and meiosis II in human oocytes, where it has been speculated to play a role in centromere orientation [62]. While these studies reveal that CEN-pairing occurs in mammals in a manner with many parallels to what is seen in budding yeast, a number of questions persist. How widespread is this phenomenon? What are the implications for differences in CEN-pairing between spermatocytes and oocytes? Where it does exist is CEN-pairing promoting segregation of exchange chromosomes? Is CEN-pairing critical for the segregation of achiasmate partners in mammals as it is in yeast? Finally, how can SC components persist at the centromeres when it is disassembled from the arms?

What mediates CEN-pairing?

The precise structure that pairs centromeres remains to be elucidated, but genetic and cytological studies have shown that many of the same components involved in the formation of the SC are involved in CEN-pairing [54,55,59,60]. SC components were initially implicated in mediating centromere associations by the finding, described above, that Zip1 is required for efficient centromere coupling in budding yeast [39]. Subsequent experiments showed that CEN-pairing of achiasmate partners in late prophase also requires Zip1 [54,55].

To consider the roles played by Zip1 and other SC proteins in CEN-pairing, it is useful to understand the basics of SC assembly (Fig. 3). The SC is a proteinaceous structure, common to most eukaryotes, that assembles during meiotic prophase and holds together the aligned homologs (reviewed in [63]). The mature SC is a tripartite structure composed of two lateral elements and a unifying central region (Fig. 3) [64–69] (reviewed in [70]). Although the major proteins of the SC from different organisms often share little sequence homology, they share structural homology and a common function: holding together homologous chromosome axes along their entire length. The exact events that trigger SC assembly are unknown. In many organisms SC assembly initiates near sites of recombination initiation, but SC assembly does not require recombination initiation events to trigger assembly and can often be observed in recombination mutants (reviewed in [71]). In fact, in organisms such as *Drosophila* and *Caenorhabditis elegans*, SC formation precedes recombination [72–76]. In budding yeast, SC formation may initiate from both sites of recombination initiation and paired centromeres [77]. In these situations, alignment and pairing of certain chromosomal sites may promote SC assembly.

As cells exit pachytene the SC disassembles and the axes of the homologous partners are free to separate. It is at this stage that CEN-pairing can be clearly

visualized. In both budding yeast and mouse spermatocytes, the homologous centromeres remain joined at this stage (Fig. 1, yeast, arrowhead, and mouse, arrow) [54,55,59,60]. Thus in mouse chromosome spreads the axes appear tacked together at the centromeres and chiasmata (Fig. 1, mouse, arrow, and Fig. 4). In both budding yeast and mouse spermatocytes, the major transverse filament protein of the SC persists at the paired centromeres (Zip1 and SYCP1 respectively). More extended studies in mice have shown that every SC component tested (SYCP1, SYCP3, SYCE1 and TEX12; see Fig. 3) persists at the centromere [59,60] consistent with the notion that the structure holding the centromeres together, at least in mice, could be structurally similar to the rest of the SC.

In *Drosophila* females, the centromeres do not appear as discrete pairs in prophase; instead they group in one to a few clusters (Fig. 1, *Drosophila*, arrow) [78]. Upon SC disassembly, as in budding yeast and mouse spermatocytes, the Zip1/SYCP1 homolog C(3)G and the central element protein Corona (Fig. 3) persist at the clustered centromeres (Fig. 1, *Drosophila*, Diplotene/Diakinesis) [79]. Recent studies have shown that the clustering of the centromeres into one or two groups occurs in the cell divisions *before* meiotic entry and that the homologous centromeres pair prior to this clustering [80,81]. Notably, the centromere clusters, but not the homologous centromere pairs, are highly diminished in SC mutants of *Drosophila* [76,79,80]. CEN-pairing (and clustering) are dependent on the conventional cohesin subunit SMC1 and the *Drosophila*-specific cohesin components ORD, SOLO and SUNN [76,82–84]. Whether these cohesin proteins participate directly in CEN-pairing or provide an environment in which pairing can occur remains to be determined.

How is it that in mice, human oocytes, yeast and *Drosophila*, SC components at the centromere (and at the chiasmata in mouse spermatocytes [60]) are able to persist when the vast majority of SC proteins leave the chromosomes? Is the structure at the centromeres somehow fundamentally different, or is it protected from the SC removal mechanism? In both yeast and rodents there is evidence that phosphorylation of the SC by polo-like kinase homologs could trigger its disassembly [85–87]. Furthermore, both SYCP1 and SYCP3 have potential PLK1 phosphorylation sites and can be phosphorylated in meiotic cell extracts [88].

Could protection of the centromeric SC from phosphorylation explain its persistence? Notably, centromeric cohesins are removed from chromosome arms in a process that includes phosphorylation, and in meiosis I centromeric cohesins are protected from removal by the protein Shugoshin and its associated phosphatases [89–92] (see accompanying minireview by Rankin [3]). Could this same or a similar mechanism protect centromeric SC components from the phosphorylation that triggers SC disassembly? Future experiments that clarify the structure, components and disassembly regulation of the CEN-pairing apparatus will help to address these questions.

What drives CEN–CEN partner choice?

In budding yeast, centromere plasmids, artificial chromosomes and homeologous chromosomes appear to pair with one another in late prophase regardless of their degree of homology at the centromere. Experiments with these model chromosomes suggest they pair by an 'exclusion mechanism' where the last two unpaired chromosomes pair after the chiasmate chromosomes have identified and paired with their partners [35]. This CEN-pairing has been suggested to be a continuation of the homology-independent CEN-coupling that occurs in early prophase [39,48]. By this model, centromeres couple, uncouple and couple with another partner until recombination-based homology search processes identify the correct partners [48]. This would leave the last two centromeres to pair by default, regardless of their homology [54,55,93].

Although budding yeast chromosomes may be dependent on an 'exclusion mechanism', a different mechanism is at work in female *Drosophila*. Once termed 'distributive segregation', the homologous achiasmate system in *Drosophila* oocytes was once hypothesized to function under a similar mechanism in which homologs or non-homologs would pair by default if they were not engaged with a homologous partner forming a chiasma [94]. But now it is understood that X and fourth chromosome partners in *Drosophila* oocytes pair by a mechanism that depends on homologous regions of peri-centric heterochromatin. Such regions are notoriously difficult to analyze at the DNA sequence level. Despite this, a study of one peri-centromeric region, sufficient for mediating CEN-pairing, found that it contained many fragments of multiple transposable element families in addition to repeats of simple satellite sequences [95]. How CEN-pairing choice is biased by this constellation of repetitious sequences, copies of some of which are scattered on more than one chromosome, is a mystery. An interesting possibility is that it is a pattern of epigenetic marks [96] rather than the DNA sequence *per se* that confers pairing choice.

Unlike budding yeast, fission yeast has complex centromere regions that bear multiple repetitive elements.

In the absence of recombination, the chromosomes' arms no longer align in meiosis, but the centromeres are still able to pair with their homologous partners [42]. The achiasmate partners are able to segregate properly but with low fidelity [97]. Here, too, the mechanism by which CEN-pairing is mediated is not known. Studies in a number of organisms including fission yeast [98–100] have implicated centromeric-encoded RNAs, or transcription, in centromere functions such as heterochromatin formation and kinetochore protein recruitment (reviewed in [101]). Recent work revealed that RNA transcripts play a key role at a specific chromosome arm pairing site in fission yeast [100], raising the possibility that this might be a general pairing mechanism [102] that could also work at centromeres.

How could CEN-pairing promote disjunction?

How could CEN-pairing help partner chromosomes to become properly oriented on the meiotic spindle? Studies in yeast and mice suggest that initial chromosome attachments to the spindle are usually incorrect, often biased towards one pole, and usually undergo two or more bi-orientation attempts before stabilizing their attachment to the spindle [103,104]. Three models have been suggested to explain how CEN-pairing might optimize this process: the Janus model [46,54,105], the connector model, and the elastic thread model [106].

The Janus model (Fig. 5A) [54,105], named after the two-faced god of beginnings and transitions from Roman mythology, suggests that CEN-pairing locks the kinetochores in a back-to-back configuration with their microtubule attachment 'faces' looking in opposite directions. This model assumes that, in the absence of CEN-pairing, the kinetochores would have rotational freedom and their orientations relative to the spindle poles would be uncoordinated (Fig. 5A). Chromosome pairs often begin the bi-orientation process by moving towards one pole [103,104], presumably due to an initial attachment to microtubules to that pole. In mice, the pole that chromosomes are pulled toward is random, whereas in yeast the pole is usually the 'mother' spindle pole body. This pulling towards one pole would serve to rotate the chromosome so that the opposite kinetochore face would be oriented towards the opposite pole. Observations of centromere pairs in many organisms show that, once they are actively moving on the spindle during the bi-orientation process, the centromeres are well separated and not

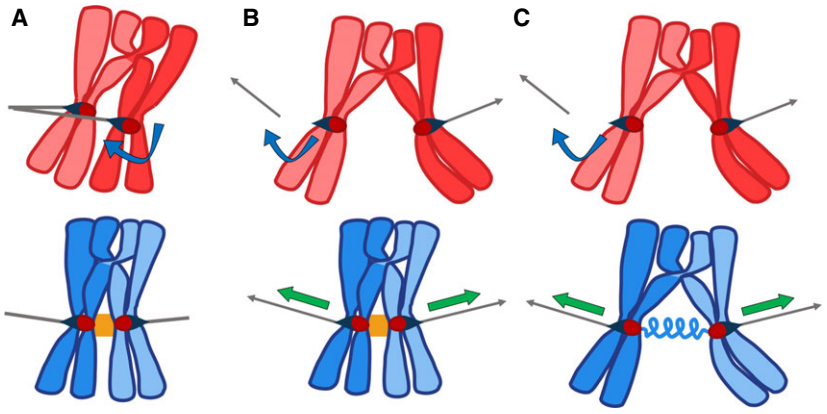

Fig. 5. Three models for CEN-pairing. (A) The Janus model. By this model, in the absence of CEN-pairing (red chromosomes), kinetochores have rotational freedom (blue arrow). This would allow both the kinetochores to attach to the same pole. CEN-pairing (orange block between centromeres of blue chromosomes) would lock the kinetochores together such that their microtubule attachment 'faces' are oriented away from one another, optimizing the chance that, if one kinetochore attaches to one pole, its partner kinetochore will be facing towards microtubules emanating from the opposite pole. (B) The centromere connector model. By this model, in the absence of CEN-pairing (red chromosomes), the chromosomes with a distal crossover would not be able to generate tension at the kinetochore–microtubule interface necessary to stabilize kinetochore–microtubule connections. CEN-pairing (orange block between centromeres of blue chromosomes) would hold the centromeres together, allowing opposing poleward forces to generate tension (green arrows) when a bipolar attachment is made. (C) The elastic thread model. In this model, similar to the centromere connector model, CEN-pairing promotes bi-orientation by providing a means for bi-oriented centromeres to generate tension (green arrows) when opposing kinetochore–microtubule connections are formed. Here, CEN-pairing does not hold centromeres together at the time of bi-orientation, but instead provides an environment in which chromatin from the two chromosomes becomes connected (symbolized by the blue spring between centromeres). By this model, direct CEN-pairing can be lost prior to the microtubule attachment process. Instead, the partner centromeres remain joined by a chromatin bridge – even in the absence of a crossover.

back-to-back. This is true in both mouse spermatocytes [59,60] and yeast (E.L.K. unpublished and [104]). Thus, this mechanism would seem to mainly optimize the chance that the *initial* microtubule attachments are correct.

The connector model (Fig. 5B) suggests that CEN-pairing acts as a connection between the centromeres over which tension can be transmitted (like chiasmata do at chromosome arms). Kinetochore–microtubule attachments that are under tension – because they are pulling against a kinetochore that is attached to a microtubule from the opposite pole – are more stable than attachments without tension (Fig. 2; reviewed in [9,107]). In meiosis, that tension must be provided across a chiasma or another connection. By this model, CEN pairing would provide that bridge. As in the previous model, the fact that homologous centromeres are often well separated in the bi-orientation process suggests that this mechanism could only work early on, prior to disengagement of the paired centromeres.

The elastic thread model has been suggested by recent work in female *Drosophila* which indicates that achiasmate (and perhaps chiasmate) partners are connected during the bi-orientation process by some sort of chromatin thread (Fig. 1, *Drosophila*, arrowhead, and Fig. 5C) [106]. By this model, CEN-pairing does not act directly to mediate bi-orientation in prometaphase. Instead, CEN-pairing in prophase acts to provide an environment in which chromatin connections can be established between the partner centromeres. It is this chromatin bridge, not the direct CEN-pairing, which then promotes bi-orientation. An elastic bridge could promote bi-orientation by transmitting tension signals or by keeping the pair in physical proximity.

In *Drosophila* females the achiasmate chromosome partners do not immediately become bi-oriented when the centromeres separate. Instead the chromosomes oscillate on the spindle before becoming bi-oriented [106]. A significant portion of the separated partners could be shown to be connected by nearly imperceptible chromatin threads (technical limitations made it impossible to determine whether every pair is joined by a thread). The notion of connections between separated meiotic partners is not a new one (see [108] and references within), and in fact these mysterious connections have been shown to have elastic properties that pull the partners towards one another. A significant development is that the most recent report [106] identifies the threads as containing peri-centromeric DNA sequences. These meiotic threads of peri-centric heterochromatin should not be confused with the ultrafine anaphase bridges (UFBs) observed in mitotic cell lines [109–112]. The mechanism of UFB formation, though still unclear, has been hypothesized to be from collapsed replication forks or DNA repair mechanisms and the UFBs are marked by proteins implicated in these processes [109–112]. In meiotic cells, the connections are between homologous partners and not sister chromatids [106]. Some of the unanswered questions regarding these threads surround their formation and components. How are the threads formed? Meiotic centromeres are rich in topoisomerase II and cohesin proteins (see review by Rankin [3]; [113–115]). Could topoisomerase, cohesins or some form of non-crossover recombination or DNA repair mechanism mediate the formation of inter-homolog connections? What mechanisms are required to dissolve the connections without causing unintended DNA damage? A recent study of *Drosophila* oocytes has shown that in the absence of topoisomerase II heterochromatin threads persist between separating homologous partners in meiosis I, blocking their segregation, suggesting the model that the threads between homologous centromeres are due, at least in part, to catenation [106].

The behavior of Zip1/SYCP1 at centromeres is consistent with a role in providing an environment hospitable to the formation of CEN–CEN connections, while not directly acting in the bi-orientation process. In budding yeast Zip1 is necessary for CEN-pairing between achiasmate partners and their subsequent disjunction. But the majority of Zip1 has left the paired centromeres before the bi-orientation process begins [54,55]. Similarly, in mouse spermatocytes, SYCP1 is present at paired centromeres in early diplotene and is necessary for CEN-pairing, but it is not detectable at paired centromeres in late diplotene [59,60]. Further, once the mouse centromeres begin to separate, they seem to be joined by bridges containing the axis component SYCP3 [60]. SYCP3 also persists at the centromeres into meiosis I in human oocytes [62], but studies that might detect SYCP3 between the centromeres of separating homologous partners have yet to be reported.

Conclusion

There is growing evidence that CEN–CEN interactions are not only a conserved phenomenon but serve an important role in promoting the fidelity of meiotic chromosome segregation. *Drosophila*, yeast and mouse have proved to be valuable model organisms to study the way in which CEN-pairing occurs and its impacts on the behavior of chromosomes. This is especially true for achiasmate partners. In humans, the mis-segregation of chromosomes that failed to establish

chiasmata is a major cause of spontaneous abortion and aneuploidy-based syndromes [4]. The smallest chromosomes (21 and 22) fail to experience crossovers in about 5% of meioses [116–118] yet are estimated to non-disjoin in fewer than 1% of meioses [117–119], suggesting that in there may be factors beyond chiasmata that promote the segregation of homologous partners in human cells. Future studies of CEN-pairing will probably reveal new general principles for meiotic chromosome behavior and may well have implications for human health.

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Author contributions

Emily Kurdzo prepared the first draft of this review. Emily Kurdzo and Dean Dawson worked together to edit, and revise the document to produce the final manuscript.

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