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Complex elaboration: making sense of meiotic cohesin dynamics

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Abstract

In mitotically dividing cells, the cohesin complex tethers sister chromatids, the products of DNA replication, together from the time they are generated during S phase until anaphase. Cohesion between sister chromatids ensures accurate chromosome segregation, and promotes normal gene regulation and certain kinds of DNA repair. In somatic cells, the core cohesin complex is composed of four subunits: Smc1, Smc3, Rad21 and an SA subunit. During meiotic cell divisions meiosis-specific isoforms of several of the cohesin subunits are also expressed and incorporated into distinct meiotic cohesin complexes. The relative contributions of these meiosis-specific forms of cohesin to chromosome dynamics during meiotic progression have not been fully worked out. However, the localization of these proteins during chromosome pairing and synapsis, and their unique loss-of-function phenotypes, suggest non-overlapping roles in controlling meiotic chromosome behavior. Many of the proteins that regulate cohesin function during mitosis also appear to regulate cohesin during meiosis. Here we review how cohesin contributes to meiotic chromosome dynamics, and explore similarities and differences between cohesin regulation during the mitotic cell cycle and meiotic progression. A deeper understanding of the regulation and function of cohesin in meiosis will provide important new insights into how the cohesin complex is able to promote distinct kinds of chromosome interactions under diverse conditions.

Keywords

cell cycle; cohesin complex; cohesin regulation; meiosis

Introduction

In somatic cells, sister chromatids are held together from the time they are made until cell division by a protein complex called cohesin. The cohesin complex and its regulators were originally identified in genetic screens in yeast for genes required for maintenance of sister chromatid association during mitotic arrest [1–3]. Subsequent isolation of vertebrate orthologs from frog egg extracts confirmed that cohesion between sister chromatids is mediated by a highly conserved complex of proteins, with readily identifiable orthologs from yeast to man [4].

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The cohesin complex is essential for normal growth and development at the cellular and organismal level [5]. In mitotically growing cells, cohesion between sister chromatids promotes cell cycle progression and accurate chromosome segregation at anaphase, and mediates DNA repair through mechanisms that depend on homologous recombination (reviewed in [6]). In addition, cohesin promotes normal gene regulation through control of chromosome structure [7]. Aberrant cohesion causes severe developmental disorders, such as Roberts syndrome and Cornelia de Lange syndrome, and is correlated with chromosome instability in tumors [8–11].

During meiotic cell divisions, a number of unique cohesin subunits are expressed and incorporated into meiosis-specific cohesin complexes. Interestingly, these meiotic cohesins, which are essential for normal meiotic chromosome dynamics and thus fertility, have non-overlapping localization and unique regulation during meiotic progression. Here, I summarize our understanding of the contributions of meiotic cohesin to proper meiotic chromosome dynamics, and explore the analogies that can be drawn between mitotic and meiotic cohesin regulation. To this end, I begin with a brief overview of cohesin regulation in mitotically dividing cells. (More comprehensive reviews of this material can be found in [6,12,13].) I then delve into how mitotic events compare and contrast with meiotic cohesin regulation.

The cohesin cycle

Genetic, biochemical and cell biological studies have contributed to our understanding of cohesin structure, regulation and function during mitotic cell cycle progression (Fig. 1). The core cohesin complex is composed of four subunits: two elongated proteins, called Smc1 and Smc3 (for structural maintenance of chromosomes), and two non-SMC subunits, called Scc1 or Mcd1 in budding yeast (Rad21 in vertebrates and fission yeast) and Scc3 (SA1 or SA2 in vertebrates) (Fig. 2). All SMC proteins share a similar structure: they fold back on themselves to form anti-parallel coiled-coils, with their N and C termini in close proximity. Smc1 and Smc3 interact at two places: the Smc1 and Smc3 head groups interact to form a pair of inter-molecular ABC type ATPases [14], and the hinge domains formed between the coil-forming regions also interact [15]. Rad21 forms a bridge between the head groups of the SMC proteins, and a fourth subunit, Scc3 (either SA1 or SA2 in vertebrates), binds to the complex through Rad21. The core cohesin complex shares sequence and structural homology with other SMC-protein-containing complexes, such as condensin and the Smc5/6 complex, which similarly promote chromatin–chromatin interactions in different contexts (reviewed in [16,17]).

The interaction of cohesin with chromosomes is regulated by a number of proteins, which collectively ensure proper cohesin dynamics in response to cell cycle progression (Table 1). This modulation of the association of cohesin with chromatin in response to cell cycle progression is often referred to as the cohesin cycle. This cycle refers to the binding of cohesin to chromatin, the tethering together of sister chromatids, and finally release of chromatids at cell division. The cycle can be broken down into three distinct molecular steps, described here.

Cohesin loading—Cohesin is loaded onto chromosomes by a heterodimeric complex composed of the Scc2 and Scc4 proteins [18]. In vertebrates cohesin is first loaded to chromosomes at mitotic exit [4,19], while in budding yeast cohesin loading occurs somewhat later, during S phase. In all cases cohesin loading requires the activity of the Scc2/Scc4 complex, which becomes dispensable for cohesion after DNA replication is complete in G2 [18]. Loading of cohesin onto chromosomes requires nucleotide hydrolysis by the SMC head domains [14,20], which is stimulated by the Scc2/Scc4 complex [21]. This hydrolysis is thought to lead to transient opening of the cohesin ring at the hinge interaction domain, and topological entrapment of DNA within [22]. Because they are thought to ensure this entrapment by forming a third component of a tripartite cohesin ring, proteins in the Rad21 family of SMC-interacting proteins have been dubbed ‘kleisins’ from the Greek word for closure [23]. Once cohesin is loaded onto chromatin, the cohesin-interacting protein Pds5 associates with the complex. Interestingly, the interaction between cohesin and Pds5 is weak in solution, and may depend upon a particular conformation of cohesin that is achieved during chromatin association [19].

Cohesion establishment

The requirement for cohesin loading prior to the completion of DNA replication reflects the fact that cohesin must be present on chromatin during DNA replication in order to be activated to tether sister chromatids together [24]. This activation process is often referred to as ‘cohesion establishment’. The precise molecular details of this activation are poorly understood, but modification of cohesin by members of the Eco1 family of acetyltransferases is critical. The Eco enzymes (called Esco1 and Esco2 in vertebrates) interact directly with components of the replication machinery and modify the Smc3 subunit of cohesin [25–29]. In the absence of Eco/Esco-dependent modification in both yeast and vertebrates, cohesin binds to chromosomes, but fails to tether sister chromatids together [30,31]. How does acetylation promote cohesion establishment? The simplest model is that acetylation of Smc3 disrupts interaction of the Wapl protein with the cohesin complex. Wapl (Rad61 in budding yeast) is the major cohesion-disrupting activity in the cell, thought to promote opening of the Rad21–Smc3 gate and unload cohesin from chromatin [32–35]. Wapl is thus sometimes referred to as an ‘anti-establishment’ factor. When Wapl activity is blocked cohesin's interaction with chromatin becomes more stable [36]. Acetylation of Smc3 by Eco1 may also have effects on the intrinsic chromatin binding activity of cohesin, independent of Wapl [37].

Metazoans express an additional essential cohesion regulator, not found in fungal systems, called Sororin [38]. This protein binds to cohesin in a replication- and acetylation-dependent manner, and is required for cohesion maintenance from the time of DNA replication until anaphase [39,40]. Sororin is thought to antagonize the activity of Wapl, perhaps by competing with it for interaction with the cohesin complex [41]. Interestingly, Sororin binds to cohesin only following cohesion establishment [26]. Thus Sororin's interaction with cohesin provides a biochemical mark for active cohesion. Understanding the nature of the Sororin binding site promises to provide critical information about the nature of the establishment mechanism.

The activities of Wapl, Eco and Sororin are all critically dependent on a cohesin-interacting protein called Pds5, which interacts with the core cohesin complex through both the SA and Rad21 [36,42–46]. Pds5 is therefore essential for both the establishment of cohesion during S phase and for cohesion maintenance in G2 [47,48]. In vertebrates, Pds5 binds cohesin when it is chromatin bound and is required for cohesin's acetylation by the Esco enzymes [19,42]. In addition, destabilization of cohesion by Wapl occurs through Pds5 [36,46]. Thus Pds5 serves a scaffold function to integrate pro- and anti-cohesion activities during cell cycle progression.

Interestingly, in vertebrates only a small pool of cohesin is stabilized on chromatin during DNA replication [49]. The bulk of cohesin associates dynamically with chromatin, constantly loading and unloading, perhaps to fulfill additional roles in modulating chromosome architecture. Through its effect on chromosome structure cohesin plays significant roles in gene regulation and programmed gene rearrangements (such immunoglobulin and T cell receptor gene rearrangements) that are likely to be independent of sister tethering *per se* [50–53]. In fact, chromatin cohesin is found associated with particular chromosomal loci throughout the cell cycle, even in G1 when there are not yet two sister chromatids to be tethered together [54]. The precise role of ‘non-cohesive’ cohesin in interphase cells is not clear and the subject of current investigation by many laboratories [55,56].

Cohesin release—Following cohesin loading and DNA replication-dependent cohesion establishment, sister chromatids remain tethered together by cohesin until the metaphase–anaphase transition. In budding and fission yeast cohesin remains largely associated with chromosomes until anaphase [57]. In vertebrate cells, the bulk of cohesin is removed from chromosome arms during mitotic entry by phosphorylation and by the activity of the Wapl protein [36,46,58]. Protection of cohesion at the centromere regions is accomplished by specific recruitment of a phosphatase, PP2A, to the centromeric region of the chromosomes by Sgo1 [59,60]. PP2A is thought to resist cohesin release by maintaining centromeric cohesin in its dephosphorylated state [61–63]. In metazoans, PP2a also prevents phosphorylation-dependent removal of Sororin from the centromeric region of chromosomes, thus protecting cohesin from Wapl-dependent removal in metaphase [64].

In the final step of the cohesin cycle, cleavage of the Rad21 subunit of cohesin by a site-specific protease called separase releases the cohesin complex and allows anaphase separation of chromosomes (reviewed in [65]). Separase is activated at the metaphase–anaphase transition both by degradation of an inhibitory protein called Securin and through loss of inhibitory phosphorylation on separase itself as mitotic kinases are inactivated [66,67]. In vertebrate cells, only a small fraction of cohesin remains associated with chromosomes and is thus cleaved at the metaphase to anaphase transition [68]. The bulk of cohesin remains intact, can be redeployed in telophase as nuclei are reforming, and is thought to play a significant role in chromosome architecture in G1 prior DNA replication. In budding yeast, in contrast, virtually all Rad21 is cleaved at anaphase and does not accumulate again until the next S phase [69].

In summary, during transit through the cohesin cycle the cohesin ring is thought to open in three distinct ways: at the hinge region during loading onto chromosomes, at the Smc3–Rad21 interface during unloading by Wapl, and by cleavage of the Rad21 subunit at anaphase. These activities of cohesin are controlled by several proteins, including Sororin, Pds5, Eco acetyltransferases and Wapl, that collectively ensure proper sister chromatid cohesion.

Cohesion and the DNA damage response

In budding yeast, cohesion between sister chromatids is increased both locally and throughout the nucleus in response to DNA double strand breaks and is critical for DNA double strand break repair [70–73]. A number of the proteins that promote cohesion establishment during cell cycle progression also promote cohesion establishment in response to DNA damage signaling. In response to DNA damage these proteins, including the Scc2/Scc4 cohesin loader and Eco1 acetyltransferase, act downstream of the ATM/Tel1 and ATR/Mec1 checkpoint kinases and phosphorylation of the histone variant H2AX at the sites of DNA damage [73,74]. Mutation or decreased expression of cohesin subunits or cohesin regulators, such as Scc2/Scc4, Wapl, Pds5, Eco1/Esco1/2, separase, and in vertebrates Sororin, all confer increased sensitivity to DNA damage [72,74–78]. Sister chromatid cohesion is thought to promote double strand break repair by ensuring the close proximity of an undamaged sister chromatid as a template for repair of the damaged sister chromatid through a recombination-based mechanism. Such a mechanism must necessarily be restricted to S phase or G2 cells, in which two sister chromatids are present. Precisely how this restriction occurs is not clear, and may differ between yeast and higher eukaryotes [74,79].

The meiotic cohesins—During meiotic prophase I chromosomes undergo an elaborate series of movements and structural rearrangements, in which homologous chromosomes sort themselves out, pair and synapse (see accompanying reviews by Sansam and Pezza [80], Kurdzo and Dawson [81]). Pairing refers to the initial DNA homology-dependent interactions between homologous chromosomes, while synapsis is the process by which the homologous chromosome pairs become intimately associated with each other through the synaptonemal complex (SC), allowing for progression of homologous recombination (reviewed in Sansam and Pezza, this issue [80]). During synapsis, a proteinaceous bridge, called the SC, is formed between homologous chromosomes (see Kurdzo and Dawson, this issue [81]). The first SC element to form is the axial element (AE), which assembles on each sister chromatid pair, called a univalent, prior to synapsis. As the chromosome cores become more tightly apposed during synapsis, additional proteins are recruited to form the transverse filaments and the central element. At this time, called the pachytene stage, the AE proteins constitute part of the lateral elements (LEs) of the mature tripartite zipper-like SC structure. Together, one pair of homologous chromosomes that are synapsed is referred to as a bivalent.

The alignment, pairing, synapsis and recombination of homologous chromosomes in meiotic prophase present an enormously complicated set of steric and topological challenges, and proper progression of these rearrangements is critically dependent upon the cohesin

complex. Interestingly, the subunit composition of cohesin is altered in meiosis, with meiosis-specific paralogs of various cohesin subunits expressed and incorporated into the holocomplex (Fig. 2 and Table 2). These cohesins, which include meiosis-specific kleisin subunits called Rec8 or in vertebrates Rad21L, as well as a meiosis-specific SMC protein in some species (Smc1β; Fig. 2), are essential for normal meiotic chromosome structure and dynamics. While many of the mitotic functions of cohesin are likely to be conserved during meiosis, the regulation of cohesin during meiotic progression is complex and not fully understood.

During meiosis cohesion is released in two steps (Fig. 1). In anaphase of meiosis I, cohesin is removed from chromosome arms, allowing separation of homologs (disjunction) by the site-specific protease called separase. At centromeres, cohesion is protected from removal in meiosis I by the activity of the Shugoshin protein Sgo1 (Japanese for ‘guardian spirit’) which recruits PP2A phosphatase to the centromere [59,60]. As phosphorylation of cohesin is required for separase-dependent cleavage, centromeric cohesion is protected from cleavage by the presence of PP2A. In meiosis II, cohesion at the centromere is no longer protected from separase and sister chomatids are thus unlinked and segregated during the second meiotic division. The mechanism by which centromeric cohesion is lost in meiosis II anaphase is controversial and may vary between species.

The geometry of bivalents after desynapsis is such that the resistance to spindle pulling forces in meiosis I is provided principally by cohesion that is distal to the sites of crossing over (Fig. 1 and [82]). In human females, cohesion established in meiosis I must have the remarkable ability to persist for up to four decades, as meiotic prophase and cohesion establishment occur before birth and cohesion must be maintained until meiosis I release at ovulation (reviewed in [83]). This has led to the proposal that failure of meiotic cohesion contributes to the age-related increase in aneuploidy seen in women [84], a hypothesis that has been experimentally validated in flies and mice [85,86]. In naturally aging female mice, centromeric cohesion declines with age and females that are genetically deficient in certain forms of meiotic cohesin, such as cohesin containing Rad21L (see below), while born fertile, show an accelerated decline in fertility as they age [87]. When their oocytes are examined, this reduced fertility is seen to be accompanied by migration of chiasmata (the cytological manifestations of crossovers) towards the distal end of chromosomes and the appearance of unpaired homologs, as would be predicted if cohesion loss were the underlying mechanism of meiotic failure [88]. Recent work in *Drosophila* suggests that cohesin is renewed throughout meiotic prophase, and that this renewal is necessary for chiasma maintenance and accurate chromosome segregation, although chiasma formation may also be compromised in this model due to premature SC disassembly [89]. The mechanism of age-dependent cohesion loss in oocytes may be analogous to the ‘cohesion fatigue’ seen in somatic cells during sustained metaphase arrest, although the absence of spindle pulling forces during meiotic arrest might suggest alternative mechanisms [90,91]. As aneuploidy is a major contributor to birth defects and spontaneous abortion, understanding the mechanisms involved in the establishment, maintenance and loss of meiotic cohesion is of great interest.

Meiotic kleisins: Rec8 and Rad21L—Virtually all eukaryotic species express a meiosis-specific paralog of Rad21 called Rec8. Rec8 is found in cohesin complexes present during meiotic prophase and is localized to the chromosome core prior to chromosome synapsis (Figs 2 and 3). Rec8 was originally identified in *Schizosaccharomyces pombe* in a screen for genes that are required for meiotic recombination [92]. Subsequent work done in numerous model organisms has demonstrated a conserved essential function for Rec8 in meiotic chromosome dynamics. Rec8-containing cohesin complexes are loaded onto chromosomes during pre-meiotic S phase. In budding yeast, mutations in Rec8 result in complete failure of sister chromatid cohesion as well as failure of homologous chromosome pairing [93]. In mice, the absence of Rec8 causes germ cell failure and sterility in both males and females. In $Rec8^{-/-}$ mice the initial stages in homologous chromosome pairing occur, but chromosomes do not synapse, and recombination fails [94,95].

In mice, loss of Rec8 leads to the aberrant assembly of axial structures, suggesting that Rec8-dependent cohesion controls proper development and homeostasis of SC structures [94]. Indeed, in $Rec8^{-/-}$ mice SYCP1, a component of the central region of mature SC, is occasionally observed between loosely associated sister chromatids (rather than between homologous partners), and there is also ultrastructural evidence of central element structures between sister chromatids. Interestingly, chromosomes with these abnormal SC structures often contain numerous breaks and discontinuities in the AEs as revealed by silver staining. In these meiocytes, recombination is initiated but does not progress beyond the initial steps [96].

Although Rad21-containing complexes can be found in meiotic cells in some organisms, several lines of evidence suggest that the tethering of sister chromatids together during meiosis occurs exclusively through Rec8 cohesin. In budding yeast, Rec8 is seen decorating meiotic chromosomes, while Rad21 is greatly diminished, and loss of Rec8 function leads to premature separation of sister chromatids prior to the first meiotic division, in a manner indistinguishable from that seen with the loss of the core cohesin subunit Smc3 [93]. In mouse oocytes, despite the presence of Rad21 cohesin complexes, the artificial cleavage of Rec8 with an engineered protease site causes premature separation of both homologs and sister chromatids in meiosis I, demonstrating unambiguously that sister chromatids are tethered exclusively by Rec8 in these cells [97].

In addition to the Rec8 protein, vertebrates express an additional Rad21 ortholog called Rad21L, also only during meiosis. Interestingly Rad21L is found on chromosome cores in a non-overlapping, alternating punctate pattern with Rec8, suggesting that Rad21L and Rec8 perform unique functions in meiotic chromosome development [98,99] (Fig. 3). In the mouse, Rad21L mutants arrest, like Rec8 mutants, in a diplotene-like state, with persistence of early-mid DNA repair markers suggesting impaired recombination and repair. In the absence of both Rec8 and Rad21L, mice are completely unable to form AE or LE structures [96]. This phenotype is reminiscent of the Rec8 phenotype in yeast, suggesting that meiosis-specific cohesin is essential for AE assembly and that Rec8-containing complexes are sufficient in yeast, while two distinct meiotic kleisins, Rec8 and Rad21L, contribute to this function in vertebrates.

The localization of Rec8 and Rad21L is consistent with a model of combined, non-redundant function for the two proteins in axis formation and synapsis. Interestingly, the patterns of Rec8 and Rad21L on the not-yet synapsed regions of homologous chromosomes in leptotene are remarkably similar between homologs. This observation has led to the proposal that Rad21L and Rec8 patterns on univalents may serve as a kind of bar code to enhance homolog recognition and thus pairing and synapsis [99]. There is some evidence for physical interaction of Rad21L, but not Rec8 or Rad21, with the transverse filament protein SYCP1 [98]. One possible model is that unique patterns of SYCP1 recruitment by Rad21L contribute to the efficiency of homolog recognition and nucleation of SC assembly. Indeed, when double strand breaks are prevented by mutation of Spo11, initial interactions between homologous chromosomes depend upon Rad21L, consistent with the model that Rad21L-dependent chromosome structure underlies initial homolog recognition [100].

Rad21L and Rec8 are clearly not functionally redundant. Unlike Rec8, Rad21L staining of the chromosome cores does not persist past pachytene [98,99,101]. Additionally, Rec8 is essential for centromere cohesion, while Rad21L is not found on the metaphase centromere and does not directly impact centromere cohesion.

The nematode *Caenorhabditis elegans* also expresses meiosis-specific kleisins, including REC-8 and two seemingly redundant additional kleisins called COH-3 and COH-4 [102,103]. Analysis of mutant phenotypes provides compelling evidence that these meiotic kleisins, as well as the SCC-1 kleisin (also present during meiosis), confer distinct functional properties to the cohesin complexes containing them. For example, REC-8 cohesin is required to establish cohesion during DNA replication, while COH-3 and COH-4 (COH-3/4) containing complexes are induced to become cohesive in response to meiotic DNA double strand breaks, well after pre-meiotic DNA replication is complete [104]. It is possible that Rad21L fulfills a function similar to COH-3/4 in vertebrates, as it is seen to load at a comparably late time during meiotic progression [87,98]. Similarly, the kleisin subunits may also determine the mechanism(s) by which particular complexes are removed from meiotic chromosomes during meiotic progression.

Additional meiotic cohesin subunits: Smc1β and STAG3—In vertebrate meiosis, not only are meiotic kleisin subunits expressed and incorporated into cohesin complexes, but meiosis-specific core subunits are also found in the complex (Fig. 2). A meiosis-specific form of Smc1 called Smc1β is found in some cohesin complexes in mammals [105]. (To avoid confusion the originally identified form is now referred to as Smc1α.) Smc1β-containing cohesin is found along chromosome axes throughout meiotic prophase, including through desynapsis in diplotene, and accumulates around centromeres in diakinesis [105]. Extensive immunoprecipitation analysis indicates that Smc1β is found in distinct separate complexes with each of the three kleisins present in meiosis: Rad21, Rad21L and Rec8 [98,101].

In the absence of Smc1β the meiotic chromosome axis–loop structure is abnormal in prophase, with chromosomes being ~ 50% shorter than their wild-type counterparts [106]. In males, meiosis arrests at a pachytene-like state, suggesting that pairing and synapsis are largely functional. Recombination fails and the animals of both sexes are sterile. Smc1β is

not present until leptotene, when it accumulates on chromosome cores and remains there until anaphase of meiosis I. Smc1β remains associated with centromeres until anaphase II, suggesting that Smc1β cohesin prevents sister chromatid separation in anaphase of meiosis I [107].

Vertebrates also express a meiosis-specific SA subunit, called STAG3 (Fig. 2). Like its mitotic counterparts SA1 and SA2, STAG3 interacts with the kleisin subunits of cohesin. It appears that STAG3 is the one invariant subunit of meiotic cohesin complexes: there is no evidence that STAG3 interacts with SMC1α-containing cohesin, and in Rec8/Rad21L double mutants STAG3 is no longer found along chromosome axes. There is conflicting evidence as to whether the mitotic SA proteins SA1 and SA2 are found in complexes with the meiotic kleisins Rad21L and Rec8 [98,99,101].

Stag3$^{-/-}$ mice have the most severe meiotic phenotype of all the single meiosis-specific cohesin mutants [108–110]. This phenotype is reminiscent of the *Rad21L*$^{-/-}$/*Rec8*$^{-/-}$ double mutant [108,110]. AEs entirely fail to develop and some markers of incomplete DNA repair such as γH2AX are present throughout chromatin. In addition, both centromeric and telomeric sister chromatid cohesion are compromised. Interestingly, in the absence of STAG3 there is still some limited recruitment of mitotic cohesins to the chromosome axes, which are grossly shortened [110]. Double strand breaks are generated, although recombination does not progress. In addition, the total level of Rec8 cohesin is reduced, suggesting that STAG3 in some way contributes to the expression or stability of these complexes [109].

Fission yeast also expresses a meiosis-specific Scc3 ortholog called Rec11. Rec11, like Rec8, is required for meiotic sister chromatid cohesion. Unlike many other meiosis-specific subunits of cohesin, this protein shows preferential localization to the chromosome arms, in association with Rec8 kleisin, while at the centromere Rec8 is found associated with the Scc3 subunit (Psm3) that is active in both mitosis and meiosis [111].

Sexual dimorphism—In mice that are compromised for meiotic cohesin expression, the meiotic phenotypes can differ between male and female animals, with the males generally being more severely compromised [112]. It is possible that the mechanisms are somehow distinct between males and females. An alternative explanation for this is that checkpoint activation in male meiosis leads to apoptotic degradation of defective cells at an earlier stage in meiotic progression. Indeed, failures in synapsis that occur due to loss of meiotic cohesion in males prevent meiotic sex chromosome inactivation as well as silencing of non-paired regions in somatic chromosomes, leading to ectopic expression of pro-apoptotic genes (reviewed in [113]). Whatever the cause, meiotic progression is generally more compromised in male meiotic cohesin mutant mice (e.g. *Smc1β*$^{-/-}$ or *Rad21L*$^{-/-}$) than in female [87,106].

Meiotic cohesion and chromosome structure: Meiotic cohesin promotes normal chromosome structure during meiotic progression. The effects may indeed fully explain the contributions of these cohesins in pairing and synapsis. In vertebrates, meiotic cohesin regulates normal axis–loop structures and thus chromosome length [94,95,106,110,114].

When meiotic cohesion is disrupted, the chromosome axes become shorter and the cloud of chromatin loops around the core is enlarged. It is easy to see how this might present a problem with pairing and ultimately synapsis, with most univalents being shorter and puffier than their wild-type counterparts. Cohesin at the core of the sister chromatid pair ensures the proper chromatin loop size and somehow resists the condensation caused by assembly of the SC. Smc1β, Stag3, Rec8 and Pds5 all contribute to normal chromosome loop–axis geometry: chromosomes are shorter in their absence.

Cohesin regulation in meiosis—Although important conclusions have been drawn based on the localization and mutant phenotypes of the meiotic cohesins, relatively little is known about how these complexes are regulated. In mitotic cells, cohesion establishment is stimulated both during DNA replication and in response to DNA damage (reviewed in [115,116]), and there is significant mechanistic overlap in these events. As described above, several proteins modulate cohesin's association with chromatin in response to mitotic cell cycle progression (Table 2). A number of these proteins have specific and interesting localization on meiotic chromosomes that suggests that they play specific roles in meiosis (Fig. 3).

The cohesin loader: Scc2/4: In mitotically growing cells, the Scc2/Scc4 complex is required both for DNA replication-mediated cohesion establishment and DNA damage-induced cohesion. In vertebrates, during mitotic cell cycle progression the association of this complex with chromatin is controlled by Dbf4-dependent kinase and is thus dependent on replication licensing, at least in the early embryo [117–119]. In budding yeast Scc2/Scc4 is recruited to nucleosome-free regions of chromatin, which are generated by the activity of the RSC chromatin remodeling complex [120]. It is required both for Rec8 expression and meiotic cohesion [121].

In *Drosophila* meiocytes, $Scc2^{Nipbl}$ colocalizes with the Smc1 and Smc3 subunits of cohesin along the arms of meiotic chromosomes in pachytene, and perhaps earlier [122] (Fig. 3). Similarly in mouse $Scc2^{Nipbl}$ is found associated with chromosome axes from zygotene until chromosomes are fully synapsed in late pachytene [123]. Interestingly, this localization suggests that cohesin loading by the $Scc2^{Nipbl}$ protein may occur well past pre-meiotic S phase, when the cohesin complexes containing Rec8 and Rad21L are loaded onto chromatin. The presence of the cohesin loader at this late stage (pachytene) is consistent with the observation that Rad21-containing cohesin complexes load onto chromosomes at this time. Thus, cohesion may be stabilized on chromosomes in meiosis by mechanisms that are distinct from the well-understood replication-dependent events in mitotic cells. It is possible that some fraction of meiotic cohesin loading is more analogous to damage-induced cohesion establishment, stimulated by signaling events downstream of meiotic DNA double strand breaks [70]. Consistent with this model, in *C. elegans* SCC2 is required for cohesin loading and for normal processing of meiotic double strand breaks [124]. In plants and insects, cohesin subunits have also been shown to bind meiotic chromosomes in a manner that suggests they are independent of DNA replication [125,126].

In humans, the $Scc2^{Nipbl}$ gene is haplo-insufficient: loss of one allele results in Cornelia de Lange syndrome, a pervasive developmental disorder [9]. In a mouse model of Cornelia de

Lange syndrome ($Scc2^{Nipbl+/-}$), although there is no direct reporting of meiotic phenotype, the frequency of mutant offspring is well below the expected Mendelian ratios and fertility is reduced, consistent with defects in gametogenesis [127]. Understanding the precise role of Scc2/Scc4 in meiosis is confounded by the pleiotropic effects that partial loss of function have on gene expression and thus growth and health throughout development.

The cohesin stability network in meiosis

As described above, several proteins modulate the stability of the interaction between cohesin and chromatin during mitotic progression. These proteins include the Eco/Esco enzymes, Wapl, Sororin and Pds5. While our mechanistic understanding of the roles that these proteins play in cohesin regulation is based on studies of mitotic cohesion, localization patterns and mutant phenotypes suggest that they play equally critical roles in meiotic chromosome dynamics.

Eco/Esco enzymes—During mitotic cell cycles, acetylation of the Smc3 subunit of cohesin by members of the Eco family of acetyltransferases is essential for the establishment of cohesion between sister chromatids [27–29]. Eco-dependent acetylation of Smc3 during DNA replication renders the cohesin complex resistant to the destabilizing activity of Wapl [41]. All vertebrates express two distinctly different Eco enzymes, called Esco1 and Esco2; both are capable of acetylating the Smc3 subunit of cohesin [26,30]. The activity of Eco1 in budding yeast is promoted through interaction of Eco with the replication machinery [128]. In contrast, the vertebrate enzymes can acetylate cohesin in a replication-independent manner, although only the acetylation during DNA replication is productive for cohesion establishment [26]. Cohesion establishment in meiosis does not precisely mimic the S phase reactions seen in mitotic cohesion establishment [26,28,31,128]. The meiosis-specific cohesin subunits Smc1β and STAG3 are both expressed in leptotene, after pre-meiotic S is complete, suggesting that their loading occurs independently of replication-dependent acetylation.

Localization of Esco enzymes has not proved informative about their roles in meiosis. The staining pattern for Esco2 during meiotic prophase is diffuse and not localized to particular structures. The exception is in the pachytene stage of male meiosis, in which the paired sex chromosomes, a structure called the sex body, stain intensely for Esco2 throughout the unpaired chromatin ([129]; S. R. and R. Pezza, unpublished). The sex body also stains intensely for markers of DNA damage signaling, including the phosphorylated histone variant H2AX (γH2AX) [130]. In budding yeast, Eco1 activity is downstream of H2AX phosphorylation during the DNA damage response [74,131]. It is possible that Esco2 localization to the sex body reflects the unique damage-signaling properties of this chromatin [132]. The expression and localization during meiosis of the other vertebrate cohesin acetylating protein Esco1 have not yet been reported.

The meiotic phenotype of loss of Eco/Esco activity has not been thoroughly investigated. In fission yeast meiosis, the homolog of Eco1, called Eso1, is essential for cohesion between sister chromatids, which is in turn required for mono-polar orientation of sister kinetochores [133,134]. In the absence of cohesin or Eso1 activity sister chromatids undergo premature

separation and thus are pulled away from each other in meiosis I. The meiotic function of Eso1 occurs primarily through acetylation of the Smc3 subunit of cohesin, called Psm3, although there may be additional acetylation substrates important for proper meiotic chromosome dynamics [133]. Esco2-deficient mice have been developed, though their meiotic phenotypes have not been described [135]. Similarly, Esco2 morphant zebrafish have been reported to have global cell cycle defects, although meiotic effects were not specifically reported [136]. Human patients with Roberts syndrome, which is caused by loss of Esco2 function, generally do not survive to sexual maturity and the effect of Esco2 on human gametogenesis has not been reported. Pregnancies have been reported among the small number of female patients who survive to adulthood, suggesting that fertility is not fully compromised [137].

Wapl and Sororin—In the absence of Wapl, mitotic chromosomes in vertebrate cells show an apparent over-cohesion phenotype, with excessive cohesin associated with interphase and mitotic chromosomes [36,46]. Although mitotic progression appears relatively normal, aneuploidy and micronuclei develop over time, suggesting that Wapl is essential for genome stability [138]. Cohesin association with chromatin throughout interphase is largely dynamic, and this dynamicity is critically dependent on Wapl [36]. In meiosis, Wapl shows specific localization to the chromosome axes both prior to and during synapsis [139,140]. The presence of Wapl on meiotic chromosome axes may suggest that cohesin's association with chromatin is dynamic throughout meiotic prophase.

In somatic cells, Sororin binds to cohesin after it is activated during DNA replication and inhibits the activity of Wapl, thereby stabilizing cohesion. Sororin recruitment requires acetylation of the cohesin complex by the Esco proteins [39,141]. In meiosis, Sororin is found on chromosome axes, but only *after* synapsis, and is retained at centromeres in diplotene (S. R. and R. Pezza, in preparation). This staining pattern suggests that during meiosis Sororin stabilizes cohesion after synapsis. This is remarkably different from the mitotic mechanism, in which Sororin is recruited *during* DNA replication to stabilize active cohesion [39], and suggests that it may be essential that cohesin remain dynamic to accommodate the complex chromosome behaviors of meiotic prophase.

Pds5—Given its critical importance to mitotic cohesion, and the fact that it promotes Eco, Wapl and Sororin function, it is not surprising that Pds5 also plays a critical role in meiosis. In budding yeast, Pds5 is required for meiotic cohesion and is found along chromosome cores in meiotic prophase, colocalizing with, and dependent upon, Rec8 [142]. In contrast, Rec8 loading does not require Pds5. At anaphase of meiosis I, Pds5 is retained on centromeres, much like the meiotic cohesin complexes containing Rec8 and Smc1β. In the absence of Pds5, sister chromatids separate prematurely. Interestingly, much like Rec8 in vertebrate meiosis, Pds5 both promotes homolog pairing and inhibits ectopic synapsis between sister chromatids [143]. Although the data are still limited, it appears that the role of Pds5 in meiosis is consistent with its role in mitotic cohesion, as was originally proposed in *Sordaria* [144]. Vertebrates express two orthologs of Pds5, called Pds5A and Pds5B [38,45]. It is still not entirely clear what the functional differences are between these two proteins, although in mouse models there are some phenotypic differences. Pds5A is not

required for gametogenesis [145], while Pds5B is highly expressed in the mouse testis and during meiotic prophase is found along chromosome axes prior to and during synapsis, in a manner similar to that of yeast Pds5 [146]. These data all suggest that Pds5 interacts with meiotic cohesin as it does with mitotic cohesins, promoting cohesin activity, most probably by integrating the activities of cohesin regulators such as Wapl and Sororin.

Cohesin phosphorylation—In vertebrates, the association of cohesin with chromatin is modified during mitotic entry by phosphorylation, particularly by the Polo-like kinase (Plk1) [58]. Phosphorylation promotes removal of cohesin from chromatin, thus promoting sister chromatid resolution and mitotic condensation in prophase I. In yeast meiosis, phosphorylation of Rec8 cohesin by both casein kinase 1 and Dbf4-dependent kinase promote its cleavage by separase, leading to separation of homologs in meiosis I [61–63].

Questions remaining

Much of what we understand about cohesin function comes from studies in model organisms, particularly budding yeast, and with a few exceptions the regulatory steps appear to be conserved throughout eukaryotic phylogeny. Currently, our understanding of the functional differences between meiotic and mitotic cohesin complexes is very limited. What, for example, are the biochemical differences between the meiotic and mitotic cohesins? Does their unique biochemistry affect their interaction with regulatory proteins such as the Eco enzymes, the Scc2/Scc4 loader complex, Pds5 or Wapl? Does STAG3 interact with Pds5 in the same manner as the mitotic counterparts SA1 and SA2?

One very interesting puzzle is the nature of cohesin dynamics throughout meiotic prophase. Smc1β is not present during pre-meiotic S phase and yet is found on chromosome cores starting in leptotene. The cohesin loaded during pre-meiotic S exclusively contains Smc1α (not Smc1β). Similarly, Rad21, which is largely absent in early meiotic prophase, is found to load onto chromosome cores in late pachytene, while Rad21L is removed. It is difficult to draw analogies with replicative mitotic cohesion establishment because this occurs exclusively during DNA replication. Does the mechanism of cohesion establishment in meiotic prophase more closely resemble replicative cohesion establishment or damage-induced cohesion? What is the role of the Scc2 cohesin loader on synapsed chromosomes?

It is possible that cohesin contributes to meiotic chromosome dynamics not only through its canonical role in tethering pieces of chromatin together in replication-dependent reactions, but also by promoting higher order interactions between meiotic structures. Experiments indicate that, at least in some systems, cohesin and separase play important roles in centrosome dynamics [147–150]. The events are thought to be DNA independent, leading to the notion that cohesin might in fact be a multi-purpose intracellular glue that can be deployed in very different circumstances. Might meiotic cohesins tether together not only sister chromatids but also other meiotic chromosome components such as elements of the SC? Should the term ‘cohesion establishment’ be reserved for replication-dependent tethering of sister chromatids, and do we need a new term to explain some of the reactions that occur in meiotic prophase? A deeper understanding of cohesin regulation during meiotic progression, as well as the development of meiotic models in which cohesin can be

conditionally inactivated, will help us address this exciting question. Biochemical analyses of meiotic cohesins and the identification of interacting proteins might contribute to a fuller understanding of meiotic cohesin function. Finally, experiments in which the stability of association of various cohesin subunits with meiotic chromosomes, such as fluorescence recovery after photobleaching analysis, would be extremely helpful in determining whether meiotic cohesin undergoes an ‘establishment’-like transition during progression through meiotic prophase.

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Abbreviations

AE	axial element
LE	lateral element
SC	synaptonemal complex

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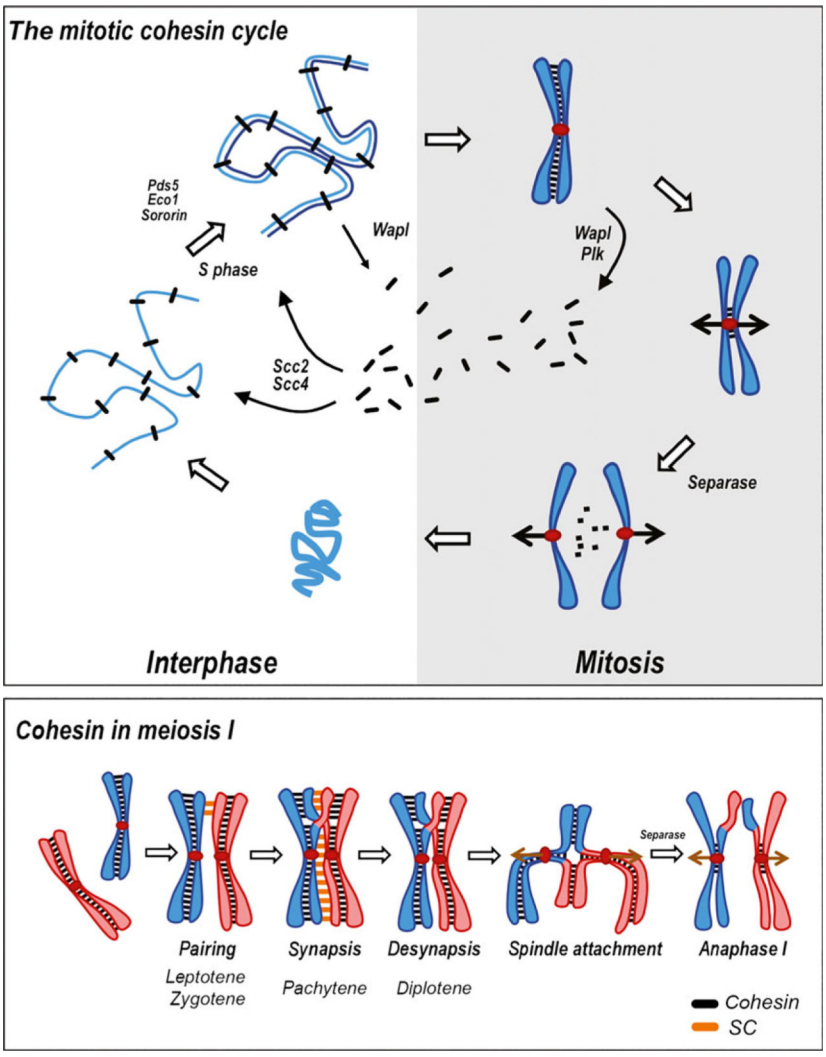

Fig. 1.

Upper panel: the mitotic cohesin cycle. Shown is the vertebrate cohesin cycle. Cohesin (black bars) is loaded onto chromosomes as cells enter interphase by the Scc2/Scc4 loader complex. Following Pds5 loading cohesin is acetylated by Eco1 during S phase, which stimulates Sororin binding and stabilization of cohesin. Throughout interphase, cohesin is kept largely dynamic by the activity of Wapl. During mitotic entry the bulk of cohesin is removed from chromosomes by both Wapl and Plk-dependent phosphorylation, although some is retained at the centromere. At anaphase onset, the site-specific protease called separase is activated and cleaves the Rad21 subunit of cohesin, allowing separation of sister chromatids. Cohesin reloads as chromosomes decondense in telophase, and the cycle begins again. Lower panel: cohesin in meiosis. This drawing illustrates the presence of cohesin during meiosis I chromosome dynamics. Cohesin (black bars) is loaded onto chromosomes during pre-meiotic S phase (not shown), tethering sister chromatids together. This cohesin is retained during homolog pairing and synapsis, and is required for the proper assembly of the synaptonemal complex (SC; orange). Following desynapsis in diplotene, cohesion between sister chromatids distal to the point of crossover provides resistance to spindle pulling forces

(brown arrows) at metaphase I arrest. At anaphase, separase-dependent cleavage of cohesin on chromosome arms allows arm and homolog separation at meiosis I anaphase. At this time, cohesin is protected from cleavage at the centromere by Sgo (not shown), preventing sister separation.

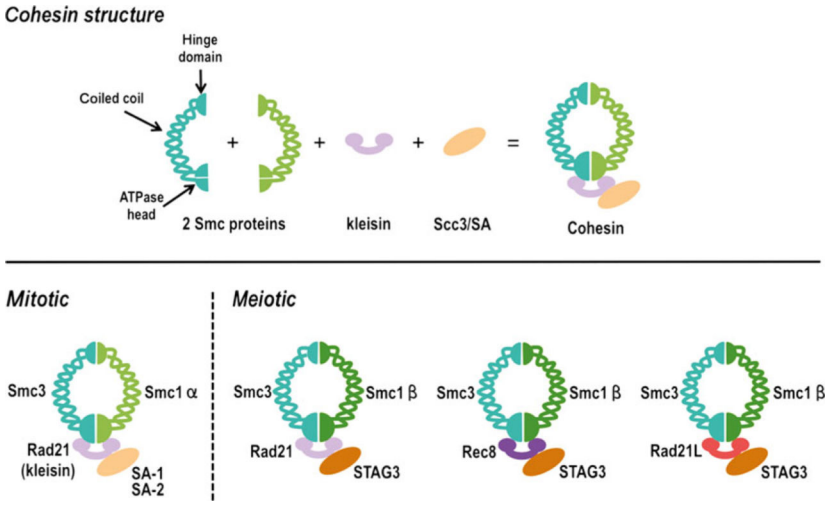

Fig. 2.

Cohesin complexes in mitosis and meiosis. Cohesin is composed of four core subunits assembled as shown (top). These include two Smc proteins that fold back on themselves to form an ATPase head domain and a central hinge. A dimer of Smc proteins interacts with a kleisin subunit and an Scc3/SA protein to form the core four-subunit complex. The subunit composition of the sole mitotic cohesin complex is shown (bottom left), and the various meiotic complexes are also indicated (bottom right). All known cohesin complexes contain the same Smc3 protein. Rec8-containing cohesin is found in most eukaryotic meiocytes, while the remaining meiotic cohesins are found only in higher eukaryotes. Additional meiosis-specific subunits of cohesin include the Smc1α-like subunit called Smc1β, as well as the meiosis-specific kleisins Rec8 and Rad21L. In vertebrates one of two SA subunits, SA1 or SA2, is found in mitotic cohesin. In meiotic cohesin this is substituted with a meiosis-specific ortholog called STAG3.

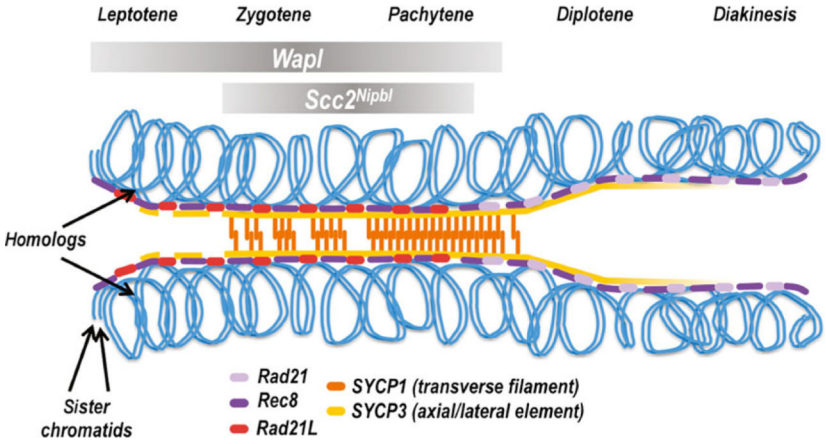

Fig. 3.

Meiotic cohesins during meiosis I prophase. The relative timing of loading of the different kleisin subunits during mammalian meiotic prophase is indicated. Rec8 and Rad21L are thought to be loaded during pre-meiotic S phase; Rad21-containing complexes are not present early and decorate the chromosome axes beginning in late pachytene. Rec8 and Rad21L have non-overlapping patterns of localization along the chromosome axes. For simplicity, the timing with which the cohesin regulators Wapl and $Scc2^{Nipbl}$ are associated with the chromosome axes is indicated by the grey bars at the top. Precise localization of these regulatory proteins relative to the SC components has not been determined.

Table 1

Cohesin regulators in mitosis and meiosis. Summary of cohesin regulatory proteins and their localization and phenotypes in meiosis, if known. In the case of Wapl, plant data were included because there were few data available from yeast or vertebrate models.

Cohesin regulators			**Meiotic roles?**	
Yeast protein	**Function**	**Metazoan form(s)**	**Meiotic localization**	**Meiotic phenotype**
Eco1 (Sc) Eso1 (Sp)	Cohesin acetylation and function	Esco1 Esco2	Along chromosome axes, LE	Fission yeast: Smc3 acetylation Budding yeast and vertebrates: ND
Scc2 Scc4	Cohesin loading complex	Nipbl Mau2	Along chromosome axes into early pachytene	Loss of cohesion in yeast. Not tested in vertebrates
Rad61	Destabilization of cohesion, blocked by Smc3 acetylation		ND	ND
		Wapl (vertebrates)	Along chromosome axes in pachytene	ND
		Wapl1, Wapl2 (plants)	ND	Cohesin not properly removed in meiosis, broken chromosomes, uneven segregation
Pds5	Scaffold for cohesin regulation	Pds5A Pds5B	Pds5A absent, Pds5B on axial cores	Pds5A: no apparent phenotype Pds5B: germ cell failure
Esp1 ‘Separase’	Site specific protease, cleaves Rad21 at anaphase	Separase	ND	Cleaves Rec8 and Rad21. Rad21L cleavage not tested
Not found	Inhibits Wapl, stabilizes cohesion	Sororin	Along chromosome axes after synapsis	ND

Table 2

Cohesin in mitosis and meiosis. Summary of cohesin subunits in yeast and mammalian mitosis and meiosis. The meiotic phenotypes are summarized in the last two columns. See text for details. DSB, double strand break.

Mitotic cohesin			**Meiotic cohesins (mammalian)**			
Yeast protein	**Metazoan form(s)**	**Function**	**Meiosis specific isoform**	**Meiotic localization**	**Meiotic arrest point**	**Other phenotypes?**
Smc1	Smc1	Core cohesin complex	Smc1β	Chromosome axes	Pachytene-like	Females: complete error-prone meiosis. Males: incomplete synapsis and meiotic failure. Shortened axes
Smc3	Smc3	Core cohesin subunit.	–			
Scc1 (Rad21, Mcd1)	Rad21	‘Kleisin’ subunit. Cleaved for cohesin release at anaphase	Rec8	Chromosome axes, alternating with Rad21L	Zygotene-like	Meiotic failure. Some pairing, failure to repair DSBs. Shortened axes
			Rad21L	Chromosome axes, alternating with Rec8	Zygotene-like	Meiotic failure. Pattern on homologs similar prior to synapsis. Failure to repair DSBs
Scc3	SA-1 SA-2	Linker to Pds5, other	Stag3	Chromosome axes	Zygotene-like	Meiotic failure. No DSB repair. Loss of Smc1β, Rec8 and Rad21L on cores, shortened axes