Focus on Meiosis

Keeping sister chromatids together: cohesins in meiosis

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Abstract

Meiosis poses unique challenges to chromosome dynamics. Before entry into meiosis, each chromosome is duplicated and gives rise to two sister chromatids linked to each other by cohesion. Production of haploid gametes requires segregation of homologous chromosomes in the first meiotic division and of sister chromatids in the second. To ensure precise distribution of chromosomes to the daughter cells, sister chromatid cohesion (SCC) has to be dissolved in two steps. Maintenance and regulation of SCC is performed by the cohesin protein complex. This short review will primarily focus on the core cohesin proteins before venturing into adjacent territories with an emphasis on interacting proteins and complexes. It will also concentrate on mammalian meiosis and only occasionally discuss cohesion in other organisms.

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Introduction

During cell division, each chromosome is duplicated, and the two resulting copies segregate to different daughter cells. The two products of replication of a chromosome are called sister chromatids. Attachment of sister chromatids to the microtubules of the spindle in correct orientation requires a fine-tuned balance between two forces, one pulling the chromosomes apart and one keeping them together. The latter is called sister chromatid cohesion (SCC).

In meiosis, the last premeiotic round of DNA replication is followed by two consecutive divisions, which lead to production of haploid gametes. In the first division, meiosis I (MI), homologous chromosomes segregate from each other. The bond between homologs necessary for their proper orientation on the spindle is created by recombination (crossover) between nonsister chromatids and by preserving SCC (Fig. 1). For the first division to occur, cohesion in chromosome arms is destroyed, but cohesion at centromeres is protected to keep sister chromatids connected until they are attached to the spindle and ready to be segregated in meiosis II (MII).

Cohesion between sister chromatids is established during S-phase and is provided by the cohesin protein complex, whose subunits are often referred to as cohesins (recently reviewed in Jessberger 2002, 2003, Hagström & Meyer 2003, Uhlmann 2004).

Multiple complexes formed by the cohesin proteins

Initially, cohesins were discovered in mitotically dividing cells and were later found to play similar roles during meiosis. Considering the complexity of meiosis, germ cell-specific cohesins were expected and indeed were soon identified (reviewed in Firooznia *et al.* 2005).

The mitotic cohesin complex contains four core subunits: two members of the structural maintenance of chromosomes (SMC) protein family, named SMC1 and SMC3; Rad21/Sccl, which is a member of the kleisin protein family; and Sccl (reviewed in Uhlmann 2004). In vertebrates, Sccl exists as two isoforms called SA1 and SA2 (Losada *et al.* 2000, Sumara *et al.* 2000). It is thought that the four proteins form a ring structure, which closes around two sister chromatids and thus keeps them together (Gruber *et al.* 2003, Haering *et al.* 2004). Proteolytic cleavage of the kleisin subunit by a specific protease called separase releases SCC at anaphase (reviewed in Nasmyth 2005). In vertebrates, phosphorylation of Rad21 located on the chromosome arms precedes this proteolytic process and makes it more efficient (Hauf *et al.* 2005).

In cells undergoing meiosis, the mitotic cohesin subunits coexist – at least initially – with meiosis-specific isoforms, which are encoded by distinct genes. Meiotic paralogs in mammals were reported for SMC1, RAD21 and SA1/SA2 and are named SMC1 β (Revenkova *et al.*

Figure 1 Outline of SCC in mammalian meiosis. Cohesin (black bars) connects two sister chromatids. Two pairs of sister chromatids, that is, two homologs, synapse and the synaptonemal complex (SC; yellow) forms. Recombination occurs between nonsister chromatids. In anaphase I, SCC in the chromosome arms is dissolved, and the homologs segregate with cohesion at the still intact centromeres. In anaphase II, centromeric cohesion is dissolved, and the sister chromatids segregate. Green arrowheads indicate orientation of kinetochores.

2001), REC8 (Parisi *et al.* 1999) and STAG3 (Prieto *et al.* 2001) respectively. At least in the context of meiosis, the originally defined mitotic SMC1 protein is called SMC1 α . The existence of mitotic and meiotic SMC and non-SMC subunits of cohesin complexes in prophase I suggests the parallel presence of more than one cohesin complex at this stage. It is currently unknown how many different cohesin complexes with unique combinations of those subunits exist throughout meiosis, which specific function each of these complexes serves, and how they relate and possibly interact with each other.

Several lines of evidence indicate the existence of at least three, if not four, distinct cohesin complexes (Fig. 2). In total testis nuclear extracts, with contributions from mitotic and meiotic cells, one expects at least the ‘stan-

dard’ mitotic cohesin and a meiotic cohesin to be present. Immunofluorescence data show that SMC1 α and SMC1 β coexist in prophase I in spermatocytes (Revenkova *et al.* 2001, 2004, Eijpe *et al.* 2003), suggesting two cohesin complexes, each built upon one specific SMC1 isoform. SMC1 α and REC8, as well as SMC1 α and STAG3, also coprecipitate (Revenkova *et al.* 2004). These cohesins may form a meiosis-specific, SMC1 α -based complex composed of SMC1 α /SMC3/REC8/STAG3 complex (Fig. 2B) or two separate complexes in which one meiosis-specific non-SMC subunit associates with a non-meiosis-specific non-SMC subunit. In immunoprecipitation experiments, REC8 associates at least with SMC1 α , SMC3, SMC1 β and STAG3, suggesting that there are two or more REC8-containing complexes – one containing SMC1 α

Figure 2 Cohesin complexes in meiocytes. Current evidence suggests the existence of at least four different cohesin complexes in mammalian meiocytes. None of the complexes shown here have been fully characterized for meiotic cells.

and one SMC1 β – in mammalian meiocytes (Fig. 2B–D) (Jessberger R, unpublished observations).

Immunofluorescence data indicate the absence of SMC1 α and STAG3 from chromosomes in meiosis II and in some instances a decrease between prophase I and anaphase I (Pezzi *et al.* 2000, Prieto *et al.* 2001, Eijpe *et al.* 2003), raising the question of whether SMC1 α is truly required for prophase I or is rather a vestige of pre-meiotic times. As SMC1 α is essential, this question may be answered only through creation of conditional knock-out (–/–) mice. However, since SMC1 α associates with STAG3 and REC8, and thus forms a meiosis-specific complex, it very likely constitutes a genuine meiotic complex.

However, REC8 does not vanish at that stage. Rather, most of it remains associated with metaphase I chromosomes, and disappears from the chromosome arms in the end of metaphase I while staying at the centromeres until the metaphase II/anaphase II transition (Eijpe *et al.* 2003). Thus, REC8 is probably one of the cohesins responsible for centromeric SCC. Two SMC proteins, SMC1 β and SMC3, were also shown to remain associated with the centromeres until the onset of anaphase II, suggesting that a complex of SMC1 β , SMC3, REC8 and a yet to be identified SCC3-like subunit acts as the centromeric cohesin (Revenkova *et al.* 2001). Whether this centromeric cohesin is identical to a complex providing arm cohesion, and is only specifically post-translationally modified and/or protected at the centromeres, whether the centromeric cohesin complex is of different composition, or whether there is more than one type of cohesin complex at the centromere is not yet known.

Recent analysis of a mouse deficient in SMC1 β demonstrated the role of this cohesin in both arm and centromeric cohesion (Revenkova *et al.* 2004). In *Smc1 β* ^{–/–} spermatocytes, the cohesins SMC1 α , SMC3, REC8 and STAG3 localize to chromosome axes in early prophase as in wild-type cells, indicating a role in establishment of SCC. However, in the absence of SMC1 β , the remaining cohesins are not sufficient for progression of meiosis beyond pachytene, and the mutant spermatocytes eventually die by apoptosis. Treatment of *Smc1 β* ^{–/–} spermatocytes with okadaic acid, which induces premature chromosome condensation to a metaphase-like state, revealed loss of SCC at centromeres. *Smc1 β* ^{–/–} oocytes progress further than spermatocytes and can reach metaphase II, when the complete loss of SCC both in the arms and at centromeres becomes evident. Both *Smc1 β* ^{–/–} males and females are completely sterile, demonstrating the essential role of SMC1 β in meiosis.

Similarly, REC8-deficient mice (Bannister *et al.* 2004, Xu *et al.* 2005) do not produce viable gametes. Premature separation of sister chromatid arms at pachytene precedes the disappearance of mutant spermatocytes. In *Rec8*^{–/–} mice, defects in chromosome synapsis (see below) are more severe. Both spermatogenesis and oogenesis are arrested at earlier stages than in *Smc1 β* ^{–/–} mice (Bannister *et al.* 2004, Revenkova *et al.* 2004, Xu *et al.* 2005).

The phenotypes of both mouse mutants, which are generally similar yet not identical, suggest that SMC1 β and REC8 form a complex and act together, but also have distinct roles that are probably fulfilled by different complexes. The engagement of REC8 in separate complexes with SMC1 α and SMC1 β may explain the more drastic phenotype of *Rec8*^{–/–} mice.

The function of the RAD21 protein at specific stages in meiotic cells is likewise not yet understood. There is controversy in the literature on whether RAD21 remains chromosome-associated beyond prophase I. One paper suggests that a mammalian complex made of RAD21, SMC3, SMC1 β and an undetermined fourth subunit persists at the centromeres until the metaphase/anaphase II transition and thus may be involved in bipolar attachment of the kinetochores to microtubules for segregation of sister chromatids (Xu *et al.* 2004). Another publication claims that RAD21 is displaced from the centromeres in telophase I and is not present at meiosis II centromeres (Parra *et al.* 2004). Time and position of RAD21 relative to other proteins accumulating at centromeres in the end of prophase I prompted the hypothesis that RAD21 in mouse plays a role in orientation of sister kinetochores (Parra *et al.* 2004). The kinetochore is a protein structure providing connection of spindle microtubules to the centromere. For sister chromatids to move together to the same pole during the first meiotic division, their kinetochores have to be oriented in the same direction, whereas for meiosis II the sister kinetochores have to be arranged back-to-back. In fission, yeast mono-orientation of sister kinetochores in meiosis I requires, among other factors, cohesin Rec8 (reviewed in Hauf & Watanabe 2004, Marston & Amon 2004). The question of whether Rec8 is involved in kinetochore orientation in mammals remains to be answered.

The SA1 and SA2 proteins are generally observed alongside their meiosis-specific variant STAG3 (Pezzi *et al.* 2000, Prieto *et al.* 2001, 2002), but their specific association with particular types of complexes and the function of those complexes are unknown.

Thus, there appears to be great variability in meiotic cohesin complexes, and one would expect specific functions for many of them. There may be some redundancies, and in mice deficient in a particular cohesin a related cohesin may be able partially to complement the loss. However, considering the unique differences in meiosis between cohesion in the arms and at the centromeres, as well as the phenotypes of cohesin mutants in yeast and cohesin-deficient mice, it is clear that unique, nonredundant complexes exist.

The patterns of cohesin association with chromosomes

Low-resolution mapping of cohesin-binding sites on mitotic *S. cerevisiae* chromosomes revealed preferential association of cohesin with regions surrounding centromeres and defined sites in the arms. Pericentric

cohesin-binding domains in yeast occupy regions of about 50 kb, whereas cohesin-binding sites in the arms are approximately 1 kb in length and separated by intervals of about 10 kb (Blat & Kleckner 1999, Megee *et al.* 1999, Tanaka *et al.* 1999, Weber *et al.* 2004).

Cohesin binding at pericentric regions depends on the presence of specific centromere sequences (Megee *et al.* 1999, Tanaka *et al.* 1999, Weber *et al.* 2004). In contrast, mapping of cohesin-binding sites in the arms did not reveal any consensus in their DNA sequences (Glynn *et al.* 2004, Lengronne *et al.* 2004). The position of most of the sites in the arms appeared to be defined by active transcription, and the vast majority of the sites are located between genes with convergent direction of transcription. This suggests that the transcription machinery pushes sliding cohesion complexes toward the ends of the transcribed genes. Several experiments demonstrated that changes in transcription activity do indeed affect cohesin binding as follows:

1. Turning off transcription erased cohesin association with a site located downstream of the gene (Lengronne *et al.* 2004).
2. Changing the transcription status of several genes by variation of growth conditions caused relocation of cohesin-binding sites downstream of actively transcribed sequences.
3. Altering transcription of several genes due to the switch to meiosis caused a corresponding relocation of cohesin (Glynn *et al.* 2004, Lengronne *et al.* 2004).

The difference between somatic and meiotic cohesin-binding sites may also be caused by the different composition of the cohesin complexes, but, in *S. cerevisiae*, the binding sites for Rec8 (meiotic) and Scc1 (mitotic; present in meiotic cells) occupy the same positions in meiotic cells (Lengronne *et al.* 2004). Importantly, Glynn *et al.* (2004) found that sites of double-strand breaks where meiotic recombination is initiated stay free of cohesin.

Further analysis (Lengronne *et al.* 2004) has revealed that, initially, cohesin is loaded at the Scc2/Scc4 (adherin)-binding sites and then relocates to sites corresponding mostly to regions between genes with converging directions of transcription (for an adherin review, see Dorsett 2004). Recently, mutations in NIPBL, which is a human homolog of Scc2, were discovered to be a cause of Cornelia de Lange syndrome (Krantz *et al.* 2004, Tonkin *et al.* 2004).

Roberts syndrome, which is also characterized by developmental abnormalities and growth retardation, is caused by mutations in the human homolog of yeast Eco1, ESCO2 (Vega *et al.* 2005). *S. cerevisiae* Eco1 is required for establishment of SCC during replication but is dispensable for cohesion maintenance (Toth *et al.* 1999) or cohesin loading (Skibbens *et al.* 1999).

Meiosis-specific factors for cohesin loading or establishment of cohesion, if required, have not yet been described.

It is not clear whether the studies performed in yeast would satisfactorily explain loading and positioning of

cohesin in mammalian meiocytes as well. For example, the kinetics of chromosome association of individual cohesin proteins or complexes seems to be more complex in mammalian cells, for REC8 appears to associate earlier than SMC1 β with meiotic chromosomes (Eijpe *et al.* 2003).

In yeast, Rec8-containing cohesin has to be loaded onto chromosomes before the premeiotic S-phase for cohesion to be established (Watanabe & Nurse 1999, Watanabe *et al.* 2001). Nevertheless, while most cohesin complexes may be loaded during the premeiotic S-phase, others may load later and may come in addition to or (partially) replace the previously loaded complexes. An argument against massive cohesin replacement at least in mitosis, however, can be derived from studies in which a noncleavable variant of Scc1p was expressed after S-phase, that is, after cohesion had been established. If the mutant Scc1p was expressed after DNA replication had been completed, no effect on sister chromatid separation was observed (Haering *et al.* 2004). Surely, meiosis is different, and mammalian cells entertain a level of cohesin complexity not seen in yeast.

In human cells, cohesin is recruited to sites of DNA double-strand breaks in S/G2 phase (Kim *et al.* 2002a), and its SMC1 subunit is phosphorylated upon DNA damage by ATM kinase (Kim *et al.* 2002b, Yazdi *et al.* 2002). After DNA damage, new cohesin-enriched domains around DNA breaks are established in yeast (Strom *et al.* 2004, Unal *et al.* 2004), illustrating one way to load new and/or distinct cohesin complexes onto chromosomes long after S-phase. Strom *et al.* (2004) also demonstrated that cohesin bound to sites of DNA damage in G2 is able to mediate SCC. DNA damage-induced recruitment of cohesin is necessary for efficient postreplicative DNA repair (Strom *et al.* 2004, Unal *et al.* 2004). Furthermore, genetic evidence from *S. cerevisiae* indicates a function for cohesin in coordinating recombinational repair through the Rad52 epistasis group pathway, as opposed to the nonhomologous end-joining pathway (Schär *et al.* 2004).

Generation and repair of double-strand breaks is a hallmark of meiosis, rendering it likely that a specific function of cohesin in processing DNA double-strand breaks may be one of the reasons for the existence of a variety of meiotic complexes.

Role of cohesin in chromosome axes formation and synapsis

The loading of cohesin has more far-reaching consequences for the meiotic chromosome structure than to keep sister chromatids together. In yeast, Rec8p loading is required for the formation of the synaptonemal complex (SC) (Klein *et al.* 1999). The SC is a meiosis-specific, zipper-like protein structure that mediates pairing of the homologs and supports recombination by mechanisms that are not yet well understood (reviewed in Zickler

& Kleckner 1999, Hunter 2003, Page & Hawley 2004). SCs consist of two axial elements (AEs), which are connected by numerous transverse filaments along their length. Each AE supports the two sister chromatids of one homolog. *S. cerevisiae* Smc3p colocalizes with an AE component during meiotic prophase and is essential for meiotic recombination and SCC (Klein *et al.* 1999). In mammals, two AE components which are specifically expressed in meiotic prophase have been identified, SYCP2 (Offenberg *et al.* 1998) and SYCP3 (Lammers *et al.* 1994). The transverse filaments are composed of SYCP1 (Meuwissen *et al.* 1992). Early studies on SMC proteins in spermatocytes suggested interactions between SC proteins and cohesins (Eijpe *et al.* 2000). Further evidence for such interactions and new insights into the role of cohesins in shaping the chromosome structure in mammalian meiosis were obtained recently through the analysis of mouse mutants deficient in cohesins SMC1 β or REC8, but also of a mouse deficient in a component of the SC, SYCP3.

The absence of SMC1 β or REC8 in spermatocytes of the mutant mice causes dramatic changes in the formation of the SC. The last stage the mutant spermatocyte could reach before meiosis arrests can be characterized as aberrant pachytene. In the mutant spermatocytes, a high incidence of unsynapsed or incompletely synapsed chromosome cores was observed (Bannister *et al.* 2004, Revenkova *et al.* 2004, Xu *et al.* 2005).

Perhaps the most striking feature of Smc1 β ^{-/-} spermatocytes, however, is a 50% length reduction of AEs (Revenkova *et al.* 2004). A similar reduction was observed in Rec8^{-/-} mice (Bannister *et al.* 2004, Xu *et al.* 2005). This phenotype suggests that cohesin determines the overall organization of chromatin during the assembly of the AE. If the quantity of cohesin loaded to a chromosome or the number of cohesin-binding sites determines the number or

the size of chromatin domains situated at the basis of chromatin loops, then cohesin deficiency may cause a decrease in the amount of chromatin packed into the AE and corresponding increase in the loop size (Fig. 3). Indeed, the loop size evaluated by measuring the distance between the AE and the most distal point of the surrounding chromosome-specific chromatin cloud, as well as the chromatin volume, was increased in the Smc1 β ^{-/-} spermatocytes compared with wild type (Revenkova *et al.* 2004).

Eliminating SYCP3 causes meiotic arrest and sterility in males. Female meiosis progresses to completion; however, SYCP3-deficient females display significantly reduced litter size (Yuan *et al.* 2000, 2002). In both wild-type and SYCP3-deficient spermatocytes, SMC1 α , SMC3 and STAG3 form fiber-like arrays of foci, likely to correspond to a chromosome scaffold that holds sister chromatids together (Pelttari *et al.* 2001). The cohesin core formed in these SC-less spermatocytes, while not of the same regular appearance as when visualized together with a complete SC, can still recruit recombination proteins and promote some pairing between homologous chromosomes. These, and other results indicate at least partial independence of cohesin core formation from the presence of an SC (Kouznetsova *et al.* 2005). Similarly, cohesin localization in early prophase I in Sycp1^{-/-} spermatocytes is like that in wild-type cells (de Vries *et al.* 2005).

Another interesting feature of Sycp3^{-/-} meocytes is the increase of AE length by about two- to four-fold (Yuan *et al.* 2002). Thus, the functional relationship between SYCP3, which seems to compact the chromosomal axis, and SMC1 β , which appears either to limit or actively counteract the compaction and may define chromatin loop attachment sites, is crucial to establishing the proper AE length (Fig. 3). A mouse mutant deficient in both proteins may reveal the nature of this relationship.

Figure 3 Hypothetical interplay between SCP3/SCP2 and SMC1 β cohesin in determining the lateral compaction of the SC. Chromosome loops and SC are shown for wild-type and two mutant mice. A speculative interpretation of the interplay between SMC1 β and SYCP3 is indicated for each genotype. SYCP3 and SYCP2 act in concert. The loop size in the Sycp3^{-/-} meocytes is not known; therefore, two alternative explanations are offered.

The chromosomes of *Smc1 β ^{-/-}* meocytes are not only short, but also fail in several other respects. Their telomeres do not properly attach to the nuclear periphery as they do in wild-type spermatocytes. The clustering of the telomeres at one spot on the nuclear periphery is characteristic of early prophase I, and the corresponding chromosome arrangement is called meiotic bouquet (reviewed in Scherthan 2003, Harper *et al.* 2004). Furthermore, as mentioned earlier, synapsis of homologs is incomplete in the *Smc1 β ^{-/-}* mutant. Both phenotypes may be a consequence of the shortened chromosome structure. For example, the short chromosomes may fail to reach the nuclear periphery because of steric problems, and may have similar steric problems in finding homolog partner for synapsis, particularly if bouquet formation would be involved in pairing. Alternatively, SMC1 β may possess a telomere-specific function and/or a function in pairing.

Progression of oocytes through meiosis I and into anaphase II makes it possible to ask whether a deficiency in SMC1 β affects the number and location of crossovers, and whether any resultant alterations in crossover patterns might be translated into aneuploidy. Such questions are crucial to an understanding of aneuploidy, which is a major reproductive health problem (Hunt & Hassold 2002).

Regulation of meiotic SCC

A number of noncohesin proteins contribute to SCC itself, may interact with the cohesins, or regulate processes that are important for the establishment, maintenance or dissolution of SCC. As the analysis of cohesin-deficient mice illustrates, there are also intimate links between meiotic recombination and SCC, and there are yet other protein interactions to consider. A thorough discussion of all these factors and processes would reach far beyond the limits of this review, which therefore concentrates on a few selected areas. One of them concerns the mechanisms that ensure the stepwise dissolution of cohesion in meiosis I and meiosis II.

In mammals, the task of cohesin removal is split between two pathways (reviewed in Uhlmann 2003). One relies upon cleavage of the kleisin subunit by a specific protease called separase. Separase activation is triggered as a result of the activity of anaphase promoting complex APC/C. The second pathway does not require kleisin to be cleaved, but involves modification of Scc1/Rad21 and the Scc3-like subunit by phosphorylation, and depends on the activity of protein kinases Aurora B and POLO-like kinase Plk1. In mitotic cells, this pathway operates in prophase and removes most of the cohesin from the chromosome arms. The prophase pathway depends on phosphorylation of cohesin subunit SA2 (Hauf *et al.* 2005), and the release of cohesin in prophase is required for sister chromatid resolution (Losada *et al.* 2002). The centromeric cohesin and the residual arm cohesin are removed at the metaphase/anaphase transition by the separase pathway.

In meiosis, a decrease in the amount of various cohesins bound to chromosome arms during prophase was also observed (Prieto *et al.* 2001, 2002, Revenkova *et al.* 2001), but the detailed mechanisms of this depletion are unknown. The separation of homologs in anaphase I correlates with the resolution of crossovers and the complete destruction of cohesion in the arms. In mouse oocytes, separase activity is required for the first metaphase/anaphase transition (Terret *et al.* 2003).

In contrast to mitotic division, in meiosis I, cohesion at the centromere has to be preserved to ensure faithful segregation of sister chromatids in anaphase II. The mechanism of protection of cohesion at the centromeres while it is being dissolved in the arms at the onset of anaphase I is best understood in yeast. The protein found to be essential for the protection of centromeric cohesion is called 'shugoshin' (Japanese for 'guardian spirit'), or Sgo1p (Kitajima *et al.* 2004). In yeast, it localizes to kinetochores and locally protects Rec8p from cleavage by separase. Mammals have two members of the shugoshin family, SGO1 and SGO2. The function of SGO2 is unknown, and SGO1 serves as a protector of cohesion at centromeres, but, in contrast to yeast, it fulfills this duty during mitotic prophase, and it counteracts not the separase pathway, but the Plk1-dependent pathway (McGuinness *et al.* 2004, Kitajima *et al.* 2005). In HeLa cells, the mechanism of SGO1-mediated protection of cohesin at centromeres appears to rely on prevention of mitosis-specific hyperphosphorylation of SA2 (McGuinness *et al.* 2004). The function of shugoshins as cohesion guard during meiosis I and II in vertebrates has not yet been demonstrated. However, in *Drosophila*, shugoshin MEI-S332 has long been known as a protector of centromeric cohesion (Kerrebrock *et al.* 1992). Recently, it was shown that dissociation of MEI-S332 from the centromere is mediated by POLO kinase (Clarke *et al.* 2005). Thus, it appears that SCC depends on the balance of antagonistic forces with shugoshin on one side and APC/C and POLO-like kinase on the other. Certainly, shugoshin is not the only protector of cohesion in meiosis. Other factors, such as Mnd2, a meiosis-specific antagonist of APC/C (Oelschaege *et al.* 2005, Penkner *et al.* 2005), or Spo13, which is involved in the maintenance of centromeric cohesion in meiosis I (Katis *et al.* 2004, Lee *et al.* 2004), were recently characterized in yeast, and they also contribute to the maintenance of centromeric cohesion. Similar mammalian meiosis-specific regulators of cohesion remain to be discovered.

If mitotic SCC and segregation appear to be complicated, meiosis adds layers of complexity. Thus, it is not surprising to see meiosis-specific proteins and complexes, and specific chromosome structure and behavior. Cohesins are no exemption and will provide many more fascinating observations. Furthermore, with their central role in faithful chromosome segregation, they may well prove to be key to our understanding of the frequent human aneuploidies.

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