

## Complex regulation of sister kinetochore orientation in meiosis-I

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Kinetochore mediate chromosome movement during cell division by interacting with the spindle microtubules. Sexual reproduction necessitates the daunting task of reducing ploidy (number of chromosome sets) in the gametes, which depends upon the specialized properties of meiosis. Kinetochore have a central role in the reduction process. In this review, we discuss the complexity of this role of kinetochores in meiosis-I.

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### 1. Introduction

Sexual reproduction in diploid eukaryotes is intimately associated with the specialized cell division named meiosis. In mitosis, which represents the vast majority of cell divisions in the life of a eukaryote, the parent cell divides to form two daughter cells, each of which receives the same number of chromosomes as the parent cell had. In contrast, the parent cell in meiosis divides to form four daughter cells (named spores in yeast and gametes in other eukaryotes), each with half the chromosomal complements of the parent cell. This reduction occurs in a way that results in the formation of haploid cells in which every chromosome is

represented singly, from diploid cells that had two copies of each chromosome. Such specific reduction in chromosomal complements results from the specialized property of meiotic division: a single S phase is followed by two rounds of chromosomal segregation without an intervening DNA replication in between. During the first meiotic division (named meiosis-I), ‘reductional’ segregation of *homologous chromosomes* (henceforth mentioned as homologs) takes place in which the homologs move to opposite poles of the *spindle*. Meiosis-I thus implements a reduction in ploidy in the gametes. During the second ‘equational’ meiotic division (meiosis-II), the *sister chromatids* move to opposite poles.

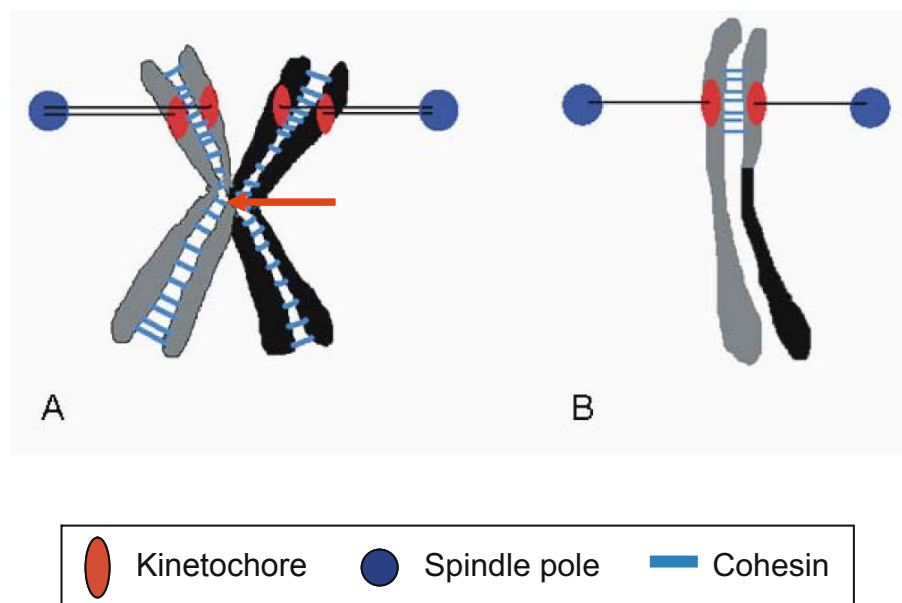
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#### Definition of terms

**Homologs:** Two copies of each chromosome present in a diploid cell. **Spindle:** The microtubular organelle that helps chromosome segregation during cell division. Spindle formation is initiated in S phase with the duplication of the spindle pole body (spb). The SPB later defines the two poles of the spindle. **Sister chromatids:** Two identical copies of DNA duplex present in each chromosome after replication in the S phase. **Kinetochore:** The large protein complex that assembles generally at a specific site (centromere) on the chromosome and interacts with spindle microtubules during cell division to aid chromosome segregation. Kinetochore assembled on sister chromatids are named sister kinetochores whereas those on the homologs are named homologous kinetochores. **Cohesion:** The physical link established between sister chromatids during DNA replication. The proteins that establish cohesion are named as cohesins. **Centromere:** The chromosomal site at which the kinetochore assembles. Budding yeast centromeres consist of a 125 bp core DNA whereas fission yeast centromeres span several kilobases of DNAs. Animal and plant centromeres are much larger and consist of megabases of DNAs. **Tension:** Tension is created when sister kinetochores (in mitosis and meiosis-II) or homologous kinetochores in a bivalent (meiosis-I) capture microtubules from opposite poles of the spindle. Tension plays an essential role in accurate chromosome segregation. **Spindle assembly checkpoint (SAC):** A surveillance mechanism that monitors correct kinetochore–microtubule interaction in mitosis and meiosis. Incorrect interaction leads to activation of the checkpoint that delays the execution of chromosome segregation at anaphase. The checkpoint inhibits an activator of anaphase, the anaphase promoting complex (APC). When SAC is satisfied owing to biorientation of all kinetochores (homologous in meiosis-I and sisters in meiosis-II), APC activates an enzyme named separase that cleaves cohesin allowing poleward movement of the chromosomes. **Metaphase:** The stage in cell division when all chromosomes establish bipolar attachments at the equator of the spindle (mitotic or meiotic) and are prepared to undergo anaphase segregation.

Reductional segregation of the homologs in meiosis-I is achieved by the interplay of several functions (for recent reviews, see Petronczki *et al.* 2003; Watanabe 2006; Brar and Amon 2008). These are: (i) configuration of the *kinetochores* (the subject of the present article); (ii) recombination between the homologs, which creates a physical link (named *chiasmata*) between them; and (iii) *cohesion* between the sister chromatids, which helps maintain the chiasmata and locks the two homologs as a unit (named *bivalent*) until the homologs segregate from each other (figure 1). All of these features act in a manner that helps the *homologous kinetochores* capture microtubules from opposite poles of the spindle (this attachment is called *bipolar attachment*). When homologous kinetochores in a bivalent establish bipolar attachment in the meiosis-I spindle, it generates *tension* owing to the opposite poleward forces exerted on the kinetochores, which are counteracted by the chiasmata. This tension in turn helps to stabilize the bipolar orientation (bipolar orientation and biorientation will be used synonymously in this article) of the bivalents (reviewed by Nicklas 1997). When every bivalent establishes bipolar orientation in the spindle, cohesin along the chromosome arms is removed by proteolysis (Buonomo *et al.* 2000; Kudo *et al.* 2006, 2009). This unlocks the bivalents and enables the reductional segregation of the homologs. The highly conserved aurora B kinase (Ipl1p in budding yeast; fission yeast has a single aurora kinase, Ark1), shugoshin and components of the *spindle assembly checkpoint* play roles in this process (Shonn *et al.* 2000,

2003; Bernard *et al.* 2001; Hauf *et al.* 2007; Kawashima *et al.* 2007; Lacefield and Murray 2007; Monje-Casas *et al.* 2007; Yu and Koshland 2007). Aurora B kinase plays a particularly important role in reductional segregation, a role that is fundamentally shared between the mitotic and meiotic divisions. When homologous kinetochores in a bivalent do not capture microtubules from the opposite spindle poles, no tension is generated. In such an instance, aurora B kinase destabilizes the kinetochore–spindle interactions until the homologous kinetochores establish bipolar attachment (Hauf *et al.* 2007; Monje-Kasas *et al.* 2007). Until recently, it was not clear why the attachments are not destabilized once bipolarity is established. Experiments done with mammalian mitotic cells suggest that the establishment of bipolar attachment and the consequent tension might sequester the kinetochore substrate(s) from aurora B kinase (Liu *et al.* 2009; also see Kelly and Funabiki 2009; and Liu and Lampson 2009 and references therein for alternative mechanisms). Kinetochore–microtubule interaction is regulated by a balance between the opposing effects of aurora B kinase and protein phosphatase I on the substrate(s) at the kinetochores (Francisco *et al.* 1994; Pinsky *et al.* 2006; Akiyoshi *et al.* 2009). It seems probable, at least partly, that spatial separation of the kinetochore substrate(s) from aurora B upon biorientation (Liu *et al.* 2009) shifts the balance toward dephosphorylation of the substrate(s) which, in turn, stabilizes the attachments (Keating *et al.* 2009). It remains to be examined whether this mechanism operates in meiosis. Immunolocalization data in mouse meiosis,



**Figure 1.** Diagram of kinetochore orientations in (A) meiosis-I and (B) meiosis-II. (A) A bivalent linked at the chiasmata (red arrow). Note that the sister kinetochores are oriented toward the same pole of the spindle while the homologous kinetochores are oriented toward the opposite poles. (B) One of the two chromosomes derived from the bivalent is shown. Sister kinetochores are oriented toward the opposite poles. Note that a pool of cohesin persists around the centromere; this helps bipolar orientation of sister kinetochores in meiosis-II.

however, are apparently inconsistent with this model (Parra *et al.* 2003, 2006).

The configuration of the sister kinetochores plays an important role in determining the specific pattern of chromosome segregation during the two meiotic divisions (figure 1). Sister kinetochores are oriented toward the same spindle pole during the first meiotic division. This orientation of the sister kinetochores is called co-orientation or monopolar orientation (monopolar orientation and mono-orientation will be used synonymously). In contrast to their monopolar orientation in meiosis-I, sister kinetochores establish bipolar orientation in meiosis-II, in which they are directed toward the opposite spindle poles. The present article reviews the current understanding of how monopolar orientation of the sister kinetochores is established in meiosis-I, primarily using information obtained over the past decade from two unicellular model eukaryotes, the budding yeast *Saccharomyces cerevisiae* and the fission yeast *Schizosaccharomyces pombe*. Reference from multicellular organisms will be drawn when necessary.

The proteins known to be involved in the establishment of monopolar orientation are summarized in table 1.

## 2. The monopolin complex and Moa1

### 2.1 The monopolin complex

In budding yeast, several screens from the laboratory of Kim Nasmyth have identified a protein complex named monopolin as the major determinant of sister kinetochore mono-orientation in meiosis-I. Since monopolar orientation of sister kinetochores is a property unique to meiosis, Toth *et al.* (2000) reasoned that protein(s) determining this could be meiosis-specific. They screened a collection of yeast strains, each of which had a deletion of a specific gene that expressed only in meiosis (and not in mitosis). This strategy identified Mam1p as the first protein essential for mono-orientation of sister kinetochores. In normal meiosis-I, sister kinetochores mono-orient in the spindle. This leads to segregation of sister

**Table 1.** Proteins required for mono-orientation of sister kinetochores in meiosis-I

Component	Budding yeast	Fission yeast	Plant	Mammal	Function
Monopolin complex and Moa1 <sup>1-6</sup>	Monopolin is a complex of 4 proteins: Mam1p, Csm1p, Lrs4p, Hrr25p. All are essential for mono-orientation	Moa1 is functional equivalent of Mam1p and essential for mono-orientation. Pcs1 (ortholog of budding yeast Csm1p) is dispensable for mono-orientation	Mam1p orthologs unidentified	Mam1p orthologs unidentified	Monopolin complex: Possible fusion of sister kinetochores yielding a single functional kinetochore for microtubule capture Moa1: Side-by-side orientation of sister kinetochores enabling microtubule capture from the same spindle pole
Spo13p <sup>7-8</sup>	Required	Ortholog unidentified	Ortholog unidentified	Ortholog unidentified	Promotes localization of monopolin to meiotic kinetochores
Rec8 <sup>1, 5, 9-11</sup>	Not essential	Essential	Essential	The mitotic version, RAD21, is implicated	In fission yeast, promotes side-by-side orientation of sister kinetochores in Moa1-dependent manner
Cohesion regulators <sup>5</sup>	Not determined	Required	Not determined	Not determined	Function in Moa1-dependent manner
Aurora kinase <sup>6,12,13</sup>	Not required	Ark1 represents a minor pathway	Not determined	Inhibition of aurora B caused chromosome alignment defect in meiosis-I	Ark1 corrects merotelic attachment
Synaptonemal complex protein <sup>11, 14-15</sup>	Zip1p required	Not determined	Not determined	SCP3 implicated.	Zip1p likely delays/prevent biorientation of sister kinetochores

References: 1. Toth *et al.* 2000; 2 and 3. Rabitsch *et al.* 2001, 2003; 4. Petronczki *et al.* 2006; 5. Yokobayashi and Watanabe 2005; 6. Monje-Casas *et al.* 2007; 7. Katis *et al.* 2004; 8. Lee *et al.* 2004; 9. Sakuno *et al.* 2009; 10. Chelysheva *et al.* 2005; 11. Parra *et al.* 2004; 12. Hauf *et al.* 2007; 13. Shuda *et al.* 2009; 14. Bardhan and Dawson, unpublished; 15. Moens and Spyropoulos 1995.

chromatids to the same pole upon completion of meiosis-I (*see earlier*). Deletion of *MAM1* resulted in biorientation of sister kinetochores in metaphase-I. Pericentromeric meiotic cohesin Rec8p is normally not removed during meiosis-I and holds sister centromeres together (*see later*). Therefore, despite being bioriented in meiosis-I in *mam1* deletion, sister chromatids could not segregate to opposite poles. Instead, they halted in the meiosis-I spindle and segregated to opposite poles only when the pericentromeric Rec8p was removed during meiosis-II (Toth *et al.* 2000). Mam1p therefore constrained sister kinetochores to mono-orient in meiosis-I.

Rabitsch *et al.* (2001) undertook a different approach to identify additional proteins required for mono-orientation of sister kinetochores. Deletion of the gene *SPO12* in budding yeast leads to a single division meiosis-I in which some chromosomes segregate reductionally as in meiosis-I, whereas others segregate equationally as in meiosis-II, leading to a reduction in viability of the spores. Deletion of the gene *SPO11* in a background of *spo12* deletion causes complete lack of viability of the spores in a *MAM1*-dependent manner, probably because both the sister chromatids co-segregate to the same spore due to mono-orientation of the sister kinetochores (Rabitsch *et al.* 2001). Since diploid budding yeast has sixteen pairs of chromosomes, this resulted in all the spores lacking copies of one or more chromosomes, thereby causing inviability. Using transposon mutagenesis to identify mutants that would rescue *spo11 spo12* spore inviability, the group identified two genes, *CSM1* and *LRS4*, which are essential for mono-orientation. Co-immunoprecipitation and other biochemical experiments demonstrated that Mam1p, Csm1p and Lrs4p are part of the same protein complex named monopolin (Rabitsch *et al.* 2001). Unlike Mam1p, which expresses only in meiosis, Csm1p and Lrs4p are nucleolar proteins and express also in mitosis (Rabitsch *et al.* 2003; Johzuka and Horiuchi 2009). During most of meiosis, Csm1p and Lrs4p localize to the nucleolus and only transiently associate with kinetochores during meiosis-I (Rabitsch *et al.* 2003). The association of these three proteins with kinetochores is interdependent. Subsequently, a proteomic approach (Petronczki *et al.* 2006) revealed that an ortholog of a highly conserved casein kinase, Hrr25p, is also an essential component of the monopolin complex (*see later*).

## 2.2 How monopolin works

How the monopolin complex establishes mono-orientation is not well understood. Monopolin does not do so by interfering with Ipl1p enzyme activity (Monje-Casas *et al.* 2007). One possible scenario is structural fusion of sister kinetochores, which generates a single functional kinetochore for microtubule capture (Toth *et al.* 2000;

Monje-Casas *et al.* 2007). This model gained credence from the fact that localization of the monopolin complex to mitotic kinetochores imposes co-segregation of sister chromatids to the same spindle pole in mitosis and partially overrides a nocodazole (a microtubule destabilizer) induced mitotic arrest (Monje-Casas *et al.* 2007). Further, in a background of *spo11* deletion (which abolishes bivalent formation and generates a mitosis-like chromosome configuration in meiosis-I), Mam1p prevents segregation of sister chromatids to opposite poles in meiosis-I, even when Rec8p is replaced by Scc1p (unlike Rec8p, centromeric Scc1p can be cleaved by separase in meiosis-I, enabling sister chromatids to segregate to opposite poles if sister kinetochores biorient [Toth *et al.* 2000]), despite the presence of Ipl1p (Toth *et al.* 2000; Monje-Casas *et al.* 2007; Bardhan and Dawson unpublished). All these are in accordance with model 1. The alternate model that Mam1p ‘inhibits’ one of the two sister kinetochores in meiosis-I (Toth *et al.* 2000) requires the additional complexity of the presence of a protector molecule that would shield the other sister kinetochore from being inhibited. No such molecule has yet been identified.

## 2.3 Moa1

Mam1p orthologs have not been found in other organisms (except for the yeasts *Ashbya* and *Kluyveromyces*, Rabitsch *et al.* 2003) including fission yeast. A genetic screen in fission yeast was performed to identify genes required for monopolar orientation (Yokobayashi and Watanabe 2005). The screen utilized a single-division meiosis programme and was designed such that mono-orientation would produce largely dead spores whereas biorientation would produce largely viable spores. A fission yeast strain was genetically altered, which enabled haploids to undergo meiosis (by expressing both mating type information, Yamamoto and Hiraoka 2003) but skipped the second meiotic division (by mutating *cdc2<sup>+</sup>*, Nakaseko *et al.* 1984). Meiosis in this strain resulted in high spore inviability because of mono-orientation of sister kinetochores. Random mutagenesis of this strain was performed with the aim of identifying mutants that would produce viable spores. This strategy identified a protein Moa1 that is essential for mono-orientation in fission yeast (Yokobayashi and Watanabe 2005). Like Mam1p in budding yeast, Moa1 appears in meiotic prophase and localizes to kinetochores in the first nuclear division. However, Moa1 shares no significant homology with budding yeast Mam1p (Yokobayashi and Watanabe 2005) and there is a difference between the two proteins in their mode of action. Unlike in budding yeast, the meiotic cohesin Rec8 is essential for Moa1-dependent monopolar orientation in fission yeast (*see later*). Furthermore, fission yeast protein Pcs1, which has significant homology with the budding yeast monopolin component Csm1p and has a similar localization pattern,



is not essential for monopolar orientation (Rabitsch *et al.* 2003).

#### 2.4 Regulators of the monopolin complex

The conserved casein kinase Hrr25p (*see earlier*) that co-purifies with the monopolin complex is required for monopolin's localization at the kinetochores. Though the kinase activity of Hrr25p is essential for mono-orientation, this activity, however, is dispensable for monopolin localization (Petronczki *et al.* 2006). Hrr25p phosphorylates Mam1p but it is unclear whether this phosphorylation is important for mono-orientation or whether Hrr25p phosphorylates other substrate(s) at kinetochores that promotes mono-orientation. Two other protein kinases, Cdc5p and Cdc7p, are also required for proper localization of the monopolin complex at kinetochores (Clyne *et al.* 2003; Lee and Amon 2003; Lo *et al.* 2008; Matos *et al.* 2008).

Spo13p is yet another protein whose absence in budding yeast leads to a very high incidence of loss of sister kinetochore mono-orientation in meiosis (Katis *et al.* 2004; Lee *et al.* 2004). The gene was identified as a mutant allele that led to a single-division meiosis producing two diploid spores (Klapholz and Esposito 1980). How Spo13p promotes mono-orientation is not clear, owing partly to the diverse effects the mutation exerts in meiosis. The protein localizes to meiotic kinetochores and is required for proper localization of the monopolin complex at kinetochores (Katis *et al.* 2004; Lee *et al.* 2004). Spo13p, however, is not known to be a part of the monopolin complex. Also, mitotic expression and localization of the monopolin complex to mitotic kinetochores leads to mono-orientation of sister kinetochores in mitosis in a Spo13p-independent manner (Monje-Kasas *et al.* 2007).

### 3. Role of cohesin in monopolar orientation

Sister chromatids are physically linked together starting from their replication in S phase. This physical linkage, named sister chromatid cohesion (SCC), is mediated by protein complexes named cohesin. The cohesin complex is made up of four conserved core subunits: Smc1, Smc3, Scc1/Rad21 (Rec8 in meiosis) and Scc3 (reviewed by Ishiguro and Watanabe 2007; Onn *et al.* 2008; Peters *et al.* 2008; Skibbens 2008; Nasmyth and Haering 2009). Rec8-containing cohesin largely replaces Scc1/Rad21-containing cohesin during meiosis, and Rec8 has diverse and specialized meiotic functions. Cohesins are largely dissociated from chromosomes after *metaphase I* except for a pool of Rec8-containing cohesin around centromeres which are protected from removal by the action of other

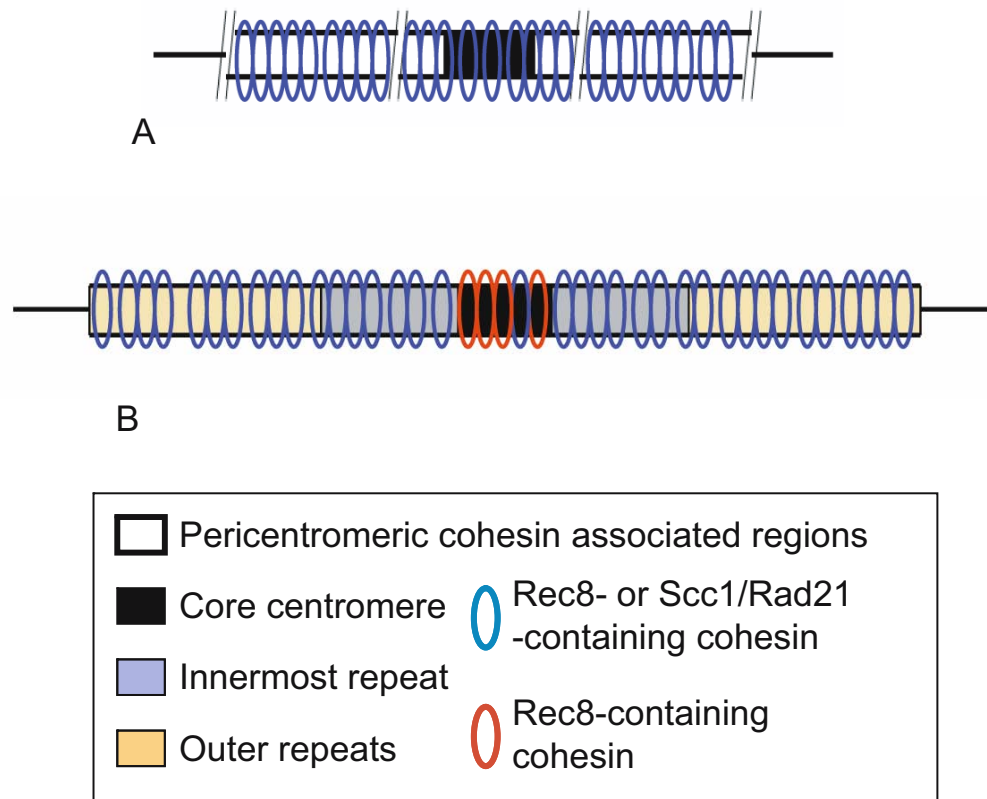
proteins (figure 1B. Discussion of this is beyond the scope of this article. Interested readers might consult Gregan *et al.* 2008 for a recent review). In budding yeast, the meiotic cohesin Rec8p is not essential for monopolar orientation of sister kinetochores. Though sister chromatids often segregate in anaphase I in the absence of Rec8p, which can be viewed as a defect in mono-orientation, this is primarily due to a high incidence of premature separation of sister chromatids in meiotic prophase (Klein *et al.* 1999; Bardhan *et al.* 2010). Accordingly, expression of the mitotic version Scc1p/Rad21 in place of Rec8p from *REC8*'s promoter completely restores monopolar orientation by restoring normal SCC (Toth *et al.* 2000). However, though meiosis-specific cohesin is dispensable for monopolar orientation, centromeric cohesion is probably a prerequisite for monopolar orientation of sister kinetochores (*see later*).

Conversely, in fission yeast, Rec8-containing cohesin and some other cohesion regulators (*viz.* Dcc1, Ctf18 and Pds5) are required for the monopolar orientation of sister kinetochores in a Moa1-dependent manner (*see earlier*) (Yokobayashi and Watanabe 2005). Individual deletions of the respective genes lead to biorientation of sister kinetochores in meiosis-I. Loss of monopolar orientation in the absence of Rec8, however, is not preceded by loss of Moa1 localization at the kinetochores. Whereas deletion of *rec8+* does not affect Moa1 binding at the centromeres, deletion of *moa1+* alters centromeric Rec8 binding. These results led the authors to propose that Moa1 promotes centromeric cohesion in a cohesin-dependent manner and this centromeric cohesion, and not Moa1 *per se*, is required for monopolar orientation (Yokobayashi and Watanabe 2005). An elegant experiment further validated the role of cohesion in mono-orientation. An artificial tether introduced between core sister centromeres rescued cohesion at this site and restored mono-orientation in the absence of Rec8 or Moa1 (Sakuno *et al.* 2009).

The difference between the two yeast situations with regard to the requirement of Rec8 for mono-orientation is perhaps not surprising. It is probably related to the difference between the structures of the respective centromeric chromatin and the manner in which cohesin binds to core centromere *vis-à-vis* pericentromeric sites (figure 2). Budding yeast has the simplest centromere known, consisting of only about 125 bp of core centromere DNA with no evidence of pericentromeric repetitive DNA (Clarke and Carbon 1980; Fitzgerald-Hayes *et al.* 1982a, b; Cottarel *et al.* 1989). Kinetochore is assembled on this 125 bp core centromere. This core centromere is essential and sufficient for accurate transmission of chromosomes into daughter cells in mitosis and meiosis (Cottarel *et al.* 1989). Fission yeast centromere, on the other hand, is more complex and is made of several kilobases of DNA (35–110 kb depending upon the chromosome) with an innermost non-repetitive

core centromere flanked by pericentric innermost and outer repeats (Pidoux and Allshire 2004, and references therein). The non-repetitive core centromere DNA assembles kinetochore but is not sufficient for accurate chromosome segregation during cell division. In fission yeast, cohesion between the innermost non-repetitive core centromeres appears to be meiosis specific and essential for monopolar orientation of sister kinetochores (*see above* and Sakuno *et al.* 2009). Whereas both Scc1/Rad21 and Rec8 can bind to pericentromeric repeats, for unclear reasons, only the Rec8- but not the Scc1/Rad21-containing cohesin binds to the core centromere DNA, generating meiosis-specific cohesion at this site (Sakuno *et al.* 2009). Loss of Rec8 in fission yeast thus leads to loss of cohesion at the core centromere and subsequent loss of monopolar orientation,

despite the presence of Moa1. Further, Rec8 can generate cohesion at the core centromere only when Moa1 is present. Rec8 expressed in mitosis (where there is no Moa1) can bind to the core centromere but is not able to generate cohesion at this site (Sakuno *et al.* 2009). In budding yeast, on the other hand, loss of Rec8p leads to premature separation of sister chromatids and expression of Scc1p/Rad21 in place of Rec8p completely restores the defective cohesion in meiosis-I, including cohesion near the core centromeres (Toth *et al.* 2000; Bardhan *et al.* 2010). The cohesins Rec8p and Scc1p/Rad21 show a similar binding pattern across the core centromere in meiosis and mitosis, respectively (Bardhan and Dawson, unpublished; Glynn *et al.* 2004; Weber *et al.* 2004). Nevertheless, sister centromeres often prematurely dissociate in the absence of monopolin despite



**Figure 2.** Schematic diagrams (not to scale) of centromeres in (A) budding yeast and (B) fission yeast and their cohesin-binding patterns. The core centromere in budding yeast has defined sequences of about 125 bp that are largely conserved among the chromosomes. The core centromere assembles kinetochore and is essential and sufficient for stable segregation of plasmid DNA (Cottarel *et al.* 1989). There are no known differences in the binding pattern of Rec8p- and Scc1p/Rad21-containing cohesins at the core centromere (Bardhan and Dawson, unpublished; Glynn *et al.* 2004; Weber *et al.* 2004). Cohesion at the core centromere is reduced in meiosis-I in the absence of monopolin (Toth *et al.* 2000). Cohesin binding in the ~50 kb pericentromeric cohesin-associated regions helps sister kinetochore biorientation in mitosis and meiosis-II. (B) The core centromere in fission yeast is made up of about 4–7 kb non-repetitive sequences that are variably shared between the chromosomes. The core centromere assembles kinetochore but is not sufficient for chromosome stability, which requires a variable amount of repetitive sequences (Pidoux and Allshire 2004 and references therein). Whereas Rec8-containing cohesin binds to the core centromere, the Scc1p/Rad21-containing cohesin is largely excluded from binding to this site and Moa1 is required for cohesion at this site (Sakuno *et al.* 2009). The innermost and outer repeats are heterochromatic and cohesin binding at these sites promotes sister kinetochore biorientation in mitosis and meiosis-II.

the presence of Rec8p, suggesting that monopolin plays a role in cohesion at the core centromere in budding yeast as well (Toth *et al.* 2000). It is possible that cohesion between the core centromeres is the primary determinant of monopolar orientation of the sister kinetochores.

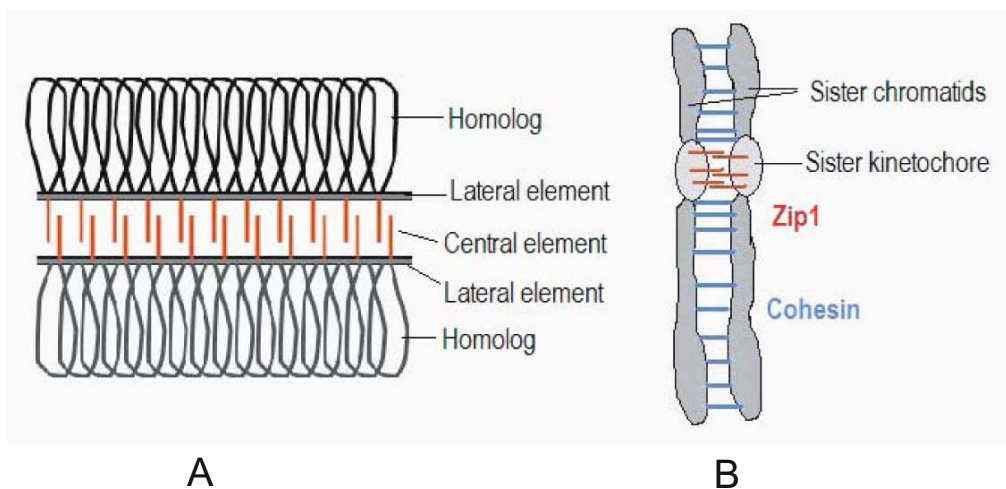
The fission yeast situation, in which Rec8 plays an essential role in mono-orientation, resembles that in plants. Similar to that in fission yeast, plant centromeres are complex and made of megabases of DNA with pericentromeric repetitive DNA. In maize and *Arabidopsis*, absence of Rec8 leads to biorientation of sister kinetochores (Yu and Dawe 2000; Chelysheva *et al.* 2005). The cohesin RAD21 in mouse has also been implicated in sister kinetochore mono-orientation (Parra *et al.* 2004). It seems probable that cohesion-dependent mono-orientation of sister kinetochores is a conserved aspect of meiotic kinetochore organization in eukaryotes, though the molecular details of its establishment might differ among organisms.

#### 4. Aurora kinase in monopolar orientation

In fission yeast, the aurora kinase Ark1 promotes mono-orientation of sister kinetochores in a Moa1- and Rec8-independent manner (Hauf *et al.* 2007). This role of Ark1 is in addition to its role in promoting homolog biorientation in meiosis-I (Hauf *et al.* 2007). Genetic experiments done by the authors suggest that this function of Ark1 represents a minor pathway and requires the spindle checkpoint protein Bub1 and the shugoshin protein Sgo2. Instead of causing complete biorientation of the sister kinetochores, however, inhibition of Ark1 leads to a more complex situation: one of

the two sister kinetochores appears to capture microtubules from both spindle poles (this attachment is called merotelic attachment). For possible kinetochore microtubule attachments, *see* figure 1 in Kelly and Funabiki 2009). This in turn leads to generation of lagging chromosomes. Ark1 therefore appears to correct merotelic attachment to promote monopolar orientation of sister kinetochores (Hauf *et al.* 2007).

In budding yeast, the aurora kinase Ipl1p promotes biorientation of homologous kinetochores in bivalents (Monje-Casas *et al.* 2007). However, as opposed to Ark1 in fission yeast, Ipl1p in budding yeast has not been shown to be involved in correction of the merotelic attachment of sister kinetochores. This difference between the two yeast situations probably stems from the difference in the number of microtubule-binding sites per kinetochore. The number of microtubules stably captured by a mitotic kinetochore seems to be related to the number of specialized CENP-A containing centromeric nucleosomes (Jogelkar *et al.* 2008). In most model eukaryotes, including fission yeast, which has a large (kilobases to megabases of DNA) centromere, each kinetochore captures multiple microtubules (2–4 microtubules per mitotic kinetochore in fission yeast, Ding *et al.* 1993). On the other hand, in budding yeast, each kinetochore assembled on the small (~125 bp) centromere DNA wrapped around a single CENP-A nucleosome captures a single microtubule in mitosis (Furuyama and Biggins 2007). The single microtubule captured by a kinetochore rules out the possibility of merotelic attachment. Ultrastructural analysis of normal meiosis-I spindle in budding yeast further indicates that a single



**Figure 3.** Zip1p in meiotic chromosome interaction. **(A)** Schematic diagram of the ultrastructure of synaptonemal complex (*see* Page and Hawley 2004, for details). Two lateral elements comprise the axes of a pair of chromosomes, one for each homologous chromosome. The central element is made of a ladder of pairs of Zip1p (in budding yeast) molecules that overlap at their N termini. **(B)** A chromosome in meiosis-I (bivalent is not shown for the sake of simplicity). In this hypothetical structure, two sister kinetochores are linked together at their respective Ndc80 complexes by pairs of Zip1p molecules, a situation analogous to the arrangement of Zip1p molecules in the SC.

kinetochore microtubule binds to a pair of sister chromatids (Winey *et al.* 2005). This analysis, however, raised further questions about the nature of kinetochore–microtubule interaction in meiosis-I in budding yeast, particularly the nature of monopolin-mediated modifications (*see earlier*) that predispose the sister kinetochores to capture a single microtubule. Since meiosis-I kinetochores were refractory to electron microscopic analysis, the issue remained unresolved (Winey *et al.* 2005).

### 5. Role of the synaptonemal complex in monopolar orientation

The synaptonemal complex (henceforth SC) is a meiosis-specific tripartite structure, composed of two lateral elements and a central element; which generally forms between paired homologs in the meiotic prophase and holds the two homologs in close proximity (figure 3A). The SC has important roles in meiotic interhomolog interactions (reviewed by Page and Hawley 2004; Kleckner 2006; Bhalla and Dernburg 2008). The SC is largely disassembled by the end of the prophase of meiosis-I, though remnants of the SC persist at meiotic kinetochores till homolog segregation at metaphase I (Moens and Spyropoulos 1995). Based on the localization pattern of SC components in the mouse, it has been proposed that SC protein might be required for monopolar orientation of sister kinetochores in meiosis-I (Moens and Spyropoulos 1995; Parra *et al.* 2004). However, in the absence of studies employing mutant mice that would not form SC, the evidence of SC components in monopolar orientation in the mouse is not unambiguous.

In budding yeast, Zip1p is a meiosis-specific protein and a component of the SC. Zip1p is a coiled coil homodimer with globular head domains (Sym *et al.* 1993; Dong and Roeder 2000). Two molecules of Zip1p overlap at their N termini and form the central element of the SC that connects the two lateral elements (figure 3A). Two independent screens (Newman *et al.* 2000; Wong *et al.* 2007) have found Zip1p to be physically interacting with two different components, Nuf2p and Spc24p, of the outer kinetochore complex Ndc80. The Ndc80 complex plays a vital role in chromosome segregation and mediates interaction between the kinetochores and the spindle microtubules during chromosome movement (reviewed by Kotwaliwale and Biggins 2006; Ciferri *et al.* 2007; Davis and Wordeman 2007; Westermann *et al.* 2007; Tanaka and Desai 2008). Zip1p's multiple interaction with this kinetochore complex raised the possibility that two molecules of Zip1p could connect two sister kinetochores in a manner analogous to the way they connect two lateral elements in the SC (figure 3B), and that this Zip1p-mediated interaction between sister kinetochores might promote mono-orientation in meiosis-I. (*Note 1*: the screen in budding yeast that identified *MAM1*

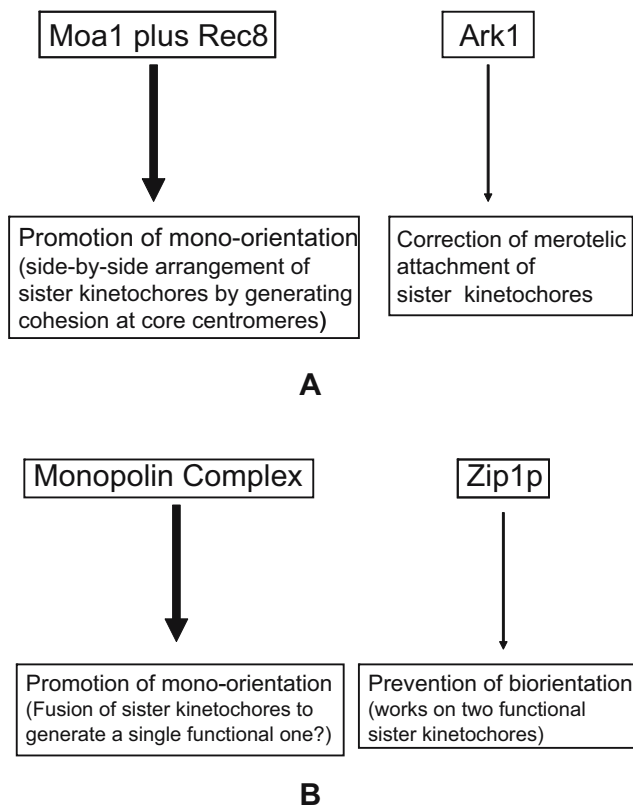
did not include a *zip1Δ* strain. *Note 2*: Zip1p expression is not observed in meiosis-II; hence, it is unlikely to have any role beyond meiosis-I.) In maize, an analogous situation determines monopolar orientation where the kinetochore protein Mis12 forms a bridge between the sister kinetochores by binding to the Ndc80 complex (Li and Dawe 2009). However, Mis12 is a bona fide kinetochore protein and is not orthologous to Zip1p.

Deletion of *ZIP1* in budding yeast in the absence of the gene *SPO11* (*ZIP1* deletion causes a checkpoint-dependent arrest in meiotic prophase and deletion of the gene *SPO11* bypasses this arrest) showed that in a small population of meioses, sister chromatids moved to the opposite spindle poles during the first observable chromosome segregation event (Bardhan and Dawson, unpublished observation). This reflects loss of monopolar orientation in meiosis-I. Accordingly, sister kinetochores were bioriented in the meiosis-I spindle in the *zip1* deletion strain. Furthermore, measurement of sister kinetochore biorientation in mitosis (King *et al.* 2007) after expressing Zip1p from an inducible promoter showed that Zip1p expression in mitosis delayed biorientation of sister kinetochores (Bardhan and Dawson, unpublished observation). These results imply that Zip1p is required for monopolar orientation, though this possibly represents a minor pathway that is independent of the monopolin complex. Zip1p's role in sister kinetochore orientation is likely independent of the SC: Zip1p associates with meiotic centromeres (Tsubouchi and Roeder 2005; Tsubouchi *et al.* 2008) and this association is independent of another essential structural component of the SC, Red1p (Bardhan *et al.* 2010).

### 6. Concluding remarks

The regulation of sister kinetochore orientation in meiosis-I appears complex. In fission yeast (figure 4A), the predominant pathway to generate mono-orientation is the Rec8–Moa1-dependent pathway that is thought to generate a side-by-side geometry of the sister kinetochores through cohesion of the centromeric central core (Yokobayashi and Watanabe 2005; Sakuno *et al.* 2009). The minor but independent Bub1–Sgo2–Ark1 pathway appears to correct merotelic attachment of sister kinetochores (Hauf *et al.* 2007). Likewise, in budding yeast (figure 4B), monopolin represents the major pathway whereas Zip1p represents a minor but possibly independent pathway. Further, the mechanism of monopolin-dependent mono-orientation appears to differ from that of the Zip1p-dependent one. Monopolin is thought to structurally modify the two sister kinetochores in a way that makes them unable to capture microtubules from opposite spindle poles (Toth *et al.* 2000; Monje-Casas *et al.* 2007). Zip1p, on the other hand, likely works on sister kinetochores that possibly escaped monopolin-dependent modification(s), and prevents





**Figure 4.** Pathways regulating sister kinetochore orientation in meiosis-I. **(A)** In fission yeast, Moa1 plus Rec8-dependent modification is the major pathway that promotes side-by-side orientation of sister kinetochores and their subsequent capture of microtubules from the same pole (*see text*). Ark1 represents a Moa1/Rec8-independent minor pathway that corrects merotelic attachment of sister kinetochores (*see text*). **(B)** In budding yeast, monopolin-dependent modification represents the major pathway that is thought to modify sister kinetochores leaving a single functional kinetochore (*see text*). Zip1p prevents/delays biorientation of two functional sister kinetochores. The Zip1p-based mechanism is hypothesized to represent a monopolin-independent minor pathway.

or delays their biorientation. This delay in biorientation of sister kinetochores that escaped monopolin-dependent modification(s) would enable them to capture microtubules from the same pole and co-segregate in meiosis-I. The mechanism by which Zip1p prevents or delays biorientation remains to be determined. It is less likely that Zip1p does so by interfering with Ipl1p enzymatic activity. Further, though orthologs of Zip1p are not found in other model organisms, Zip1p-like proteins with similar coiled coil and globular domains are characteristic of all the SCs studied. It remains to be seen whether Zip1p-like proteins contribute to monopolar orientation of sister kinetochores in other model organisms as well.

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## References

- Akiyoshi B, Nelson C R, Ranish J A and Biggins S 2009 Quantitative proteomic analysis of purified yeast kinetochores identifies a PP1 regulatory subunit; *Genes Dev.* **23** 2887–2899
- Bardhan A, Chuong H and Dawson D 2010 Meiotic cohesin promotes pairing of non-homologous centromeres in early meiotic prophase; *Mol. Biol. Cell.* (in press)
- Bernard P, Maure J F and Javerzat J P 2001 Fission yeast Bub1 is essential in setting up the meiotic pattern of chromosome segregation; *Nat. Cell Biol.* **3** 522–526
- Bhalla N and Dernburg A F 2008 Prelude to a division; *Annu. Rev. Cell Dev. Biol.* **24** 397–424
- Brar G A and Amon A 2008 Emerging roles for centromeres in meiosis-I chromosome segregation; *Nat. Rev. Genet.* **9** 899–910
- Buonomo S B, Clyne R K, Fuchs J, Loidl J, Uhlmann F and Nasmyth K 2000 Disjunction of homologous chromosomes in meiosis-I depends on proteolytic cleavage of the meiotic cohesin Rec8 by separin; *Cell* **103** 387–398
- Chelysheva L, Diallo S, Vezon D, Gendrot G, Vrielynck N, Belcram K, Rocques N, Márquez-Lema A *et al.* 2005 AtREC8 and AtSCC3 are essential to the monopolar orientation of the kinetochores during meiosis; *J. Cell Sci.* **118** 4621–4632
- Ciferri C, Musacchio A and Petrovic A 2007 The Ndc80 complex: hub of kinetochore activity; *FEBS Lett.* **581** 2862–2869
- Clarke L and Carbon J 1980 Isolation of the centromere-linked CDC10 gene by complementation in yeast; *Proc. Natl. Acad. Sci. USA* **77** 2173–2177
- Clyne R K, Katis V L, Jessop L, Benjamin K R, Herskowitz I, Lichten M and Nasmyth K 2003 Polo-like kinase Cdc5 promotes chiasmata formation and cosegregation of sister centromeres at meiosis-I; *Nat. Cell Biol.* **5** 480–485
- Cottarel G, Shero J H, Hieter P and Hegemann J H 1989 A 125-base-pair CEN6 DNA fragment is sufficient for complete meiotic and mitotic centromere functions in *Saccharomyces cerevisiae*; *Mol. Cell Biol.* **9** 3342–3349
- Davis T N and Wordeman L 2007 Rings, bracelets, sleeves, and chevrons: new structures of kinetochore proteins; *Trends Cell Biol.* **17** 377–382
- Ding R, McDonald K L and McIntosh J R 1993 Three-dimensional reconstruction and analysis of mitotic spindles from the yeast, *Schizosaccharomyces pombe*; *J. Cell Biol.* **120** 141–151
- Dong H and Roeder G S 2000 Organization of the yeast Zip1 protein within the central region of the synaptonemal complex; *J. Cell Biol.* **148** 417–426

- Fitzgerald-Hayes M, Buhler J M, Cooper T G and Carbon J 1982 Isolation and subcloning analysis of functional centromere DNA (CEN11) from *Saccharomyces cerevisiae* chromosome XI; *Mol. Cell Biol.* **2** 82–87
- Fitzgerald-Hayes M, Clarke L and Carbon J 1982 Nucleotide sequence comparisons and functional analysis of yeast centromere DNAs; *Cell* **29** 235–244
- Francisco L, Wang W and Chan C S 1994 Type 1 protein phosphatase acts in opposition to IpL1 protein kinase in regulating yeast chromosome segregation; *Mol. Cell. Biol.* **14** 4731–4740
- Furuyama S and Biggins S 2007 Centromere identity is specified by a single centromeric nucleosome in budding yeast; *Proc. Natl. Acad. Sci. USA* **104** 14706–14711
- Glynn E F, Megee P C, Yu H-G, Mistrot C, Unal E, Koshland D E, DeRisi J L and Gerton J L 2004 Genome-wide mapping of the cohesin complex in the yeast *Saccharomyces cerevisiae*; *PLoS Biol.* **2** e259
- Gregan J, Spirek M and Rumpf C 2008 Solving the shugoshin puzzle; *Trends Genet.* **24** 205–207
- Hauf S, Biswas A, Langeegger M, Kawashima S A, Tsukahara T and Watanabe Y 2007 Aurora controls sister kinetochore mono-orientation and homolog bi-orientation in meiosis-I; *EMBO J.* **26** 4475–4486
- Ishiguro K and Watanabe Y 2007 Chromosome cohesion in mitosis and meiosis; *J. Cell Sci.* **120** 367–369
- Joglekar A P, Bouck D, Finley K, Liu X, Wan Y, Berman J, He X, Salmon E D and Bloom K S 2008 Molecular architecture of the kinetochore–microtubule attachment site is conserved between point and regional centromeres; *J. Cell Biol.* **181** 587–594
- Johzuka K and Horiuchi T 2009 The cis element and factors required for condensin recruitment to chromosomes; *Mol. Cell* **34** 26–35
- Katis V L, Matos J, Mori S, Shirahige K, Zachariae W and Nasmyth K 2004 Spo13 facilitates monopolin recruitment to kinetochores and regulates maintenance of centromeric cohesion during yeast meiosis; *Curr. Biol.* **14** 2183–2196
- Kawashima S A, Tsukahara T, Langeegger M, Hauf S, Kitajima T S and Watanabe Y 2007 Shugoshin enables tension-generating attachment of kinetochores by loading Aurora to centromeres; *Genes Dev.* **21** 420–435
- Keating P, Rachidi N, Tanaka T U and Stark M J 2009 Ipl1-dependent phosphorylation of Dam1 is reduced by tension applied on kinetochores; *J. Cell Sci.* **122** 4375–4382
- Kelly A E and Funabiki H 2009 Correcting aberrant kinetochore microtubule attachments: an Aurora B-centric view; *Curr. Opin. Cell Biol.* **21** 51–58
- King E M, van der Sar S J and Hardwick K G 2007 Mad3 KEN boxes mediate both Cdc20 and Mad3 turnover, and are critical for the spindle checkpoint; *PLoS One* **2** e342
- Klapholz S and Esposito R E 1980 Isolation of SPO12-1 and SPO13-1 from a natural variant of yeast that undergoes a single meiotic division; *Genetics* **96** 567–588
- Kleckner N 2006 Chiasma formation: chromatin/axis interplay and the role(s) of the synaptonemal complex; *Chromosoma* **115** 175–194
- Klein F, Mahr P, Galova M, Buonomo S B, Michaelis C, Nairz K and Nasmyth K 1999 A central role for cohesins in sister chromatid cohesion, formation of axial elements, and recombination during yeast meiosis; *Cell* **98** 91–103
- Kotwaliwale C and Biggins S 2006 Microtubule capture: a concerted effort; *Cell* **127** 1105–1108
- Kudo N R, Anger M, Peters A H, Stemmann O, Theussl H C, Helmhart W, Kudo H, Heyting C *et al.* 2009 Role of cleavage by separase of the Rec8 kleisin subunit of cohesin during mammalian meiosis-I; *J. Cell Sci.* **122** 2686–2698
- Kudo N R, Wassmann K, Anger M, Schuh M, Wirth K G, Xu H, Helmhart W, Kudo H *et al.* 2006 Resolution of chiasmata in oocytes requires separase-mediated proteolysis; *Cell* **126** 135–146
- Lacefield S and Murray A W 2007 The spindle checkpoint rescues the meiotic segregation of chromosomes whose crossovers are far from the centromere; *Nat. Genet.* **39** 1273–1277
- Lee B H and Amon A 2003 Polo kinase--meiotic cell cycle coordinator; *Cell Cycle* **2** 400–402
- Lee B H, Kiburz B M and Amon A 2004 Spo13 maintains centromeric cohesion and kinetochore coorientation during meiosis-I; *Curr. Biol.* **14** 2168–2182
- Li X and Dawe R K 2009 Fused sister kinetochores initiate the reductional division in meiosis-I; *Nat. Cell Biol.* **11** 1103–1108
- Liu D and Lampson M A 2009 Regulation of kinetochore–microtubule attachments by Aurora B kinase; *Biochem. Soc. Trans.* **37** 976–980
- Liu D, Vader G, Vromans M J, Lampson M A and Lens S M 2009 Sensing chromosome bi-orientation by spatial separation of aurora B kinase from kinetochore substrates; *Science* **323** 1350–1353
- Lo H C, Wan L, Rosebrock A, Fitcher B and Hollingsworth N M 2008 Cdc7-Dbf4 regulates NDT80 transcription as well as reductional segregation during budding yeast meiosis; *Mol. Biol. Cell* **19** 4956–4967
- Matos J, Lipp J J, Bogdanova A, Guillot S, Okaz E, Junqueira M, Shevchenko A and Zachariae W 2008 Dbf4-dependent CDC7 kinase links DNA replication to the segregation of homologous chromosomes in meiosis-I; *Cell* **135** 662–678
- Moens P B and Spyropoulos B 1995 Immunocytology of chiasmata and chromosomal disjunction at mouse meiosis; *Chromosoma* **104** 175–182
- Monje-Casas F, Prabhu V R, Lee B H, Boselli M and Amon A 2007 Kinetochore orientation during meiosis-Is controlled by Aurora B and the monopolin complex; *Cell* **128** 477–490
- Nakaseko Y, Niwa O and Yanagida M 1984 A meiotic mutant of the fission yeast *Schizosaccharomyces pombe* that produces mature asci containing two diploid spores; *J. Bacteriol.* **157** 334–336
- Nasmyth K and Haering C H 2009 Cohesin: its roles and mechanisms; *Annu. Rev. Genet.* **43** 525–558
- Newman J R, Wolf E and Kim P S 2000 A computationally directed screen identifying interacting coiled coils from *Saccharomyces cerevisiae*; *Proc. Natl. Acad. Sci. USA* **97** 13203–13208
- Nicklas R B 1997 How cells get the right chromosomes; *Science* **275** 632–637
- Onn I, Heidinger-Pauli J M, Guacci V, Unal E and Koshland D E 2008 Sister chromatid cohesion: a simple concept with a complex reality; *Annu. Rev. Cell Dev. Biol.* **24** 105–129
- Page S L and Hawley R S 2004 The genetics and molecular biology of the synaptonemal complex; *Annu. Rev. Cell Dev. Biol.* **20** 525–558

- Parra M T, Viera A, Gomez R, Page J, Carmena M, Earnshaw W C, Rufas J S and Suja J A 2003 Dynamic relocalization of the chromosomal passenger complex proteins inner centromere protein (INCENP) and aurora-B kinase during male mouse meiosis; *J. Cell Sci.* **116** 961–974
- Parra M T, Viera A, Gómez R, Page J, Benavente R, Santos J L, Rufas J S and Suja J A 2004 Involvement of the cohesin Rad21 and SCP3 in monopolar attachment of sister kinetochores during mouse meiosis-I; *J. Cell Sci.* **117** 1221–1234
- Parra M T, Gomez R, Viera A, Page J, Calvente A, Wordeman L, Rufas J S and Suja J A 2006 A perikinetochoic ring defined by MCAK and Aurora-B as a novel centromere domain; *PLoS Genet.* **2** e84
- Peters J M, Tedeschi A and Schmitz J 2008 The cohesin complex and its roles in chromosome biology; *Genes Dev.* **22** 3089–3114
- Petronczki M, Matos J, Mori S, Gregan J, Bogdanova A, Schwickart M, Mechtler K, Shirahige K *et al.* 2006 Monopolar attachment of sister kinetochores at meiosis-I requires casein kinase 1; *Cell* **126** 1049–1064
- Petronczki M, Siomos M F and Nasmyth K 2003 Un ménage à quatre: the molecular biology of chromosome segregation in meiosis; *Cell* **112** 423–440
- Pidoux A L and Allshire R C 2004 Kinetochore and heterochromatin domains of the fission yeast centromere; *Chromosome Res.* **12** 521–534
- Pinsky B A, Kotwaliwale C V, Tatsutani S Y, Breed C A and Biggins S 2006 Glc7/protein phosphatase 1 regulatory subunits can oppose the Ipl1/Aurora protein kinase by redistributing Glc7; *Mol. Cell Biol.* **26** 2648–2660
- Rabitsch K P, Petronczki M, Javerzat J P, Genier S, Chwalla B, Schleiffer A, Tanaka T U and Nasmyth K 2003 Kinetochore recruitment of two nucleolar proteins is required for homolog segregation in meiosis-I; *Dev. Cell* **4** 535–548
- Rabitsch K P, Tóth A, Gálová M, Schleiffer A, Schaffner G, Aigner E, Rupp C, Penkner A M *et al.* 2001 A screen for genes required for meiosis and spore formation based on whole-genome expression; *Curr. Biol.* **11** 1001–1009
- Sakuno T, Tada K and Watanabe Y 2009 Kinetochore geometry defined by cohesion within the centromere; *Nature (London)* **458** 852–858
- Shonn M A, McCarroll R and Murray A W 2000 Requirement of the spindle checkpoint for proper chromosome segregation in budding yeast meiosis; *Science* **289** 300–303
- Shonn M A, Murray A L and Murray A W 2003 Spindle checkpoint component Mad2 contributes to biorientation of homologous chromosomes; *Curr. Biol.* **13** 1979–1984
- Shuda K, Schindler K, Ma J, Schultz R M and Donovan P J 2009 Aurora kinase B modulates chromosome alignment in mouse oocytes; *Mol. Reprod. Dev.* **76** 1094–1105
- Skibbens R V 2008 Mechanisms of sister chromatid pairing. *Int. Rev. Cell Mol. Biol.* **269** 283–339
- Sym M, Engebrecht J A and Roeder G S 1993 ZIP1 is a synaptonemal complex protein required for meiotic chromosome synapsis; *Cell* **72** 365–378
- Tanaka T U and Desai A 2008 Kinetochore–microtubule interactions: the means to the end; *Curr. Opin. Cell Biol.* **20** 53–63
- Tóth A, Rabitsch K P, Gálová M, Schleiffer A, Buonomo S B and Nasmyth K 2000 Functional genomics identifies monopolin: a kinetochore protein required for segregation of homologs during meiosis-I; *Cell* **103** 1155–1168
- Tsubouchi T and Roeder G S 2005 A synaptonemal complex protein promotes homology independent centromere coupling; *Science* **308** 870–873
- Tsubouchi T, Macqueen A J and Roeder G S 2008 Initiation of meiotic chromosome synapsis at centromeres in budding yeast; *Genes Dev.* **22** 3217–3226
- Watanabe Y 2006 A one-sided view of kinetochore attachment in meiosis; *Cell* **126** 1030–1032
- Weber S A, Gerton J L, Polancic J E, DeRisi J L, Koshland D and Megee P C 2004 The kinetochore is an enhancer of pericentric cohesion binding; *PLoS Biol.* **2** e260
- Westermann S, Drubin D G and Barnes G 2007 Structures and functions of yeast kinetochore complexes; *Annu. Rev. Biochem.* **76** 563–591
- Winey M, Morgan G P, Straight P D, Giddings T H Jr and Mastronarde D N 2005 *Mol. Biol. Cell* **16** 1178–1188
- Wong J, Nakajima Y, Westermann S, Shang C, Kang J S, Goodner C, Houshmand P, Fields S *et al.* 2007 A protein interaction map of the mitotic spindle; *Mol. Biol. Cell* **18** 3800–3809
- Yamamoto A and Hiraoka Y 2003 Monopolar spindle attachment of sister chromatids is ensured by two distinct mechanisms at the first meiotic division in fission yeast; *EMBO J.* **22** 2284–2296
- Yokobayashi S and Watanabe Y 2005 The kinetochore protein Moa1 enables cohesion-mediated monopolar attachment at meiosis-I; *Cell* **123** 803–817
- Yu H G and Dawe R K 2000 Functional redundancy in the maize meiotic kinetochore; *J. Cell Biol.* **151** 131–141
- Yu H G and Koshland D 2007 The Aurora kinase Ipl1 maintains the centromeric localization of PP2A to protect cohesin during meiosis; *J. Cell Biol.* **176** 911–918

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