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REVIEW ARTICLE

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The cohesin complex in mammalian meiosis

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Abstract

Cohesin is an evolutionary conserved multi-protein complex that plays a pivotal role in chromosome dynamics. It plays a role both in sister chromatid cohesion and in establishing higher order chromosome architecture, in somatic and germ cells. Notably, the cohesin complex in meiosis differs from that in mitosis. In mammalian meiosis, distinct types of cohesin complexes are produced by altering the combination of meiosis-specific subunits. The meiosis-specific subunits endow the cohesin complex with specific functions for numerous meiosis-associated chromosomal events, such as chromosome axis formation, homologue association, meiotic recombination and centromeric cohesion for sister kinetochore geometry. This review mainly focuses on the cohesin complex in mammalian meiosis, pointing out the differences in its roles from those in mitosis. Further, common and divergent aspects of the meiosis-specific cohesin complex between mammals and other organisms are discussed.

1 | OVERVIEW OF CHROMOSOME DYNAMICS DURING MEIOSIS

The meiotic cell cycle consists of a single DNA replication followed by two rounds of chromosome segregation (meiosis I and meiosis II), which halves the chromosome number to ultimately produce haploid gametes (Figure 1a). Remarkably, the structure and behavior of the chromosomes during meiosis are markedly different to those in mitosis. During meiotic prophase I, sister chromatids are organized into proteinaceous structures, termed axial element (AE) or chromosome axis, on which the synaptonemal complex (SC) is assembled (Figure 1b; Zickler & Kleckner, 1999). Homologous chromosomes (homologues) then undergo pairing (Barzel & Kupiec, 2008; Bhalla & Dernburg, 2008; Gerton & Hawley, 2005), synapsis (Cahoon & Hawley, 2016; Page & Hawley, 2004) and meiotic recombination yielding crossovers, a process that produces physical linkages between homologues called chiasmata (Figure 1b,c; Baudat, Imai, & Massy, 2013; Handel & Schimenti, 2010; Keeney, Lange, & Mohibullah, 2014; Lam & Keeney, 2015; Zickler & Kleckner, 2015). A crucial point concerning meiotic recombination is that a specific active mechanism confers dominance on homologues for recombination to suppress sister chromatid exchange (SCE; Zickler & Kleckner, 1999). During these processes, the chromosomes undergo dynamic movement to facilitate homologue pairing and synapsis, which is driven by telomeres attached to the nuclear membrane (Hiraoka & Dernburg, 2009; Koszul & Kleckner, 2009; Shibuya & Watanabe, 2014). Consequently, those processes yield bivalent chromosomes, whereby two homologous chromosomes are physically connected by chiasmata. Chiasmata play an essential role in positioning homologous chromosomes so that they are captured by microtubules from opposite poles during metaphase I (Sakuno, Tanaka, Hauf, & Watanabe, 2011). At anaphase I, homologous chromosomes are segregated toward opposite poles of the spindle by dissolution of chiasmata (Buonomo, Clyne, Fuchs, Loidl, & Uhlmann, 2000; Kudo, Wassmann, Anger, Schuh, & Wirth, 2006). Thus, in contrast to mitosis, meiosis I homologous chromosomes rather than sister chromatids are segregated into opposite directions to reduce the chromosome number by half (Watanabe, 2012). To accomplish this process in meiosis I, sister kinetochores face the same direction so that sister chromatids are co-segregated into the

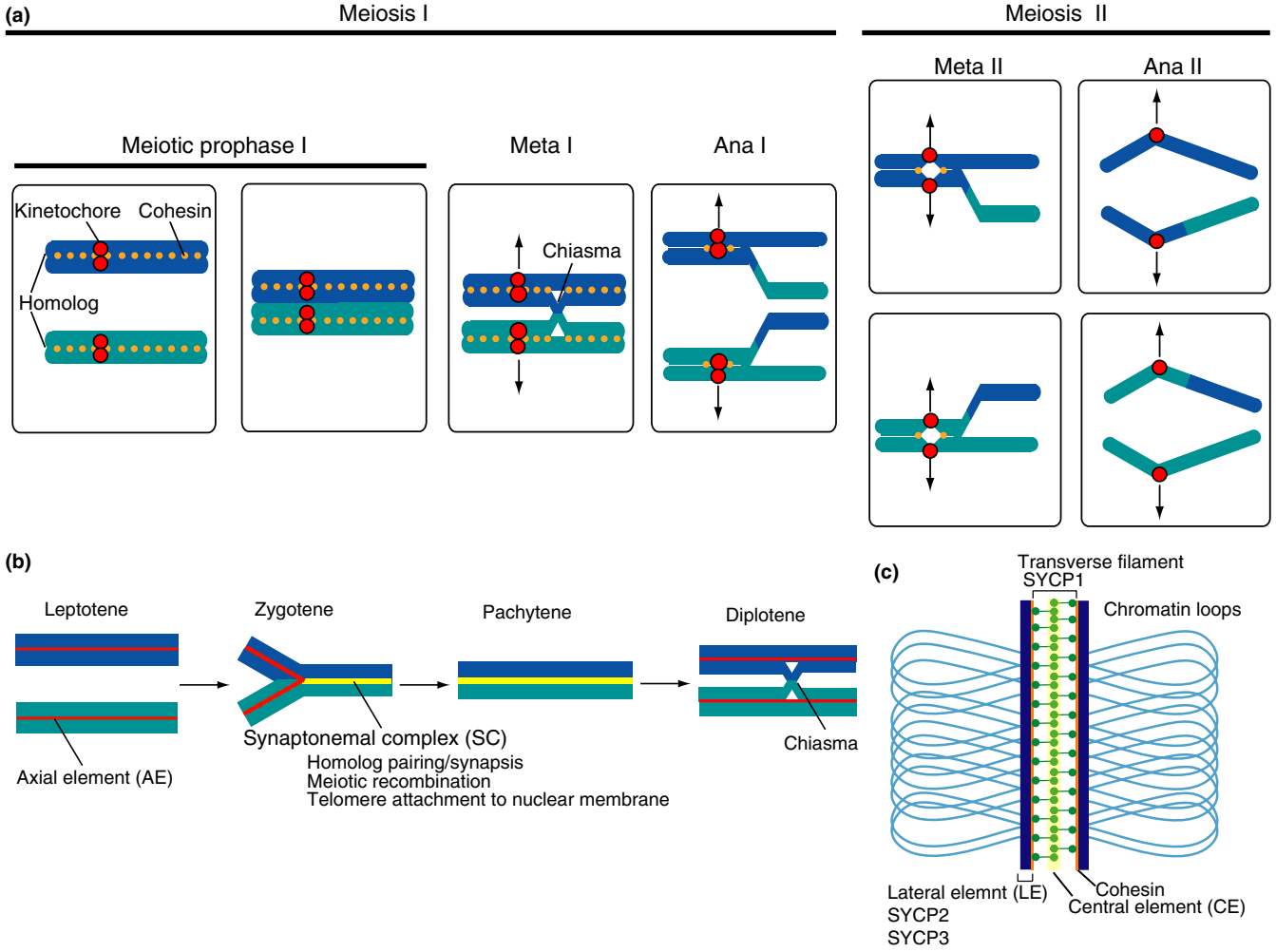
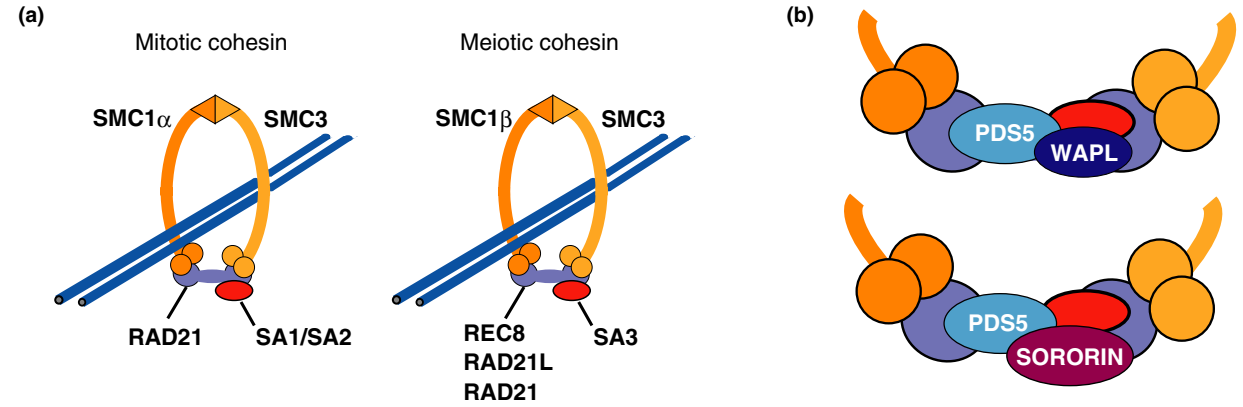


FIGURE 1 Schematic of chromosome dynamics during meiosis. (a) Schematics of Meiosis I and Meiosis II. In meiosis I, homologous chromosomes, rather than sister chromatids, are segregated in opposite directions. At anaphase I, homologous chromosomes are segregated toward opposite poles of the spindle by the dissolution of chiasmata. In meiosis II, sister chromatids are segregated. (b) Cohesin plays crucial roles in meiosis-specific chromosomal events during meiotic prophase I. Meiotic prophase I is prolonged compared to canonical G2 phase of cell cycle and is divided into five substages according to chromosome morphology. During meiotic prophase I, sister chromatids are organized into an axial element (AE). Cohesin loads onto chromatin during leptotene. Homologous chromosomes undergo pairing and synapsis through leptotene to zygotene. The synaptonemal complex (SC) is fully assembled between homologous chromosomes at pachytene. Meiotic recombination generates crossover between homologous chromosomes, yielding physical linkages called chiasmata. At diplotene, the SC is disassembled. Although cohesin largely dissociates from the chromosome arm after late pachytene, it persists around centromeres until metaphase II. (c) Schematic of the synaptonemal complex (SC). When the SC is assembled between homologous chromosomes, the AE is called lateral element (LE). Transverse filaments link two LEs. Cohesin locates at the most inner side of the LE

same daughter cell, a process named monopolar kinetochore orientation. In meiosis II, pairs of sister chromatids are segregated at anaphase II, which employs the same mechanisms as mitosis. As described later, cohesin plays crucial roles in all of these sequential chromosomal events during meiosis.

2 | COHESIN COMPLEXES IN MITOSIS

When the chromosomes are replicated in the S-phase, sister chromatids are held together by a mechanism called sister chromatid cohesion, which enables accurate chromosome segregation in both mitosis and meiosis. In mammalian somatic cells, sister chromatid cohesion is mediated by cohesin, an evolutionary conserved multi-protein complex. Cohesin contains four core subunits: two subunits of the structural maintenance of chromosomes (SMC) protein family, SMC1α and SMC3; the kleisin family protein RAD21/SCC1; and either one of two accessory subunits, SA1/STAG1 or SA2/STAG2 (Figure 2a,c; Losada & Hirano, 2005; Nasmyth & Haering, 2009). Other accessory proteins, PDS5A/PDS5B (Losada, Yokochi, & Hirano, 2005; Shintomi & Hirano, 2009), WAPL (Gandhi, Gillespie, & Hirano, 2006; Kueng,



(c)

		Vertebrates	Budding yeast	Fission yeast	Fly	Nematoda
Cohesin subunits	SMC	SMC1α SMC1β*	Smc1	Psm1	SMC1	SMC-1
		SMC3	Smc3	Psm3	SMC3	SMC-3
	αKleisin	RAD21/SCC1 RAD21L* REC8*	Scc1/Mcd1 Rec8*	Rad21 Rec8*	RAD21/Vtd C(2)M* SOLO*	COH-1 SCC-1/COH-2 COH-3* COH-4* REC-8*
		SA1 SA2 SA3*	Scc3	Psc3 Rec11*	Stromalin/SA SUNN*	SCC-3
		PDS5A PDS5B	Pds5	Pds5	PDS5	PDS-5
		WAPL	Wpl1/Rad61	Wpl1	WAPL	WAPL-1
		SORORIN			Dalmatian	

(* meiosis specific)

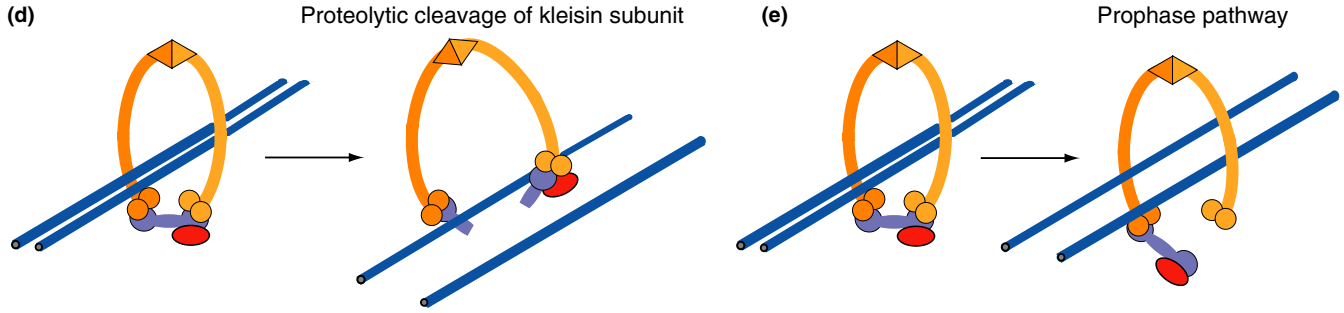


FIGURE 2 The cohesin complex in mitosis and meiosis. (a) Sister chromatids (indicated by blue bars) are held together by cohesin complexes in mitosis and meiosis. Cohesin contains four core subunits, SMC1α, SMC3, the kleisin family protein RAD21/SCC1 and SA1 or SA2. The cohesin complex in meiosis differs from that in mitosis. In mammalian germ cells, there are two meiosis-specific kleisin subunits, REC8 and RAD21L. SMC1α and SA1/SA2 are substituted by the meiosis-specific cohesin subunits, SMC1β and SA3, respectively. (b) PDS5A/PDS5B, WAPL and SORORIN are associated with the cohesin complex and regulate the dynamic interaction of cohesin with chromatin. SORORIN-PDS5B interaction stabilizes cohesin loading onto the chromatin (lower). WAPL facilitates cohesin removal by competing with SORORIN for PDS5 binding (upper). (c) Mitotic and meiotic cohesin subunits are widely conserved throughout diverse species, as listed. (d) When sister chromatids are segregated, the kleisin subunit of the cohesin complex is cleaved by separase, dissolving sister chromatid cohesion. (e) In the prophase pathway, WAPL facilitates dissociation of cohesin by cleavage-independent mechanism

Hegemann, Peters, Lipp, & Schleiffer, 2006) and SORORIN (Nishiyama, Ladurner, Schmitz, Kreidl, & Schleiffer, 2010; Nishiyama, Sykora, Huis in 't Veld, Mechtler, & Peters, 2013; Schmitz, Watrin, Lenart, Mechtler, & Peters, 2007) are weakly associated with the cohesin complex and regulate the dynamic interaction between cohesin and the chromatin (Figure 2b). Although SORORIN-PDS5B interaction stabilizes cohesin loading onto the chromatin, WAPL facilitates dissociation of cohesin by competing with SORORIN for the binding to PDS5B (Figure 2e; Nishiyama et al., 2010). Other components such as SCC2/SCC4 (NIPBL/MAU2) complex act for cohesion loading during G1 phase (Ciosk,

Shirayama, Shevchenko, Tanaka, & Toth, 2000; Watrin, Schleiffer, Tanaka, Eisenhaber, & Nasmyth, 2006). Eco1 homologues, ESCO1 and ESCO2, acetylate SMC3, which acts for the establishment of cohesion and regulates cohesin dynamics on the chromatin (Alomer, Silva, Chen, Piekarz, & McDonald, 2017; Ivanov, Schleiffer, Eisenhaber, Mechtler, & Haering, 2002; Kenna, & Skibbens, 2003; Minamino, Ishibashi, Nakato, Akiyama, & Tanaka, 2015; Skibbens, Corson, Koshland, & Hieter, 1999; Zhang, Shi, Li, Kim, & Jia, 2008). HDAC8 deacetylates SMC3 (Deardorff, Bando, Nakato, Watrin, & Itoh, 2012). It is proposed that the cohesin complex forms a ring structure that encircles sister chromatids during DNA replication. Replicated DNA strands are topologically embraced by SMC1α and SMC3 heterodimers through their coiled-coil stretches, whose ends are closed by the kleisin RAD21/SCC1. Sister chromatid cohesion persists until anaphase when sister chromatids are segregated after the kleisin subunit of the cohesin complex is cleaved by the protease separase (Figure 2d). This cohesion is important, not only for pairwise alignment of the chromosomes on the mitotic spindle, but also for the generation of tension across the centromeres, which ensures bipolar attachment of the chromosomes during mitosis. Moreover, in somatic cells, the cohesin complex participates in transcriptional regulation by collaborating with an insulator-binding factor, CTCF (Wendt & Peters, 2009; Wendt, Yoshida, Itoh, Bando, & Koch, 2008), and a transcriptional coactivator, Mediator (Kagey, Newman, Bilodeau, Zhan, & Orlando, 2010). CTCF establishes chromatin loops by cooperating with cohesin and forms topologically associated domains (TAD) in interphase nuclei (Gassler, Brandao, Imakaev, Flyamer, & Ladstatter, 2017; Ghirlando & Felsenfeld, 2016; Wendt, 2017; Wutz, Varnai, Nagasaka, Cisneros, & Stocsits, 2017; Zuin, Dixon, Reijden, Ye, & Kolovos, 2014). Accordingly, it has been known that mutations in cohesin-related genes lead to human developmental disorders, called cohesinopathies, caused by transcriptional dysregulation rather than defect in sister chromatid cohesion (Barbero, 2013; Horsfield, Print, & Monnich, 2012). It is presently unknown whether the meiosis-specific cohesin plays a role in the transcription during meiosis.

3 | COHESIN COMPLEXES IN MEIOSIS

In meiosis, the cohesin complex is crucial, not only for sister chromatid cohesion but also for numerous meiosis-specific chromosomal events. Notably, the cohesin complex in meiosis differs from that in mitosis (Figure 2a,c). In mammalian germ cells, there are two meiosis-specific kleisin subunits, REC8 (Eijpe, Offenberg, Jessberger, Revenkova, & Heyting, 2003; Lee, Iwai, Yokota, & Yamashita, 2003; Parisi, McKay, Molnar, Thompson, & Spek, 1999) and RAD21L (Gutierrez-Caballero, Herran, Sanchez-Martin, Suja, & Barbero, 2011; Ishiguro, Kim, Fujiyama-Nakamura, Kato, & Watanabe, 2011; Lee & Hirano, 2011), in addition to somatic kleisin subunit, RAD21/SCC1 (Parra, Viera, Gomez, Page, & Benavente, 2004). Furthermore, in mammalian germ cells, SMC1α and SA1/SA2 are largely replaced by other meiosis-specific cohesin subunits, SMC1β (Revenkova, Eijpe, Heyting, Gross, & Jessberger, 2001) and SA3/STAG3 (Bayes, Prieto, Noguchi, Barbero, & Perez Jurado, 2001; Prieto, Suja, Pezzi, Kremer, & Martinez, 2001), respectively. Although it has been shown that a minor fraction of the meiotic cohesin complex contains the somatic subunits SA2 and/or SMC1α in spermatocytes (Prieto, Pezzi, Buesa, Kremer, & Barthelemy, 2002; Revenkova, Eijpe, Heyting, Hodges, & Hunt, 2004), their precise role during meiosis has yet to be fully clarified. Transfection studies in somatic cells suggest that SA3, but not SA1/SA2, interacts with REC8 to import it into the nuclei (Wolf, Cuba Ramos, Kenzel, Neumann, & Stemmann, 2018), suggesting a specific role of SA3 subunit in the assembly of meiotic cohesin. Although SMC1α can substitute SMC1β in the AE formation and homologue synapsis, SMC1β plays an essential role in telomere integrity for chromosome dynamics during meiosis (Biswas, Wetzker, Lange, Christodoulou, & Seifert, 2013; Biswas, Stevense, & Jessberger, 2018). Since genetic disruption of either one of the meiosis-specific cohesin subunits leads to infertility with different phenotypes of chromosome structure, each of them plays an essential role in chromosome dynamics during meiosis (Bannister, Reinholdt, Munroe, & Schimenti, 2004; Fukuda, Fukuda, Agostinho, Hernandez-Hernandez, & Kouznetsova, 2014; Herran, Gutierrez-Caballero, Sanchez-Martin, Hernandez, & Viera, 2011; Hodges, Revenkova, Jessberger, Hassold, & Hunt, 2005; Hopkins, Hwang, Jacob, Sapp, & Bedigian, 2014; Ishiguro, Kim, Shibuya, Hernandez-Hernandez, & Suzuki, 2014; Llano, Gomez, Garcia-Tunon, Sanchez-Martin, & Caburet, 2014; Revenkova et al., 2004; Winters, McNicoll, & Jessberger, 2014; Xu, Beasley, Warren, Horst, & McKay, 2005). The accessory proteins, PDS5B (Fukuda & Hoog, 2010), WAPL (Adelfalk, Janschek, Revenkova, Blei, & Liebe, 2009; Brieno-Enriquez, Moak, Toledo, Filter, & Gray, 2016; Zhang, Hakansson, Kuroda, & Yuan, 2008) and SORORIN (Gomez, Felipe-Medina, Ruiz-Torres, Berenguer, & Viera, 2016; Jordan, Eyster, Chen, Pezza, & Rankin, 2017), also appear on chromosomes during meiotic prophase I and regulate the stability of the binding of cohesin on the chromatin. Thus, in addition to a canonical somatic cell-type cohesin complex, different combinations of subunits generate distinct cohesin complexes during meiosis, which provide specialized functions for generating meiotic chromosomes. As described below, meiosis-specific cohesin complexes are crucial not only for sister chromatid cohesion but also for the formation of the AEs of the chromosomes and for the SC assembly during prophase I (Cahoon & Hawley, 2016; Page & Hawley, 2004; Zickler & Kleckner, 1999).

4 | KLEISIN SUBUNITS DETERMINE THE SPATIOTEMPORAL DISTRIBUTION PATTERNS OF DISTINCT COHESIN COMPLEXES ON THE CHROMOSOMES DURING MEIOSIS

Three different types of cohesin complexes exist in mammalian meiotic cells that contain one of the kleisin subunits REC8, RAD21L or RAD21 (Figure 2a). Given that other subunits such as SA3, SMC1β and SMC3 are commonly shared in most of these cohesin complexes (Ishiguro et al., 2011; Lee & Hirano, 2011), it is considered that the kleisin subunits produce different specificities of cohesin complexes during meiosis.

In meiotic prophase, REC8-type cohesin localizes along the chromosomes before meiotic DNA replication and persists throughout the first meiotic division, at least at the centromeres, until metaphase II (Figure 3a). In contrast, the RAD21L-type cohesin mostly appears on the chromosomes after DNA replication, which culminates at the leptotene/zygotene stage. Then, RAD21L-type cohesin mostly dissociates from the chromosomes after late pachytene (Figure 3a), which contrasts to the persistent localization of REC8-type cohesion until meiosis II (Ishiguro et al., 2014; Lee & Hirano, 2011). Cohesin removal at later stages of meiotic prophase I is mediated by WAPL (Brieno-Enriquez et al., 2016), whose mechanisms are similar to the prophase pathway in mitosis (Figure 2e; Buheitel & Stemmann, 2013; Gandhi et al., 2006; Hauf, Roitinger, Koch, Dittrich, & Mechtler, 2005; Kueng et al., 2006; Sumara, Vorlaufer, Stukenberg, Kelm, & Redemann, 2002; Waizenegger, Hauf, Meinke, & Peters, 2000): Dephosphorylation of WAPL by PP1γ promotes its association with PDS5B, which in turn facilitates the cohesin removal during late meiotic prophase I (Brieno-Enriquez et al., 2016). NEK1 facilitates this process through PP1γ phosphorylation. WAPL-mediated cohesin removal during meiotic prophase I is also conserved in budding yeast (Challa, Lee,

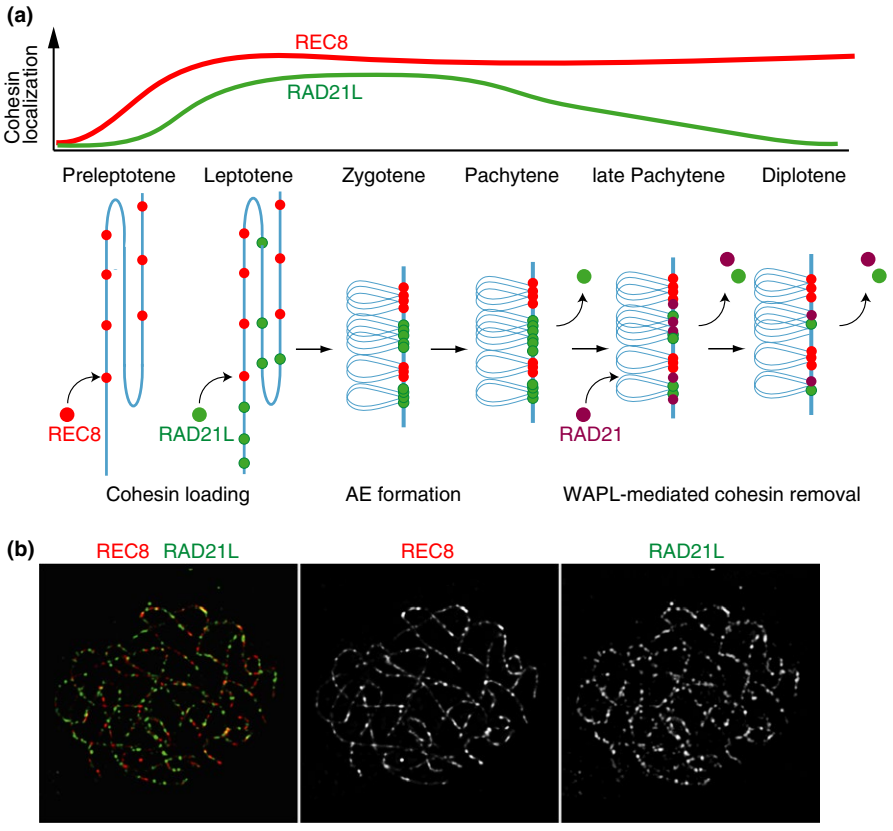


FIGURE 3 RAD21L- and REC8-cohesin exhibit different spatiotemporal localization patterns on the chromosomes during meiotic prophase. (a) Levels of REC8 and RAD21L localization on the chromatin (upper). Schematic model of REC8, RAD21L and RAD21 localization during meiotic prophase (lower). Chromatins are shown in blue. REC8-, RAD21L-, and RAD21-cohesins are shown in red, green and purple circles, respectively. In meiotic prophase, REC8-type cohesin localizes along chromosomes before or during pre-meiotic DNA replication (preleptotene) and persists throughout the first meiotic division. RAD21L-type cohesin mostly appears on the chromosomes after DNA replication and culminates at the leptotene/zygotene stage. REC8 and RAD21L show mutually exclusive localization along the chromosomes. RAD21L-type cohesin mostly dissociates from the chromosomes after late pachytene by WAPL-mediated mechanism. RAD21 transiently appears on the chromosomes in late pachytene and mostly dissociates after diplotene onward. Cohesin removal at later stage of meiotic prophase I is mediated by WAPL. (b) Immunostaining of REC8 and RAD21L on chromosome spread of zygotene oocyte

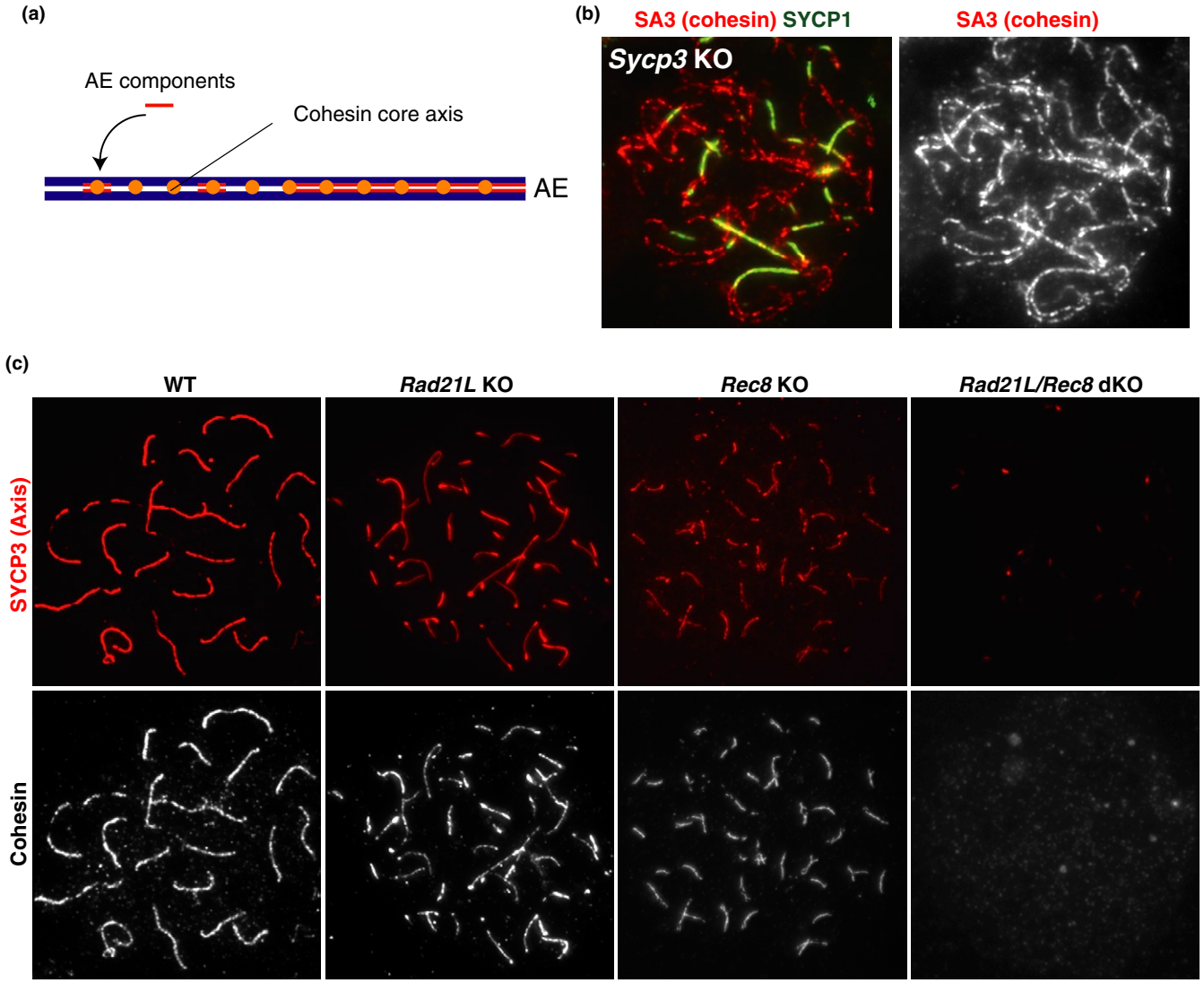


FIGURE 4 Chromosome axis formation depends on meiotic cohesins. (a) Cohesin is loaded on the chromatin before the AE components, forming an axis-like structure "cohesin core axis," along the chromosome. Red line: the AE components, SYCP2, SYCP3. (b) The "cohesin core axis," which is marked by cohesin subunits SA3, is organized even in the absence of the AE component SYCP3. (c) Chromosome spread of spermatocytes from WT and cohesin mutants was immunostained for SYCP3, a component of the AE, and cohesion subunit. Cohesin immunostaining was probed with SMC3 for WT and *Rec8/Rad21L* dKO, REC8 for *Rad21L* KO or RAD21L for *Rec8* KO. In the absence of either REC8 or RAD21L, AE formation is partially impaired and exhibits a shorter axis length, compared to wild type. In *Rec8* KO, partial AE is formed depending on RAD21L-cohesin. In *Rad21L* KO, AE is formed depending on REC8-cohesin. AE formation is mostly abolished in *Rec8/Rad21L* dKO during meiotic prophase

Shinohara, Kim, & Shinohara, 2016), nematoda (Crawley, Barroso, Testori, Ferrandiz, & Silva, 2016) and *Arabidopsis* (De, Sterle, Krueger, Yang, & Makaroff, 2014). Like RAD21 at anaphase, REC8 is cleaved by separase (Kudo et al., 2006, 2009); however, the question of whether RAD21L undergoes separase-mediated cleavage remains unresolved.

Intriguingly, REC8 and RAD21L exhibit mutually exclusive localization rather than co-localization along the chromosomes of spermatocytes and oocytes (Figure 3b; Ishiguro et al., 2011; Lee & Hirano, 2011). Notably, the distribution patterns of REC8 and RAD21L are identical between the two not-yet synapsed homologous chromosomes. This localization pattern suggests that REC8- and RAD21L-type cohesins have their intrinsic loading sites on the chromosomes and form distinct cohesin-enriched domains along the AEs during early meiotic prophase, although the primary DNA sequences or chromatin-bound factors that underlie these cohesin-enriched domains is elusive.

Although RAD21 is detectable in testicular mitotic cells, it disappears in the nuclei from early leptotene until zygotene, which is in sharp contrast to the localization patterns of RAD21L and REC8. The absence of RAD21-containing cohesin during the early stage of meiotic prophase has been also supported by the observation that no cohesin is

detectable in *Rec8/Rad21L* double-knockout (dKO) spermatocytes and oocytes (Figure 4; Ishiguro et al., 2014; Llano, Herran, Garcia-Tunon, Gutierrez-Caballero, & Alava, 2012). Nevertheless, RAD21 transiently reappears on the chromosomes in late pachytene, concomitantly with dissociation of RAD21L (Figure 3a; Ishiguro et al., 2011; Lee & Hirano, 2011; Parra et al., 2004). RAD21 rarely colocalizes with either RAD21L or REC8, suggesting that RAD21-type cohesin replaces them or localizes at different sites. From diplotene onward, RAD21 mostly dissociates from AEs and residually remains around the centromeres at metaphase I in spermatocytes (Ishiguro et al., 2011; Parra et al., 2004; Xu, Beasley, Verschoor, Inselman, & Handel, 2004). Although physiological involvement of RAD21 during late prophase has yet to be elucidated, the mechanism on loading RAD21-cohesin during late pachytene stage also remains unknown. The kleisin subunits endow distinct cohesin complexes with different spatiotemporal localization patterns on the chromosomes in mammalian meiotic prophase. Corresponding to the unique distribution patterns of meiotic cohesin complexes, kleisin subunits also specify unique functions in mammalian meiosis, as discussed below.

5 | MEIOTIC COHESINS UNDERLIE A STRUCTURAL BASIS FOR CHROMOSOME AXIS

During meiotic prophase, sister chromatids are organized into a chromosome axis, termed the AE (Figure 1a). The AE acts as a structural framework for recruiting meiotic recombination machineries that promote DSB introduction and repair (Baudat et al., 2013; Handel & Schimenti, 2010; Keeney et al., 2014; Kumar, Ghyselinck, Ishiguro, Watanabe, & Kouznetsova, 2015; Lam & Keeney, 2015; Zickler & Kleckner, 2015), and the HORMA domain-containing proteins HORMAD1 and HORMAD2 that work for the surveillance of homologue synapsis (Daniel, Lange, Hached, Fu, & Anastassiadis, 2011; Fukuda, Daniel, Wojtasz, Toth, & Hoog, 2010; Kogo et al., 2012, 2012; Shin, Choi, Erdin, Yatsenko, & Kloc, 2010; Wojtasz, Daniel, Roig, Bolcun-Filas, & Xu, 2009). The AE appears at leptotene, which is marked by its main components, SYCP2 and SYCP3, and develops into a continuous linear structure along sister chromatid axis. Notably, the appearance of SYCP2 or SYCP3 in the nucleus is preceded by loading of cohesin at pre-meiotic S phase or in early leptotene, suggesting that a "cohesin core axis" is pre-formed between sister chromatids and subsequently acts as a framework to organize the AE (Figure 4a). This notion is supported by the observation that the "cohesin core axis," which is marked by the cohesin subunits (Eijpe, Heyting, Gross, & Jessberger, 2000), is formed even in *Sycp3* and *Sycp2* knockouts (Figure 4b; Kouznetsova, Novak, Jessberger, & Hoog, 2005; Pelttari, Hoja, Yuan, Liu, & Brundell, 2001; Yang, De La Fuente, Leu, Baumann, & McLaughlin, 2006). Moreover, the chromosome axis, defined by an electron-dense structure observed under electron microscope, is formed and can be immunolabeled for cohesin in *Sycp3* KOs (Ortiz, Kouznetsova, Echeverria-Martinez, Vazquez-Nin, & Hernandez-Hernandez, 2016), asserting the notion that a "cohesin core axis" acts as the structural basis for chromosome organization during meiosis. Indeed, it has been shown that AE formation depends on meiotic cohesins (Figure 4c). In *SA3/Stag3* KOs, where the subunit common among meiotic cohesin complexes is absent, AE formation is largely nullified with residual short stretches of axes, suggesting that the meiosis-specific subunit SA3/Stag3, but not mitotic SA1 or SA2, is essential for AE formation (Fukuda et al., 2014; Hopkins et al., 2014; Llano et al., 2014; Ward, Hopkins, McKay, Murray, & Jordan, 2016; Winters et al., 2014). It should be noted that the phenotypes observed in these studies differ somewhat depending on the knockout allele of SA3/Stag3. Although SMC1α can partly substitute SMC1β in AE formation, SMC1β is required for telomere integrity in the AE (Biswas et al., 2018).

In the absence of either REC8 (Bannister et al., 2004; Xu et al., 2005) or RAD21L (Herran et al., 2011; Ishiguro et al., 2014), AE formation is partially impaired: In the absence of REC8, AE length is shorter compared to wild type or *Rad21L* KO (Figure 4c); in the absence of RAD21L, AE is discontinuous and fragmented. Thus, RAD21L and REC8 differently contribute to the formation of the AE. Strikingly, AE formation is mostly nullified in *Rec8/Rad21L* dKOs (Ishiguro et al., 2014; Llano et al., 2012). Since *Rec8/Rad21L* dKO exhibits a complete defect in AE formation, REC8- and RAD21L-type cohesin complexes, but not RAD21-type, are required for chromosome axis formation. Thus, the meiotic "cohesin core axis" assembled by REC8- and RAD21L-type cohesin complexes plays an essential role in AE formation.

Immunogold electron microscopic analyses showed that cohesin complexes localize on the innermost sides of the two LEs in bivalents (Ishiguro et al., 2014), resembling the observation in *Drosophila* (Anderson, Royer, Page, McKim, & Lai, 2005). Accordingly, both REC8 and RAD21L co-immunoprecipitate with the transverse filament protein SYCP1 of the SC (Figure 1c), but much less so with central element proteins. Thus, the assembly of meiotic chromosome axis structures (both the AE and SC) is largely mediated by REC8- and RAD21L-type cohesins in a redundant manner.

It has been shown that AE components and meiotic cohesin complexes coordinate the axis-loop organization (Novak, Wang, Revenkova, Jessberger, & Scherthan, 2008; Yuan, Liu, Zhao, Brundell, & Daneholt, 2000). In the absence of SYCP3, the meiotic "cohesin core axis" is extended with reciprocal shortening of chromatin loop size, suggesting that the "cohesin core axis" is longitudinally compacted by

AE components. In *Smc1β* KOs, where only SMC1α-containing cohesin complexes are present, the meiotic cohesin core axis is shortened whereas chromatin loops are heterogeneously extended, suggesting that the cohesin complexes on the chromosome axis act as chromatin loop attachment sites (Novak et al., 2008). In contrast, in *Smc1β*/*Sycp3* dKOs, the length of the meiotic "cohesin core axis" is restored to the levels comparable to wild type, further suggesting that the AE components act in longitudinal axial compaction of the "cohesin core axis." Moreover, in *Sycp3* KO oocytes, it has been shown that the "cohesin core axis" is prematurely disassembled before the entry into dictyate arrest, suggesting that AE components are required for the stability of the "cohesin core axis" in late meiotic prophase in oocytes (Kouznetsova et al., 2005). Thus, the interaction between meiotic cohesin and AE components is required to maintain the integrity of the chromosome axis and for the subsequent organization of chromatin loop architecture during the meiotic prophase.

Although it is largely unclear how cohesin regulates axis assembly, a clue emerges from a study on fission yeast. There are two SA/Scc3 homologues in fission yeast, mitotic Psc3 and the meiosis-specific Rec11, each of which forms a distinct cohesin complex with Rec8 during meiosis (Kitajima, Yokobayashi, Yamamoto, & Watanabe, 2003). Although the Rec8-Psc3-containing cohesin complex is enriched around the centromeres, the Rec8-Rec11-containing complex is localized along the chromosome arms and plays a crucial role in meiotic recombination. Notably, phosphorylation of Rec11 by casein kinase I (Hhp1 and Hhp2, the fission yeast homologues of CK1) is required for the assembly of the meiotic chromosome axis called the linear element (LinE) and the subsequent promotion of meiotic recombination (Phadnis, Cipak, Polakova, Hyppa, & Cipakova, 2015; Sakuno & Watanabe, 2015). Non-phosphorylatable mutations of Rec11 at casein kinase I target residues result in defects in LinE assembly where sister chromatid cohesion is still preserved, suggesting that phosphorylation of the Rec11 subunit plays a specific role in assembling the meiotic chromosome axis in a way independent of cohesion. Crucially, phosphorylation of Rec11 by Hhp1 or Hhp2 mediates the interaction of Rec11 with a LinE component, Rec10 (Sakuno & Watanabe, 2015), whose functional homologue is SYCP2 in vertebrates and Red1 in budding yeast. Since Rec10 promotes tethering between the DSB hot spots in the loop domain and the chromosome axis through interaction with the pre-DSB recombination complex (Miyoshi, Ito, Kugou, Yamada, & Furuichi, 2012; Panizza, Mendoza, Berlinger, Huang, & Nicolas, 2011), phosphorylation of Rec11 by Hhp1 or Hhp2 acts as a basis for LinE assembly and in turn promotes DSB formation. It is worth noting that mouse cohesin subunits, including SA3, are highly phosphorylated during meiotic prophase I (Fukuda et al., 2014), raising a question whether a similar mechanism of chromosome axis assembly is conserved in vertebrates. Given that the AE formation and DSB repair process are both abolished in *SA3* KOs (Fukuda et al., 2014; Hopkins et al., 2014; Llano et al., 2014; Ward et al., 2016; Winters et al., 2014), further analyses with mutant mice expressing *SA3* with non-phosphorylatable will answer the question.

6 | ROLE OF MEIOTIC COHESINS IN HOMOLOGUE PAIRING/ SYNAPSIS AND RECOMBINATION DURING MEIOSIS

Homologous chromosomes undergo pairing, synapsis, and meiotic recombination. A number of mechanisms are involved in chromosome pairing and alignment. Although a tight association of homologues is established by DSB-dependent recombination and subsequent synapsis, DSB-independent mechanisms are also involved in the juxtaposition or gathering of interstitial homologues (Boateng, Bellani, Gregoretti, Pratto, & Camerini-Otero, 2013; Ding, Yamamoto, Haraguchi, & Hiraoka, 2004; Peoples, Dean, Gonzalez, Lambourne, & Burgess, 2002; Peoples-Holst & Burgess, 2005; Storlazzi, Tesse, Gargano, James, & Kleckner, 2003; Takada, Naruse, Costa, Shirakawa, & Tachibana, 2011; Weiner & Kleckner, 1994). Consequently, these processes yield bivalent chromosomes, whereby two homologous chromosomes are physically connected by chiasmata.

The first step for meiotic chromosome pairing and alignment is the attachment of telomeres to the nuclear envelope (Hiraoka & Dernburg, 2009; Scherthan, 2001). Telomere-led nuclear movement and the polarized chromosome arrangement called "bouquet" facilitate chromosome alignment, homologue pairing and synapsis (Page & Hawley, 2004; Scherthan, 2001; Zickler & Kleckner, 1999, 2015). This chromosome movement is mediated by meiosis-specific telomere-binding proteins (Horn, Kim, Wright, Wong, & Stewart, 2013; Morimoto, Shibuya, Zhu, Kim, & Ishiguro, 2012; Shibuya, Hernandez-Hernandez, Morimoto, Negishi, & Hoog, 2015; Shibuya, Ishiguro, & Watanabe, 2014; Zhang, Tu, Watanabe, & Shibuya, 2017) that form complexes and attach to the nuclear membrane. Cohesin subunit SA3 mediates connections between the chromosome axis and the telomere-binding protein TERB1 (Shibuya et al., 2014). Consequently, the telomere–cohesin connection transmits the driving force for the chromosome movement.

RAD21L and REC8 play distinct roles in homologue pairing/synapsis during meiosis. *Rad21L* KO and *Rec8* KO spermatocytes and oocytes are arrested at the leptotene/zygotene stage with aberrant recombination and SC formation, but the outcomes are different between the two KOs (Figure 5a). Both *Rec8* KO and *Rad21L* KO spermatocytes show an accumulation of DMC1 and RAD51 foci at the zygotene-like arrest, suggesting that some recombination process is initiated

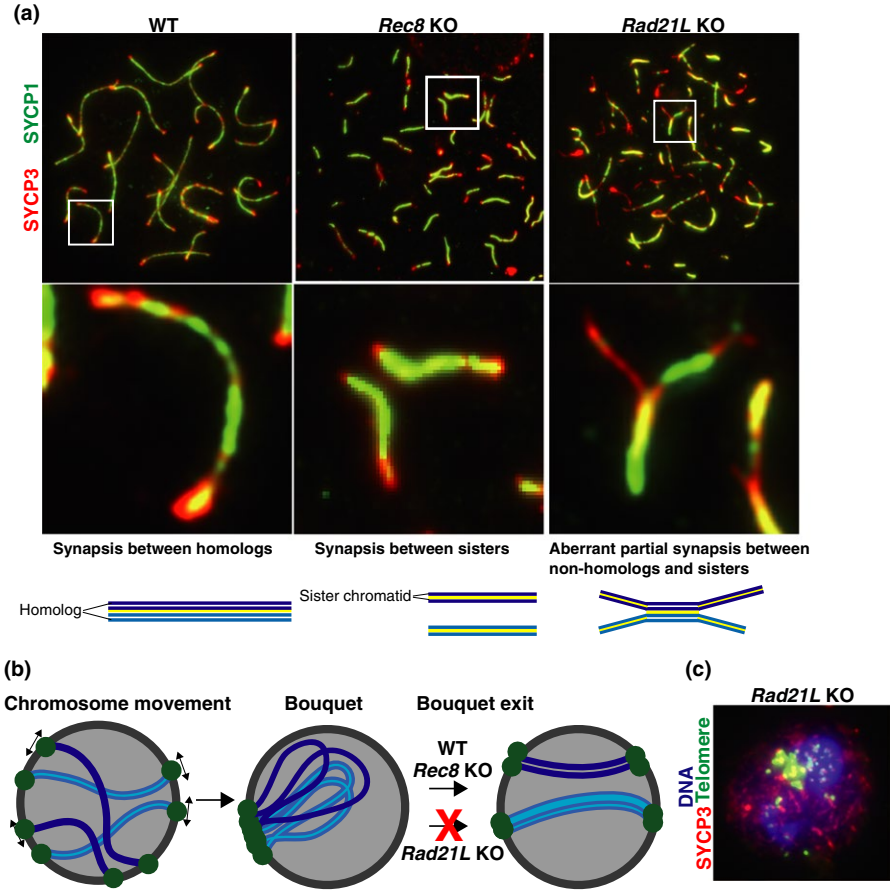


FIGURE 5 RAD21L and REC8 play distinct roles in homologue interaction. (a) SC assembly occurs between homologues in the wild type. *Rad21L* KO and *Rec8* KO spermatocytes and oocytes are arrested at the leptotene/zygotene stage and exhibit different phenotypes in homologue synapsis. In *Rec8* KO, SC assembly occurs only between sisters. In *Rad21L* KO, the SC is assembled aberrantly between sister chromatids together with non-homologous chromosomes. Schematics of SC assembly are shown at the bottom. Yellow: SC. (b) *Rad21L* KO spermatocytes exhibit bouquet arrest with extensive telomere clustering along the nuclear membrane, whereas WT and *Rec8* KO spermatocytes do not. It is possible that RAD21L-type cohesin might provide the chromosome structure necessary for bouquet release. (c) Example of *Rad21L* KO spermatocytes with extensive telomere clustering

in both of these KOs, at least in part (Ishiguro et al., 2014; Llano et al., 2012). However, although SC assembly occurs solely between sisters in the *Rec8* KO (Bannister et al., 2004; Xu et al., 2005), as observed in budding yeast *pds5* mutant (Jin, Guacci, & Yu, 2009), the SC is assembled between sister chromatids, and between non-homologous chromosomes in the *Rad21L* KO (Ishiguro et al., 2014; Llano et al., 2012). These results suggest REC8- and RAD21L-cohesins suppress inter-sister SC formation. At present, it remains largely elusive whether the meiotic cohesins play an active role in the homologue bias in recombination in mammals, as in yeast Rec8 (Kim, Weiner, Zhang, Jordan, & Dekker, 2010).

Given that cohesin-deficient spermatocytes do not develop beyond the zygotene-like stage, homologue pairing was examined in *Rad21L* and *Rec8* KO mutants using FISH analysis (Ishiguro et al., 2014). Despite the absence of synapsis between homologues in the *Rec8* KO spermatocytes, a significant population of spermatocytes exhibit homologue pairing. In contrast, homologue association is impaired in *Rad21L* KO spermatocytes. In *Spo11* KO background, DSB formation and subsequent meiotic recombination are defective. Even in the *Spo11* KO background, *Rec8* KO spermatocytes still exhibit significant homologue association, whereas *Rad21L/Spo11* dKO spermatocytes do not. Thus, RAD21L plays a notable role in homologue association independently of DSB, whereas REC8 may play only a minor role in this process. Although the precise mechanisms how RAD21L rather than REC8 contributes to this process have yet to be clarified, it is noteworthy that *Rad21L* KO spermatocytes lack the ability to release the bouquet and often exhibit prolonged telomere clustering along their nuclear membrane, while *Rec8* KO spermatocytes as well as wild-type spermatocytes do not accumulate bouquet-nuclei (Figure 5b,c). SUN1 acts for the connection between telomeres and the nuclear membrane, and mediates chromosome movement along the nuclear membrane. In the *Sun1*-deficient background, the bouquet arrest observed in the *Rad21L* KO is suppressed (*Rad21L/Sun1* dKO), suggesting that without chromosome movement mediated by SUN1, the bouquet do not accumulate even without RAD21L. Importantly, *Rad21L/Sun1* dKO spermatocytes still exhibit defects in homologue pairing. Thus, bouquet arrest can be a consequence of *Rad21L* KO but not the cause of defective homologue pairing. It is worth noting that *rec8* KO-meiotic cells in budding yeast also exhibit pairing defects and bouquet arrest (Conrad, Lee, Wilkerson, & Dresser, 2007; Trelles-Sticken, Adelfalk, Loidl, & Scherthan, 2005), similar phenomenon observed in mouse *Rad21L* KO. Thus, the function for bouquet exit is conserved in meiotic cohesins, and in mammalian meiosis, RAD21L plays a dominant role.

It should be noted that sexual dimorphism is observed in *Rad21L* KO mice: spermatocytes progress to a zygotene-like stage while some populations of oocytes progress further

into a pachytene-like stage where many more homologues are synapsed (Ishiguro et al., 2014). Thus, the contribution of REC8 and RAD21L to homologue pairing/synapsis might be weighted differently in meiosis between male and female mice. Altogether, homologue pairing/synapsis is primarily mediated by a specific chromosome architecture defined by meiosis-specific cohesins. REC8- and RAD21L-cohesins play different roles in this process in mammalian meiosis.

7 | SISTER CHROMATID COHESION DURING MEIOSIS

Given that different types of meiosis-specific cohesin complexes exist, which contain any one of the three kleisin subunits REC8, RAD21L or RAD21, the question how individual cohesin complexes contribute to sister chromatid cohesion has remained elusive. This question has been addressed by genetic assays using *Rec8*$^{TEV/TEV}$ and *Rad21/Scc1*$^{TEV/TEV}$ knock-in mouse lines, in which the endogenous *Rec8* or *Rad21/Scc1* allele is genetically modified so that REC8 or RAD21/SCC1 can be artificially depleted by TEV protease in oocytes (Tachibana-Konwalski, Godwin, Weyden, Champion, & Kudo, 2010). When TEV protease is introduced into MI-arrested oocytes from *Rec8*$^{TEV/TEV}$ and *Rad21/Scc1*$^{TEV/TEV}$ knocked-in females, all the bivalent chromosomes are converted into single chromatids in *Rec8*$^{TEV/TEV}$, while they remain intact in *Rad21/Scc1*$^{TEV/TEV}$. Thus, sister chromatid cohesion in metaphase I oocytes is solely dependent on REC8 but not on RAD21/SCC1. Then what is the role of the other meiosis-specific subunit RAD21L? The following three questions will be discussed: the first question is whether both REC8 and RAD21L equally act for sister chromatid cohesion during meiotic prophase, or whether either of them has a dominant role in this process; the second question is whether RAD21 contributes to sister chromatid cohesion during meiotic prophase; the third question is how REC8- and RAD21L-type cohesins establish sister chromatid cohesion.

Sister chromatid cohesion at leptotene, when any potential SC-mediated linkage of sister chromatids can be excluded, was assessed by FISH in *Rec8* KO-, *Rad21L* KO and *Rec8/Rad21L* dKO spermatocytes (Figure 6a; Ishiguro et al., 2014). Notably, sister chromatid cohesion is only partially impaired in *Rad21L* KO compared to wild type. Sister chromatid cohesion in *Rec8* KO is more impaired at a leptotene-like stage compared to *Rad21L* KO, implying that REC8-type cohesin contributes to sister chromatid cohesion more than RAD21L-type cohesin, at least during leptotene. Furthermore, sister chromatid cohesion is completely suppressed in *Rec8/Rad21L* dKO spermatocytes, emphasizing that it is exclusively mediated by REC8- and RAD21L-type cohesins and not by RAD21-type cohesin during meiotic prophase I. This notion is further supported by the fact that *Stag3* KO, in which the common subunit of meiotic cohesins is absent, recapitulates the cohesion defect observed in *Rec8/Rad21L* dKO (Hopkins et al., 2014; Winters et al., 2014).

It has been shown that loss of cohesin accompanies splitting of the sister chromatid axes (Figure 6b). In wild type, the chromosome axis, which consists of two sister chromatids, is labeled by a single line of the AE component, SYCP3. In *Rec8* KOs, however, the entire length of the chromosome axis becomes two separate SYCP3-labeled structures, despite the fully localized RAD21L-cohesin along the sister chromatid axes (Ishiguro et al., 2014; Xu et al., 2005). Similar to the observation in *Rec8* KOs, super-resolution microscopic analyses showed that the chromosome axis is regionally separated in hypomorphic *Stag3* mutants and *Smc1*β KOs, in which REC8-cohesin levels are partly reduced (Agostinho, Manneberg, Schendel, Hernandez-Hernandez, & Kouznetsova, 2016; Fukuda et al., 2014; Ishiguro & Watanabe, 2016). Notably, illegitimate SCs are assembled between sister chromatids at the REC8 free "axial opening" regions in these mutants (Agostinho et al., 2016; Ishiguro & Watanabe, 2016), as has also been shown in *Rec8* KOs (Bannister et al., 2004; Xu et al., 2005). Thus, REC8 protects the chromosome axis from local "axial opening" and illegitimate SC assembly between sister chromatids (Figure 6b). The causal relationship between inter-sister SC assembly and local "axial opening" remains elusive. One possibility is that ectopic inter-sister SC assembly forces sister chromatid axes to be separated. If this is the case, illegitimate SC formation between sister chromatids does not necessarily mean loss of cohesion. However, a recent study (Ishiguro et al., 2014) provides strong evidence that sister chromatid cohesion in *Rec8* KO is indeed once lost during early leptotene shown by AEs discontinuously separated throughout the chromosome length and then become closely connected in late leptotene depending on SC formation between sister chromatids. Thus, the characteristic structures between sister chromatids in REC8-free chromosome regions surely represent the loss of sister chromatid cohesion.

Given that REC8-cohesin plays a dominant role in sister chromatid cohesion in meiotic prophase I, it remains unclear how RAD21L-cohesin contributes to cohesion. The mode of inter-sister SC formation in *Rec8* KO versus *Rec8/Spo11* dKO provides a clue (Figure 6c,d; Ishiguro et al., 2014). Spo11 introduces DNA double-strand breaks. Intriguingly, despite the full localization of RAD21L-cohesin on chromosomes, inter-sister SC formation in *Rec8* KO is mostly suppressed and the sister chromatid axes are entirely separated in the absence of SPO11 (Figure 6c,d; Ishiguro et al., 2014). Thus, it is possible that RAD21L-cohesin establishes sister chromatid cohesion depending on DSB, as reported in mitotic yeast cells (Heidinger-Pauli, Unal, Guacci, & Koshland, 2008; Strom, Karlsson, Lindroos, Wedahl, & Katou, 2007; Unal, Heidinger-Pauli, & Koshland, 2007) and nematode oocytes (also see below; Severson & Meyer, 2014), while REC8-cohesin establishes sister chromatid cohesion depending on DNA

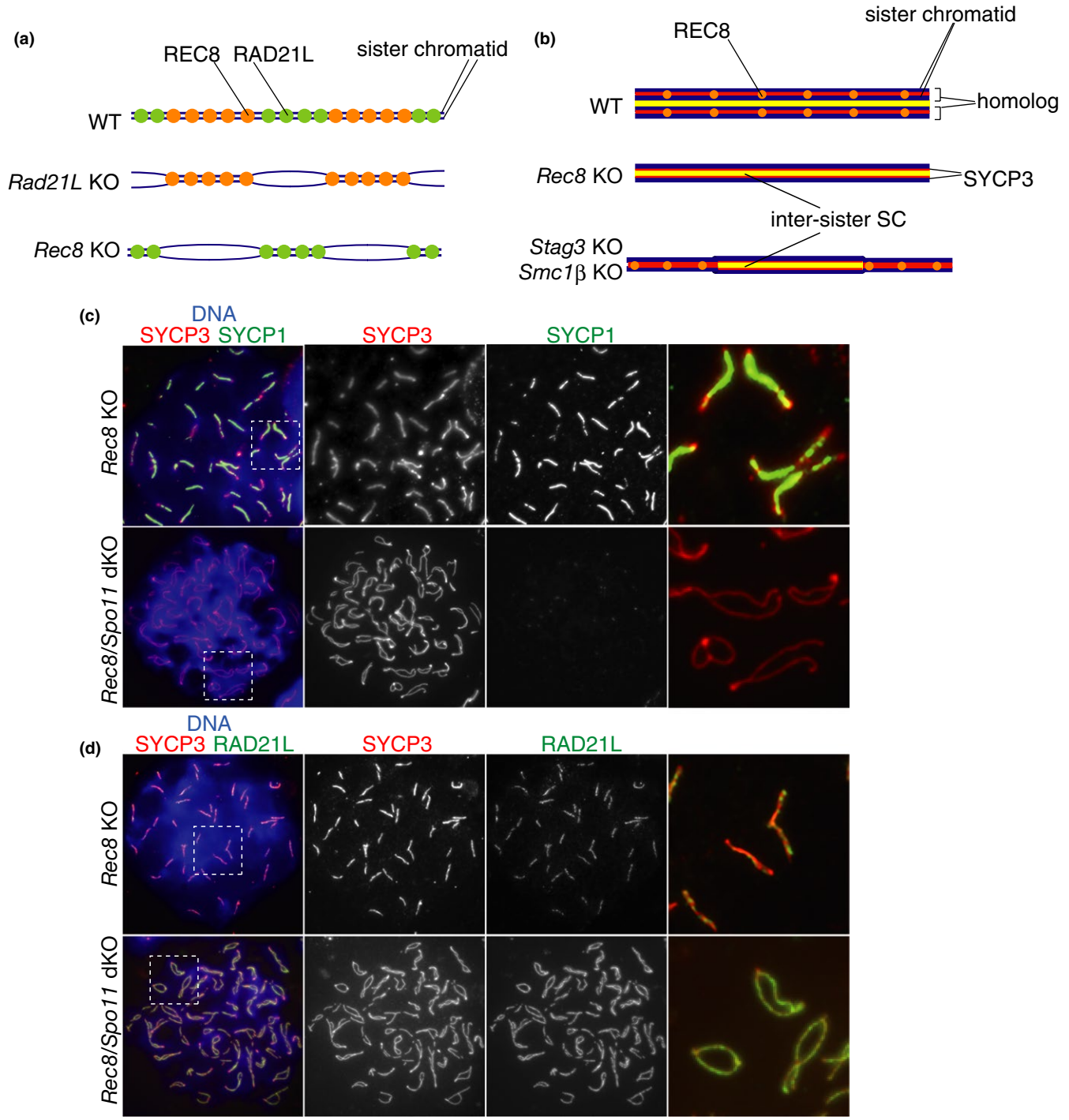


FIGURE 6 RAD21L and REC8 exhibit different modes of sister chromatid cohesion. (a) Sister chromatid cohesion is only partially impaired in *Rad21L* KO at a leptotene-like stage. Sister chromatid cohesion in *Rec8* KO is further impaired at a leptotene-like stage compared to *Rad21L* KO. REC8-type cohesin contributes to sister chromatid cohesion more than RAD21L-type cohesin, at least during leptotene. Although establishment of REC8-cohesin cohesion is dependent on DNA replication, establishment of RAD21L-cohesin is dependent on DSB. (b) In wild types, the sister chromatid axis is recognizable as a single line of SYCP3-labeled structures, along with high density of REC8. In *Rec8* KO, the sister chromatid axis of univalents is separated into two SYCP3-labeled structures. In *Stag3* and *Smc1*β KOs, the sister chromatid axis is separated in the regions where REC8 is absent. The "axial opening" is accompanied by inter-sister SC formation. (c) Example of *Rec8* KO spermatocytes with inter-sister SC, which is indicated with SYCP1 immunostaining (upper). Enlarged images are shown on the right. The inter-sister SC formation is suppressed in *Rec8/Spo11* dKO spermatocytes (lower). (d) Sister chromatids are cohered in *Rec8* KO spermatocytes (upper). Despite full localization of RAD21L, sister chromatids are separated in *Rec8/Spo11* dKO spermatocytes (lower). Enlarged images are shown on the right

replication in a similar manner to mitotic cohesin. Another interpretation is that inter-sister SC depends on DSBs, and without SC, the sister axes are separated even in the presence of RAD21L. The distinct roles of REC8 and RAD21L in sister chromatid cohesion needs to be further investigated.

It has been suggested that SMC1α and SMC1β have different roles in cohesion. Although these proteins have redundant roles in cohesion at chromosome arms, at the centromeric region SMC1β plays an essential role during meiosis (Biswas et al., 2013, 2018).

8 | CENTROMERIC COHESION IS PRESERVED BY COUNTERACTING PHOSPHORYLATION OF COHESIN DURING MEIOSIS I

In meiosis I, cohesin is enriched around the centromeric regions. Cytologically, cohesin is detected between the closely associated kinetochores and the inner centromere regions (Suja, Antonio, Debec, & Rufas, 1999). Proteolytic removal of cohesin triggers separation of homologous chromosomes toward opposite poles during metaphase I–anaphase I transition. Separase cleaves the kleisin subunit of cohesin in both mitosis (Hauf, Waizenegger, & Peters, 2001; Nakajima, Kumada, Hatakeyama, Noda, & Peters, 2007; Uhlmann, Wernic, Poupart, Koonin, & Nasmyth, 2000) and meiosis (Buonomo et al., 2000; Kitajima, Miyazaki, Yamamoto, & Watanabe, 2003; Kudo et al., 2006), and this mechanism is widely conserved in eukaryotic organisms (Figure 2d). Crucially, Rec8 phosphorylation contributes to cohesin removal during meiosis (Brar, Kiburz, Zhang, Kim, & White, 2006). Rec8 becomes susceptible to separase cleavage when phosphorylated by casein kinase 1 (CK1) in fission yeast (Ishiguro, Tanaka, Sakuno, & Watanabe, 2010), and by a casein kinase 1 homologue Hrr25, a catalytic subunit of Dbf4-dependent protein kinase (DDK) Cdc7, and/or Cdc5 (PLK) in budding yeast (Attner, Miller, Ee, Elkin, & Amon, 2013; Brar et al., 2006; Katis, Lipp, Imre, Bogdanova, & Okaz, 2010). In mice, phosphorylation by Polo-like kinase (PLK1) makes REC8 susceptible to separase cleavage in vitro (Kudo, Anger, Peters, Stemmann, & Theussl, 2009). Thus, by phosphorylation REC8 becomes more susceptible to cleavage.

During anaphase I, REC8-cohesin is cleaved by separase only along the chromosome arms, but is maintained in the centromere regions throughout anaphase I until meiosis II, allowing the resolution of chiasmata and the consequent release of the homologous chromosomes (Figure 1; Buonomo et al., 2000; Kitajima et al., 2003; Kudo et al., 2006). Thus, REC8 in centromere regions is protected from cleavage during anaphase I. The centromeric cohesion must be preserved during meiosis I to ensure sister chromatid separation in the following meiosis II, a period when bipolar attachment is established by the preserved centromeric cohesion. During interkinesis, preserved cohesin is distributed between sister kinetochores (Parra et al., 2004). At the onset of anaphase II, residual centromeric REC8 is cleaved by separase, which results in segregation of sister chromatids into each gamete.

In a wide variety of organisms, centromeric proteins of Shugoshin (Sgo)/Mei-S332 family protect centromeric cohesion during meiosis I, whose loss leads to precocious sister chromatid separation (Hamant, Golubovskaya, Meeley, Fiume, & Timofejeva, 2005; Katis, Galova, Rabitsch, Gregan, & Nasmyth, 2004; Kerrebrock, Miyazaki, Birnby, & Orr-Weaver, 1992; Kitajima, Kawashima, & Watanabe, 2004; Lee, Dej, Lopez, & Orr-Weaver, 2004; Marston, Tham, Shah, & Amon, 2004; Miyazaki & Orr-Weaver, 1994; Rabitsch, Gregan, Schleiffer, Javerzat, & Eisenhaber, 2004). For this activity, Shugoshin forms complex with PP2A phosphatase that contains B56 subunit (Kitajima, Sakuno, Ishiguro, Iemura, & Natsume, 2006; Riedel, Katis, Katou, Mori, & Itoh, 2006; Tang, Shu, Qi, Mahmood, & Mumby, 2006). In fission and budding yeast, Sgo1-PP2A counteracts Rec8 phosphorylation at the centromere, protecting centromeric cohesin from separase-mediated cleavage during meiosis I.

Depletion of either Sgo1 or PP2A leads to precocious loss of centromeric cohesion during anaphase I, but homologous chromosomes still co-segregate toward the same poles owing to monopolar attachment (see below). Defects resulting from Sgo1 or PP2A depletion in chromosome segregation are detected as the random segregation of prematurely separated sister chromatids in meiosis II.

In mammals, there are two paralogs of Shugoshin-like proteins, SGO1 and SGO2 (Kitajima et al., 2006; McGuinness, Hirota, Kudo, Peters, & Nasmyth, 2005; Salic, Waters, & Mitchison, 2004; Tanno, Kitajima, Honda, Ando, & Ishiguro, 2010), each of which forms a complex with PP2A phosphatase (Kitajima et al., 2006). In mitosis, SGO1-PP2A protects cohesin from dissociation at the centromeres (Kitajima et al., 2006; McGuinness et al., 2005; Salic et al., 2004). In meiosis, SGO2-PP2A localizes to the centromeres to protect centromeric REC8 cohesin from separase-mediated cleavage during anaphase I (Lee, Kitajima, Tanno, Yoshida, & Morita, 2008; Llano, Gomez, Gutierrez-Caballero, Herran, & Sanchez-Martin, 2008). Thus, centromeric cohesion is preserved by the action of SGO2-PP2A that counteracts REC8 phosphorylation. On the other hand, the kinases responsible for REC8 phosphorylation remain to be identified.

9 | CENTROMERIC COHESION PLAYS A CONSERVED ROLE IN ESTABLISHING MONO-ORIENTATION OF SISTER KINETOCHORES DURING MEIOSIS I

Sister chromatid cohesion at the centromeres plays a crucial role in defining kinetochore geometry, which determines the

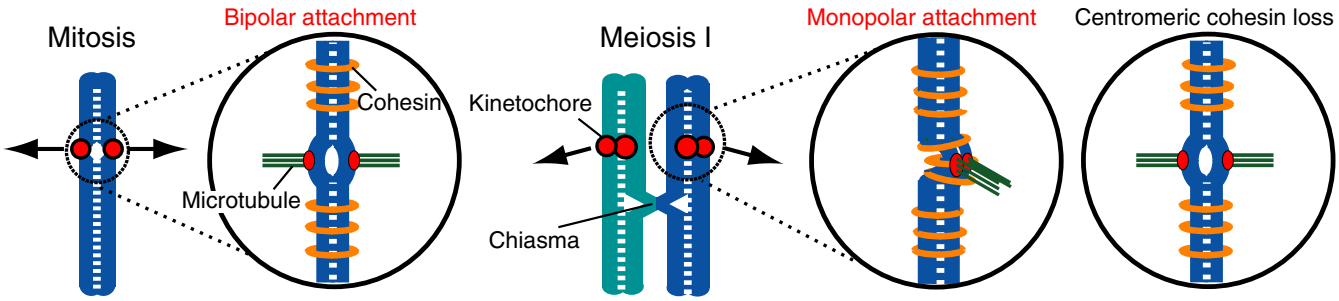


FIGURE 7 REC8-cohesin at centromeres determines sister kinetochore orientation. Sister chromatid cohesion in the centromeric region determines the mode of sister kinetochore orientation and, in turn, the chromosome orientation. In mitosis, sister kinetochores are bi-oriented and captured by microtubules from the opposite poles (bipolar attachment). In meiosis I, sister kinetochores on one homologous chromosome are captured by microtubules from the same pole (monopolar attachment). REC8-cohesin at the core centromeric region is necessary for the mono-orientation the kinetochores in meiosis

mode of sister kinetochore orientation and, in turn, the chromosome orientation (Figure 7). During mitosis, sister kinetochores are placed in a back-to-back configuration so that they are bi-oriented and captured by microtubules from the opposite poles, causing the sister chromatids to separate into opposite directions (equational segregation). In contrast, during meiosis I, sister kinetochores of one homologous chromosome are juxtaposed side by side, so that they are captured by microtubules from the same pole (monopolar attachment). Consequently, homologous chromosomes separate into opposite directions (reductional segregation).

Accumulating evidence suggests that Rec8 orthologs play a role in the mono-orientation of kinetochores in diverse eukaryotic organisms. It is assumed that the geometric restriction imposed by Rec8-mediated sister chromatid cohesion at the core centromeres promotes a side-by-side configuration of sister kinetochore geometry at meiosis I. In fission yeast, mutation in *rec8* results in equational rather than reductional segregation at meiosis I, suggesting that Rec8 plays a specific role in establishing the monopolar attachment of sister kinetochores at meiosis I (Sakuno, Tada, & Watanabe, 2009; Watanabe & Nurse, 1999; Watanabe, Yokobayashi, Yamamoto, & Nurse, 2001; Yokobayashi & Watanabe, 2005; Yokobayashi, Yamamoto, & Watanabe, 2003). In contrast to fission yeast, it is unclear in budding yeast whether Rec8-cohesin, or even cohesion itself, is involved in the regulation of the mono-orientation of the kinetochores. Mutations in *rec8* homologues in maize and *Arabidopsis* cause similar equational segregation at meiosis I, suggesting that the same mechanism for mono-orientation is conserved in plants (Chelysheva, Daiallo, Vezon, Gendrot, & Vrielynck, 2005; Yu & Dawe, 2000). Furthermore, in mouse, region-specific depletion of REC8 at core centromeres (under kinetochore region) leads to bi-orientation, suggesting that REC8-cohesin at the core centromeric region is necessary for kinetochore mono-orientation in mammals (Tachibana-Konwalski, Godwin, Borsos, Rattani, & Adams, 2013). Consistent with this notion, although disruption of mouse SGO2 causes precocious separation of sister chromatids because the loss of peri-centric cohesion, sister chromatids still co-segregate toward the same direction during meiosis I, indicating that monopolar attachment has already been established before the onset of anaphase I. Thus, the role of REC8-cohesin in establishing the monopolar orientation of sister kinetochores at meiosis I is widely conserved through eukaryotic organisms.

10 | THE MEIOSIS-SPECIFIC KINETOCHORE PROTEIN MEIKIN PLAYS A CRUCIAL ROLE IN MONO-ORIENTATION OF SISTER KINETOCHORES DURING MEIOSIS I

The establishment of mono-orientation of sister kinetochores requires not only REC8-cohesin but also meiosis-specific kinetochore proteins. The fission yeast meiosis-specific protein Moa1 (monopolar attachment protein 1) localizes to the core centromere from prophase I to metaphase I by interacting with the constitutive kinetochore protein CENP-C, a homologue of Cnp3, but disappears at anaphase I (Tanaka, Chang, Kagami, & Watanabe, 2009). Moa1 is required for establishing the mono-orientation of kinetochores at meiosis I (Yokobayashi & Watanabe, 2005). It is worth noting that the core centromere is intrinsically refractory to cohesion in mitosis, and this is also the case in meiosis I in *moa1* mutants. Similarly to *rec8* mutants, sister chromatid cohesion at the core centromere is abolished in the absence of Moa1, leading to subsequent equational segregation in meiosis I, despite the enrichment of Rec8 at the core centromere compared to wild type (Sakuno et al., 2009; Yokobayashi & Watanabe, 2005).

In vertebrates, the meiosis-specific kinetochore protein MEIKIN plays a crucial role in mono-orientation of sister kinetochores (Figure 8a; Kim, Ishiguro, Nambu, Akiyoshi, & Yokobayashi, 2015). Notably, mouse MEIKIN has functionally similar characteristics to fission yeast Moa1, despite

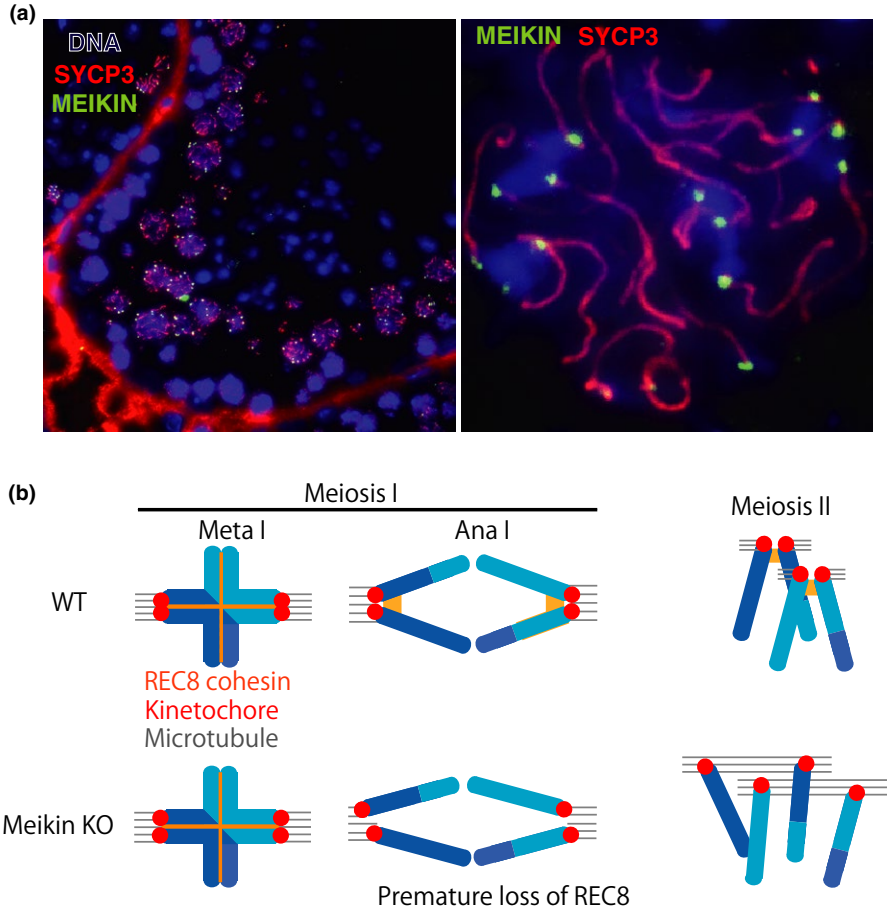


FIGURE 8 MEIKIN plays a role in mono-orientation of sister kinetochores by regulating centromeric REC8. (a) MEIKIN localizes to centromeres from pachytene to metaphase I. Seminiferous tubules were immunostained for SYCP3 (red), MEIKIN (green) and DAPI (blue). (b) In *Meikin* KO mice, sister chromatids are separated at the onset of anaphase I, resulting in defective chromosome alignment in meiosis II. Although REC8 normally localizes to the bivalent chromosomes until metaphase I in *Meikin* KO, centromeric REC8 is entirely lost from metaphase II chromosomes

their little sequence homology. MEIKIN localizes to the core centromere from pachytene to metaphase I through the interaction with CENP-C, but disappears at anaphase I. Crucially, the distance between sister kinetochores in prometaphase I increases significantly in *Meikin* KOs compared to wild type, suggesting that the conjunction between sister kinetochores is weakened in the absence of MEIKIN. In *Meikin* KO mice, sister chromatids are separated at the onset of anaphase I (Figure 8b), resulting in infertility because of defective chromosome alignment in oocytes at meiosis II, and the accumulation of abnormally large, round spermatid-like cells that cannot undergo meiosis II in testes. Accordingly, although REC8 shows normal localization at bivalent chromosomes until metaphase I in *Meikin* KO, centromeric REC8 is lost entirely from metaphase II chromosomes. The loss of centromeric REC8 and the premature separation of sister chromatids during anaphase I in *Meikin* KO mice resemble the phenotype of mice defective in SGO2, although the phenotype is less severe than in *Sgo2* KO.

MEIKIN physically interacts with Polo-like kinase 1 (PLK1) through the Polo-box domain (PBD)-binding site (Ser-Thr-Pro) and recruits it to the kinetochore from diplotene to metaphase I. Accordingly, PLK1 localization at kinetochores is diminished in *Meikin* KO. Furthermore, perturbation of PLK1 activity with a PLK inhibitor causes sister chromatid separation during anaphase I and subsequent loss of REC8 on metaphase II chromosomes, similar to the *Meikin* KO. Thus, during meiosis I, PLK1 recruited to kinetochores by MEIKIN acts to protect centromeric cohesion and mono-orientation.

Although the amino acid sequences are not conserved between vertebrate MEIKIN and fission yeast Moa1 overall, Moa1 possesses a putative PBD-binding motif. Indeed, fission yeast Polo-like kinase 1 (Plo1) associates with Moa1 and localizes to the kinetochores during meiosis I. Strikingly, region-specific inactivation of kinetochore-bound Plo1 during meiosis I results in equational segregation, similar to the Moa1 mutant. Thus, Plo1 recruited by Moa1 to the kinetochores acts similarly to PLK1 in vertebrates for mono-orientation during meiosis I.

Although the involvement of Rec8 in the regulation of the mono-orientation of kinetochores is unclear in budding yeast, a different set of meiosis-specific proteins, Mam1, a subunit of the monopolin complex that organizes the centromere architecture (Matos, Lipp, Bogdanova, Guillot, & Okaz, 2008; Toth, Rabitsch, Galova, Schleiffer, & Buonomo, 2000), and Spo13 (Katis, Matos, Mori, Shirahige, & Zachariae, 2004; Lee, Amon, & Prinz, 2002; Lee, Kiburz, & Amon, 2004; Shonn, McCarroll, & Murray, 2002) are required for mono-orientation during meiosis I. Although neither Mam1 nor Spo13 shares amino acid

sequence homology with Moa1 or MEIKIN, Spo13 has a PBD-binding motif and collaborates with the PLK/Cdc5 (Clyne, Katis, Jessop, Benjamin, & Herskowitz, 2003; Lee & Amon, 2003) to promote mono-orientation during meiosis I. Strikingly, ectopic expression of kinetochore-targeting Spo13 (Spo13-Cnp3), but not a PBD-binding-motif-defective Spo13 mutant, rescues mono-orientation defects, even in a Moa1 mutant of fission yeast (Kim et al., 2015). Thus, budding yeast Spo13 and budding yeast Cdc5 act together to produce mono-orientation in a similar manner to fission yeast Moa1 or vertebrate MEIKIN. Taken together, although the critical substrate of Polo-like kinase is still largely elusive, MEIKIN, together with Polo-like kinase, underlies the conserved mechanisms for mono-orientation of sister kinetochores during meiosis I in a wide range of eukaryotic organisms.

11 | SIMILARITIES AND DIFFERENCES IN MEIOTIC KLEISINS BETWEEN MAMMALS AND *CAENORHABDITIS ELEGANS*

The nematode *C. elegans* possesses meiosis-specific kleisins, REC-8 and nearly identical COH-3 and COH-4, in addition to the somatic kleisin SCC-1 (Severson, Ling, Zuylen, & Meyer, 2009). Interestingly, *C. elegans* REC-8 and COH-3/COH-4 exhibit similarity to mammalian REC8 and RAD21L in the temporal localization patterns on the chromosomes and the mode of sister chromatid cohesion (Severson & Meyer, 2014). Notably, although REC-8 appears in the nucleus during pre-meiotic S phase in *C. elegans* oocytes, COH-3/COH-4 localizes along the chromosomes after the entry into meiotic prophase I, which resembles the chromosome localization patterns of mammalian REC8 and RAD21L. This phenomenon accompanies the highest loading of WAPL-1, the *C. elegans* homologue of WAPL, along chromosomes before the entry into meiotic prophase I. WAPL-1 destabilizes chromatin binding of cohesion and acts to selectively remove COH-3/COH-4 but not REC-8 from chromosomes during meiotic prophase I (Crawley et al., 2016). REC-8 and COH-3/COH-4 are essential for sister chromatid cohesion, but their mode of action is different. COH-3/COH-4 establishes cohesion in a DSB-dependent manner, while REC-8 establishes cohesion during DNA replication (Severson & Meyer, 2014). Thus, the distinction between the role of nematode REC-8 and COH-3/COH-4 during meiosis I is in part parallel to mammalian REC8 and RAD21L. Moreover, this notion can be extrapolated to cohesin complexes in plants. Four different kleisins are present in *Arabidopsis thaliana*: mitotic SCC1 homologues SYN2 and SYN4, a REC8 homologue meiotic SYN1, and the fourth kleisin SYN3 which acts for homologue synapsis during meiosis (Yuan, Yang, Ellis, Fisher, & Makaroff, 2012).

In *C. elegans* diakinesis/prometaphase I, the chromosomes are reorganized into cruciform-shaped bivalents with short and long arms divided by the crossover (CO) site (Chan, Severson, & Meyer, 2004; Nabeshima, Villeneuve, & Colaiacovo, 2005). Although the holocentric chromosome of *C. elegans* does not possess a regionally defined centromere, the longer arm has a feature of the centromere during meiosis. Accordingly, sister chromatid cohesion is maintained at the longer arm until anaphase II to hold sister chromatids together. Remarkably, reorganization of bivalent chromosomes into short and long arms accompanies redistribution of REC-8 and COH-3/COH-4 in diakinesis/prometaphase I. REC-8 is selectively removed from the short arm and remains only along the long arm (de Carvalho, Zaaijer, Smolikov, Gu, & Schumacher, 2008; Severson & Meyer, 2014). Reciprocally, COH-3/COH-4 dissociates from the long arm and persists along the short arm (Kaitna, Pasierbek, Jantsch, Loidl, & Glotzer, 2002; Rogers, Bishop, Waddle, Schumacher, & Lin, 2002; Severson & Meyer, 2014). REC-8-mediated cohesion along the long arm persists through meiosis I and until meiosis II and acts in the mono-orientation of sister chromatids during meiosis I (Severson et al., 2009). This evidence strengthens the notion that REC8 plays evolutionally conserved roles in preserving centromeric cohesion until meiosis II, which ensures mono-orientation of sister chromatids during meiosis I.

12 | TWO DISTINCT MEIOTIC COHESIN COMPLEXES IN *DROSOPHILA* PARALLEL TO MAMMALIAN RAD21L- AND REC8-TYPE COHESIN COMPLEXES

In *Drosophila* meiosis, there are at least two distinct types of meiosis-specific cohesin complexes that play different roles in sister chromatid cohesion, SC assembly and centromere clustering. C(2)M is a meiosis-specific kleisin subunit that forms a complex with SMC1, SMC3 and stromalin/SA subunits (Heidmann, Horn, Heidmann, Schleiffer, & Nasmyth, 2004; Manheim & McKim, 2003). Another type of cohesin complex consists of SOLO and SUNN together with common subunits SMC1 and SMC3. Based on predicted protein folding, SUNN is considered to be a meiosis-specific counterpart of stromalin/SA, although there is little homology in overall primary sequence, except for the HEAT motif (Gyuricza, Manheimer, Apte, Krishnan, & Joyce, 2016; Krishnan, Thomas, Yan, Yamada, & Zhulin, 2014). SOLO has a sequence motif similar to the SMC1 interaction domain of kleisin (Yan & McKee, 2013; Yan, Thomas, Tsai, Yamada, & McKee, 2010). Thus, C(2)M-SA-type and SOLO-SUNN-type cohesin complexes participate in *Drosophila* meiosis, which resemble RAD21L- and REC8-cohesins in mammals, respectively.

C(2)M-SA-type cohesin accumulates along the chromosome arms, but not at the centromeres, after pre-meiotic S phase

and dissociates from chromosomes after pachytene. In either *C(2)M* or *SA* female mutants, sister centromere cohesion is intact, but SC formation and subsequent crossover are impaired (Gyuricza et al., 2016; Manheim & McKim, 2003), suggesting that C(2)M-SA-type cohesin acts primarily in homologue interaction rather than sister chromatid cohesion. Thus, C(2)M-SA-type cohesin has similar features to RAD21L-cohesin in mammals (Ishiguro et al., 2014). In contrast to C(2)M-SA-type cohesin, SOLO-SUNN-type cohesin localizes to centromeres before meiotic prophase I and persists until metaphase II in spermatocytes and oocytes (Khetani & Bickel, 2007; Krishnan et al., 2014; Yan et al., 2010). SOLO-SUNN-type cohesin plays crucial roles in centromeric cohesion and mono-orientation of sister centromeres during meiosis I (Krishnan et al., 2014; Yan & McKee, 2013; Yan et al., 2010). Thus, SOLO-SUNN-type cohesin has similar features to REC8-cohesin in mammals. Once SOLO-SUNN-type cohesin is loaded on the chromosomes before meiotic prophase, its de novo incorporation into chromosomes is not detectable during meiotic prophase, suggesting that chromosome-bound SOLO-SUNN-type cohesin is stable rather than dynamic (Gyuricza et al., 2016). This phenomenon is similar to what has been reported in mouse REC8-cohesin dynamics in oocytes (Revenkova, Herrmann, Adelfalk, & Jessberger, 2010; Tachibana-Konwalski et al., 2010).

In *Drosophila,* which lack typical telomere repeats, no bouquet is observed during homologue synapsis. Instead, *Drosophila* oocytes exhibit centromere clustering as a prerequisite for homologue synapsis, which is analogous to bouquet formation (Takeo, Lake, Morais-de-Sa, Sunkel, & Hawley, 2011; Tanneti, Landy, Joyce, & McKim, 2011). In *Drosophila* oocytes, the centromeres act as the earliest sites of synapsis initiation, while synapsis is also initiated at the interstitial sites along the chromosomal arms at the later stage. Centromere clustering and synapsis initiation at the centromeres depend on the chromosome cohesion protein ORD and presumably on SOLO-SUNN-type cohesin (Takeo et al., 2011; Tanneti et al., 2011). Although C(2)M is less important for centromere clustering, it is required for synapsis initiation at the interstitial sites (Tanneti et al., 2011).

Thus, different organisms including *Drosophila* may use evolutionarily conserved systems for meiotic chromosome regulation, of which mechanisms are endowed by distinct kleisins of the cohesin complexes, "the REC8-type" and "the RAD21L-type" subunits.

13 | PREMATURE LOSS OF COHESIN IS ASSOCIATED WITH AGE-RELATED ANEUPLOIDY IN FEMALE MEIOSIS

In mammals, oocytes begin meiosis in the fetal ovary and then enter the dictyate stage, when they undergo long-term cell cycle arrest while awaiting the hormonal stimulus for resumption of meiosis (Jones, 2008). There is a gradual loss of cohesin from the nuclei at this stage in mouse and human oocytes (Garcia-Cruz, Brieno, Roig, Grossmann, & Velilla, 2010; Prieto, Tease, Pezzi, Buesa, & Ortega, 2004). Oocytes subsequently resume meiosis by entering metaphase I and again become arrested at metaphase II before ovulation. Thus, the time interval from the establishment to the final resolution of sister chromatid cohesion is remarkably prolonged in female meiosis, which lasts for decades in humans and many months in mice. Notably, aneuploidy predominantly arises as a consequence of chromosome missegregation in female meiosis, which leads to severe birth defects such as Down's syndrome and miscarriage (Hassold & Hunt, 2001). Given that the frequency of clinically recognized trisomy largely correlates with advancing maternal age (Herbert, Kalleas, Cooney, Lamb, & Lister, 2015; Nagaoka, Hassold, & Hunt, 2012), it has been suggested that premature loss of sister chromatid cohesion could be one of the primary causes of chromosome segregation errors in oocytes, because cohesin has already localized along the chromosomes during meiotic prophase in fetal ovaries (Prieto et al., 2004).

Indeed, accumulating evidence suggests that cohesion levels are decreased in aged human and mouse oocytes (Chiang, Duncan, Schindler, Schultz, & Lampson, 2010; Lister, Kouznetsova, Hyslop, Kalleas, & Pace, 2010; Liu & Keefe, 2008; Sakakibara, Hashimoto, Nakaoka, Kouznetsova, & Hoog, 2015; Tsutsumi, Fujiwara, Nishizawa, Ito, & Kogo, 2014; Zielinska, Holubcova, Blayney, Elder, & Schuh, 2015). It has been shown that, despite the invariable levels of total REC8 protein in oocytes from old to young mice, the level of chromosome-bound REC8 is severely reduced at the centromeres and on the arms in both naturally aged oocytes (Chiang et al., 2010; Lister et al., 2010) and senescence-accelerated mouse oocytes (Liu & Keefe, 2008), suggesting that the REC8 cohesin has dissociated from chromosomes in the aged cells. Consequently, aged oocytes exhibit a high incidence of distally associated homologous chromosomes without visible chiasma compared to young cells (Lister et al., 2010). This is accompanied by a significant reduction in the proportion of bivalents with a single chiasma, like in *Smc1*β KO oocytes, where distally associated homologues without skewed crossover sites are prevalent (Hodges et al., 2005). This phenomenon can be explained by the notion that low levels of arm cohesion cannot prevent chiasmata from moving and slipping off the chromosome. Thus, gradual reduction of sister chromatid cohesion along the arm regions leads to destabilization of the physical linkage between homologues in aged oocytes.

Furthermore, coincident with the reduced levels of REC8 at the centromeres, sister kinetochores are significantly separated apart at metaphase I and metaphase II in aged oocytes, indicating that sister chromatid cohesion at the centromeric regions is weakened (Chiang et al., 2010; Lister et al., 2010;

Zielinska et al., 2015). As a result of the disruption in centromere geometry, weakened centromeric cohesion accompanies a high incidence of chromosome missegregation during the transition from metaphase I to anaphase I in aged oocytes. Recent live imaging analysis has shown that the majority of chromosome segregation errors are preceded by premature separation of bivalents into univalents during metaphase I in aged oocytes (Sakakibara et al., 2015). Moreover, it should be noted that retention of SGO2 on the chromosomes is also reduced in aged oocytes, which may, in turn, partly amplify the premature loss of chromosome-bound cohesin (Lister et al., 2010). Thus, dissociation and degradation of chromosome-bound REC8-cohesin over time account for the high frequency of aneuploidy in aged oocytes, raising a question whether cohesin on the chromosomes is renewed during prolonged oocyte arrest.

The cohesin loading factor NIPBL/SCC2 localizes along chromosome axes during meiotic prophase in fetal oocytes and becomes undetectable after dictyate arrest is commenced (Kuleszewicz, Fu, & Kudo, 2013; Visnes, Giordano, Kuznetsova, Suja, & Lander, 2014). Concomitantly, before dictyate arrest, cohesins significantly dissociate from desynapsing chromosomes, leaving protein aggregates called polycomplexes (Prieto et al., 2004). Thus, whether in oocytes sister chromatid cohesion is maintained on the chromosomes without turnover, or is complemented by de novo synthesis and reloading of cohesins during prolonged arrest, remains unclear. This question has been addressed by a genetic approach using $Rec8^{TEV/TEV}$ mouse lines, in which the endogenous *Rec8* allele is genetically modified so that REC8 can be artificially cleaved by TEV protease (Burkhardt, Borsos, Szydlowska, Godwin, & Williams, 2016; Tachibana-Konwalski et al., 2010). When TEV protease is introduced into M I-arrested oocytes from $Rec8^{TEV/TEV}$ females, all the bivalent chromosomes are converted into single chromatids, indicating that cohesion is lost completely after $REC8^{TEV}$ depletion. However, when TEV-resistant REC8 is exogenously expressed from a conditionally activated *Rec8* transgene in $Rec8^{TEV/TEV}$ oocytes before pre-meiotic DNA replication, conversion of bivalents into single chromatids is suppressed in M I oocytes, indicating that cohesion is established by the exogenous REC8 compensating the loss of $REC8^{TEV}$. However, it is important to note, that when TEV-resistant REC8 is expressed in $Rec8^{TEV/TEV}$ oocytes during or after dictyate arrest, it no longer suppresses the conversion of bivalents into single chromatids in M I oocytes, suggesting that the exogenous REC8 cannot contribute to cohesion during or after dictyate arrest. Crucially, the REC8 exogenously expressed at those times exhibits little localization to chromosomes, suggesting that oocytes during or after dictyate arrest do not have the ability to reload cohesin onto chromosomes. In agreement with this notion, when SMC1β is conditionally disrupted in primordial follicle oocytes shortly after birth, cohesion and chiasma positions still remain normal in M I oocytes (Revenkova et al., 2010). This indicates that de novo SMC1β expression is dispensable for the maintenance of cohesion during dictyate arrest once cohesion has been established in pre-meiotic S phase. Thus, REC8-mediated cohesion is maintained without detectable turnover from dictyate arrest until resumption of meiosis I in oocytes. Since it has been shown that chromosome abnormalities are slightly elevated in oocytes from heterozygous *Smc1*β or *Rec8* mice, gene dosage of cohesin may potentially affect aneuploidy (Murdoch, Owen, Stevense, Smith, & Nagaoka, 2013). This implies that heterozygous human carriers of cohesin gene mutations may be at higher risk of aneuploidy, which should be focused in future clinical studies.

14 | CONCLUSION

In mammalian germ cells, the meiosis-specific cohesin complex plays critical roles in chromosome axis formation, homologue association, meiotic recombination and centromeric cohesion, which cannot be substituted by mitotic cohesin. These specific functions are endowed by the meiosis-specific subunits of the cohesin complex. The kleisin subunit REC8 and RAD21L, in particular, provide distinct functions and specificities of cohesin complexes during meiosis I. It is noteworthy that a system similar to REC8 and RAD21L in mammalian meiosis is also observed in other organisms. Over a wide range of organisms, REC8-type cohesin largely contributes to canonical sister chromatid cohesion and primarily acts for centromeric cohesion during meiosis I. In contrast, RAD21L-type is an atypical cohesin because it less contributes to sister chromatid cohesion, but possesses more specific role in homologue interaction.

At present, several questions remain to be answered. REC8- and RAD21L-type cohesins have their intrinsic loading sites on the chromosomes and form distinct cohesin-enriched domains. The primary DNA sequence or loading factor that underlies these cohesin-enriched domains remains elusive. Although the establishment of REC8-mediated cohesion is dependent on DNA replication, that of RAD21L is dependent on DSB. The mechanism of RAD21L-mediated cohesion is an important question to be addressed. Furthermore, REC8- and RAD21L-type cohesins have different functions in homologue association. It is largely unexplained how RAD21L acts during bouquet exit to complete homologue association. Given that the loss of meiosis-specific cohesin is associated with age-related aneuploidy, it is an enigma how meiotic cohesion is preserved without turnover over the long spans of time involved in maternal meiotic arrest. Further study will shed light on the mechanistic insight of meiotic cohesion and its role in chromosome dynamics during meiosis.

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REFERENCES

Adelfalk, C., Janschek, J., Revenkova, E., Blei, C., Liebe, B., Gob, E., … Jessberger, R. (2009). Cohesin SMC1beta protects telomeres in meiocytes. *Journal of Cell Biology*, *187*(2), 185–199. https://doi.org/10.1083/jcb.200808016

Agostinho, A., Manneberg, O., van Schendel, R., Hernandez-Hernandez, A., Kouznetsova, A., Blom, H., … Höög, C. (2016). High density of REC8 constrains sister chromatid axes and prevents illegitimate synaptonemal complex formation. *EMBO Reports*, *17*(6), 901–913. https://doi.org/10.15252/embr.201642030

Alomer, R. M., da Silva, E. M. L., Chen, J., Piekarz, K. M., McDonald, K., Sansam, C. G., & Rankin, S. (2017). Esco1 and Esco2 regulate distinct cohesin functions during cell cycle progression. *Proceedings of the National Academy of Sciences of the United States of America*, *114*(37), 9906–9911. https://doi.org/10.1073/pnas.1708291114

Anderson, L. K., Royer, S. M., Page, S. L., McKim, K. S., Lai, A., Lilly, M. A., & Hawley, R. S. (2005). Juxtaposition of C(2)M and the transverse filament protein C(3)G within the central region of *Drosophila* synaptonemal complex. *Proceedings of the National Academy of Sciences of the United States of America*, *102*(12), 4482–4487. https://doi.org/10.1073/pnas.0500172102

Attner, M. A., Miller, M. P., Ee, L. S., Elkin, S. K., & Amon, A. (2013). Polo kinase Cdc5 is a central regulator of meiosis I. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(35), 14278–14283. https://doi.org/10.1073/pnas.1311845110

Bannister, L. A., Reinholdt, L. G., Munroe, R. J., & Schimenti, J. C. (2004). Positional cloning and characterization of mouse mei8, a disrupted allelle of the meiotic cohesin Rec8. *Genesis*, *40*(3), 184–194. https://doi.org/10.1002/(ISSN)1526-968X

Barbero, J. L. (2013). Genetic basis of cohesinopathies. *The Application of Clinical Genetics*, *6*, 15–23. https://doi.org/10.2147/TACG

Barzel, A., & Kupiec, M. (2008). Finding a match: How do homologous sequences get together for recombination? *Nature Reviews Genetics*, *9*(1), 27–37. https://doi.org/10.1038/nrg2224

Baudat, F., Imai, Y., & de Massy, B. (2013). Meiotic recombination in mammals: Localization and regulation. *Nature Reviews Genetics*, *14*(11), 794–806. https://doi.org/10.1038/nrg3573

Bayes, M., Prieto, I., Noguchi, J., Barbero, J. L., & Perez Jurado, L. A. (2001). Evaluation of the Stag3 gene and the synaptonemal complex in a rat model (as/as) for male infertility. *Molecular Reproduction and Development*, *60*(3), 414–417. https://doi.org/10.1002/mrd.1104

Bhalla, N., & Dernburg, A. F. (2008). Prelude to a division. *Annual Review of Cell and Developmental Biology*, *24*, 397–424. https://doi.org/10.1146/annurev.cellbio.23.090506.123245

Biswas, U., Wetzker, C., Lange, J., Christodoulou, E. G., Seifert, M., Beyer, A., & Jessberger, R. (2013). Meiotic cohesin SMC1beta provides prophase I centromeric cohesion and is required for multiple synapsis-associated functions. *PLoS Genetics*, *9*(12), e1003985. https://doi.org/10.1371/journal.pgen.1003985

Biswas, U., Stevense, M., & Jessberger, R. (2018). SMC1alpha substitutes for many meiotic functions of SMC1beta but cannot protect telomeres from damage. *Current Biology*, *28*(2), 249–261 e4. https://doi.org/10.1016/j.cub.2017.12.020

Boateng, K. A., Bellani, M. A., Gregoretti, I. V., Pratto, F., & Camerini-Otero, R. D. (2013). Homologous pairing preceding SPO11-mediated double-strand breaks in mice. *Developmental Cell*, *24*(2), 196–205. https://doi.org/10.1016/j.devcel.2012.12.002

Brar, G. A., Kiburz, B. M., Zhang, Y., Kim, J. E., White, F., & Amon, A. (2006). Rec8 phosphorylation and recombination promote the step-wise loss of cohesins in meiosis. *Nature*, *441*(7092), 532–536. https://doi.org/10.1038/nature04794

Brieno-Enriquez, M. A., Moak, S. L., Toledo, M., Filter, J. J., Gray, S., Barbero, J. L., … Holloway, J. K. (2016). Cohesin removal along the chromosome arms during the first meiotic division depends on a NEK1-PP1gamma-WAPL axis in the mouse. *Cell Reports*, *17*(4), 977–986. https://doi.org/10.1016/j.celrep.2016.09.059

Buheitel, J., & Stemmann, O. (2013). Prophase pathway-dependent removal of cohesin from human chromosomes requires opening of the Smc3-Scc1 gate. *EMBO Journal*, *32*(5), 666–676. https://doi.org/10.1038/emboj.2013.7

Buonomo, S. B., Clyne, R. K., Fuchs, J., Loidl, J., Uhlmann, F., & Nasmyth, K. (2000). Disjunction of homologous chromosomes in meiosis I depends on proteolytic cleavage of the meiotic cohesin Rec8 by separin. *Cell*, *103*(3), 387–398. https://doi.org/10.1016/S0092-8674(00)00131-8

Burkhardt, S., Borsos, M., Szydlowska, A., Godwin, J., Williams, S. A., Cohen, P. E., … Tachibana-Konwalski, K. (2016). Chromosome cohesion established by Rec8-cohesin in fetal oocytes is maintained without detectable turnover in oocytes arrested for months in mice. *Current Biology*, *26*(5), 678–685. https://doi.org/10.1016/j.cub.2015.12.073

Cahoon, C. K., & Hawley, R. S. (2016). Regulating the construction and demolition of the synaptonemal complex. *Nature Structural and Molecular Biology*, *23*(5), 369–377. https://doi.org/10.1038/nsmb.3208

Challa, K., Lee, M. S., Shinohara, M., Kim, K. P., & Shinohara, A. (2016). Rad61/Wpl1 (Wapl), a cohesin regulator, controls chromosome compaction during meiosis. *Nucleic Acids Research*, *44*(7), 3190–3203. https://doi.org/10.1093/nar/gkw034

Chan, R. C., Severson, A. F., & Meyer, B. J. (2004). Condensin restructures chromosomes in preparation for meiotic divisions. *Journal of Cell Biology*, *167*(4), 613–625. https://doi.org/10.1083/jcb.200408061

Chelysheva, L., Daiallo, S., Vezon, D., Gendrot, G., Vrielynck, N., Belcram, K., … Grelon, M. (2005). AtREC8 and AtSCC3 are essential to the monopolar orientation of the kinetochores during meiosis. *Journal of Cell Science*, *118*, 4621–4632. https://doi.org/10.1242/jcs.02583

Chiang, T., Duncan, F. E., Schindler, K., Schultz, R. M., & Lampson, M. A. (2010). Evidence that weakened centromere cohesion is a leading cause of age-related aneuploidy in oocytes. *Current Biology*, *20*(17), 1522–1528. https://doi.org/10.1016/j.cub.2010.06.069

Ciosk, R., Shirayama, M., Shevchenko, A., Tanaka, T., Toth, A., Shevchenko, A., & Nasmyth, K. (2000). Cohesin's binding to chromosomes depends on a separate complex consisting of Scc2 and Scc4 proteins. *Molecular Cell*, *5*(2), 243–254. https://doi.org/10.1016/S1097-2765(00)80420-7

Clyne, R. K., Katis, V. L., Jessop, L., Benjamin, K. R., Herskowitz, I., Lichten, M., & Nasmyth, K. (2003). Polo-like kinase Cdc5 promotes chiasmata formation and cosegregation of sister centromeres at meiosis I. *Nature Cell Biology*, *5*(5), 480–485. https://doi.org/10.1038/ncb977

Conrad, M. N., Lee, C. Y., Wilkerson, J. L., & Dresser, M. E. (2007). MPS3 mediates meiotic bouquet formation in Saccharomyces cerevisiae. *Proceedings of the National Academy of Sciences of the United States of America*, *104*(21), 8863–8868. https://doi.org/10.1073/pnas.0606165104

Crawley, O., Barroso, C., Testori, S., Ferrandiz, N., Silva, N., Castellano-Pozo, M., & Jaso-Tamame, A. L. (2016). Cohesin-interacting protein WAPL-1 regulates meiotic chromosome structure and cohesion by antagonizing specific cohesin complexes. *Elife*, *5*, e10851. https://doi.org/10.7554/eLife.10851

Daniel, K., Lange, J., Hached, K., Fu, J., Anastassiadis, K., Roig, I., … Tóth, A. (2011). Meiotic homologue alignment and its quality surveillance are controlled by mouse HORMAD1. *Nature Cell Biology*, *13*(5), 599–610. https://doi.org/10.1038/ncb2213

De, K., Sterle, L., Krueger, L., Yang, X., & Makaroff, C. A. (2014). *Arabidopsis thaliana* WAPL is essential for the prophase removal of cohesin during meiosis. *PLoS Genetics*, *10*(7), e1004497. https://doi.org/10.1371/journal.pgen.1004497

de Carvalho, C. E., Zaaijer, S., Smolikov, S., Gu, Y., Schumacher, J. M., & Colaiacovo, M. P. (2008). LAB-1 antagonizes the Aurora B kinase in *C. elegans*. *Genes and Development*, *22*(20), 2869–2885. https://doi.org/10.1101/gad.1691208

Deardorff, M. A., Bando, M., Nakato, R., Watrin, E., Itoh, T., Minamino, M., … Shirahige, K. (2012). HDAC8 mutations in Cornelia de Lange syndrome affect the cohesin acetylation cycle. *Nature*, *489*(7415), 313–317. https://doi.org/10.1038/nature11316

Ding, D. Q., Yamamoto, A., Haraguchi, T., & Hiraoka, Y. (2004). Dynamics of homologous chromosome pairing during meiotic prophase in fission yeast. *Developmental Cell*, *6*(3), 329–341. https://doi.org/10.1016/S1534-5807(04)00059-0

Eijpe, M., Heyting, C., Gross, B., & Jessberger, R. (2000). Association of mammalian SMC1 and SMC3 proteins with meiotic chromosomes and synaptonemal complexes. *Journal of Cell Science*, *113*(Pt 4), 673–682.

Eijpe, M., Offenberg, H., Jessberger, R., Revenkova, E., & Heyting, C. (2003). Meiotic cohesin REC8 marks the axial elements of rat synaptonemal complexes before cohesins SMC1beta and SMC3. *Journal of Cell Biology*, *160*(5), 657–670. https://doi.org/10.1083/jcb.200212080

Fukuda, T., Daniel, K., Wojtasz, L., Toth, A., & Hoog, C. (2010). A novel mammalian HORMA domain-containing protein, HORMAD1, preferentially associates with unsynapsed meiotic chromosomes. *Experimental Cell Research*, *316*(2), 158–171. https://doi.org/10.1016/j.yexcr.2009.08.007

Fukuda, T., & Hoog, C. (2010). The mouse cohesin-associated protein PDS5B is expressed in testicular cells and is associated with the meiotic chromosome axes. *Genes (Basel)*, *1*(3), 484–494. https://doi.org/10.3390/genes1030484

Fukuda, T., Fukuda, N., Agostinho, A., Hernandez-Hernandez, A., Kouznetsova, A., & Hoog, C. (2014). STAG3-mediated stabilization of REC8 cohesin complexes promotes chromosome synapsis during meiosis. *EMBO Journal*, *33*(11), 1243–1255.

Gandhi, R., Gillespie, P. J., & Hirano, T. (2006). Human Wapl is a cohesin-binding protein that promotes sister-chromatid resolution in mitotic prophase. *Current Biology*, *16*(24), 2406–2417. https://doi.org/10.1016/j.cub.2006.10.061

Garcia-Cruz, R., Brieno, M. A., Roig, I., Grossmann, M., Velilla, E., Pujol, A., … Garcia Caldés, M. (2010). Dynamics of cohesin proteins REC8, STAG3, SMC1 beta and SMC3 are consistent with a role in sister chromatid cohesion during meiosis in human oocytes. *Human Reproduction*, *25*(9), 2316–2327. https://doi.org/10.1093/humrep/deq180

Gassler, J., Brandao, H. B., Imakaev, M., Flyamer, I. M., Ladstatter, S., Bickmore, W. A., … Mirny, L. A. (2017). A mechanism of cohesin-dependent loop extrusion organizes zygotic genome architecture. *EMBO Journal*, *36*(24), 3600–3618. https://doi.org/10.15252/embj.201798083

Gerton, J. L., & Hawley, R. S. (2005). Homologous chromosome interactions in meiosis: Diversity amidst conservation. *Nature Reviews Genetics*, *6*(6), 477–487. https://doi.org/10.1038/nrg1614

Ghirlando, R., & Felsenfeld, G. (2016). CTCF: Making the right connections. *Genes and Development*, *30*(8), 881–891. https://doi.org/10.1101/gad.277863.116

Gomez, R., Felipe-Medina, N., Ruiz-Torres, M., Berenguer, I., Viera, A., Perez, S., … Suja, J. A. (2016). Sororin loads to the synaptonemal complex central region independently of meiotic cohesin complexes. *EMBO Reports*, *17*(5), 695–707. https://doi.org/10.15252/embr.201541060

Gutierrez-Caballero, C., Herran, Y., Sanchez-Martin, M., Suja, J. A., Barbero, J. L., Llano, E., & Pendás, A. M. (2011). Identification and molecular characterization of the mammalian alpha-kleisin RAD21L. *Cell Cycle*, *10*(9), 1477–1487. https://doi.org/10.4161/cc.10.9.15515

Gyuricza, M. R., Manheimer, K. B., Apte, V., Krishnan, B., Joyce, E. F., McKee, B. D., & McKim, K. S. (2016). Dynamic and stable cohesins regulate synaptonemal complex assembly and chromosome segregation. *Current Biology*, *26*, 1688–1698. https://doi.org/10.1016/j.cub.2016.05.006

Hamant, O., Golubovskaya, I., Meeley, R., Fiume, E., Timofejeva, L., Schleiffer, A., … Cande, W. Z. (2005). A REC8-dependent plant Shugoshin is required for maintenance of centromeric cohesion during meiosis and has no mitotic functions. *Current Biology*, *15*(10), 948–954. https://doi.org/10.1016/j.cub.2005.04.049

Handel, M. A., & Schimenti, J. C. (2010). Genetics of mammalian meiosis: Regulation, dynamics and impact on fertility. *Nature Reviews Genetics*, *11*(2), 124–136. https://doi.org/10.1038/nrg2723

Hassold, T., & Hunt, P. (2001). To err (meiotically) is human: The genesis of human aneuploidy. *Nature Reviews Genetics*, *2*(4), 280–291. https://doi.org/10.1038/35066065

Hauf, S., Waizenegger, I. C., & Peters, J. M. (2001). Cohesin cleavage by separase required for anaphase and cytokinesis in human cells. *Science*, *293*(5533), 1320–1323. https://doi.org/10.1126/science.1061376

Hauf, S., Roitinger, E., Koch, B., Dittrich, C. M., Mechtler, K., & Peters, J. M. (2005). Dissociation of cohesin from chromosome arms and loss of arm cohesion during early mitosis depends on phosphorylation of SA2. *PLoS Biology*, *3*(3), e69. https://doi.org/10.1371/journal.pbio.0030069

Heidinger-Pauli, J. M., Unal, E., Guacci, V., & Koshland, D. (2008). The kleisin subunit of cohesin dictates damage-induced cohesion. *Molecular Cell*, *31*(1), 47–56. https://doi.org/10.1016/j.molcel.2008.06.005

Heidmann, D., Horn, S., Heidmann, S., Schleiffer, A., Nasmyth, K., & Lehner, C. F. (2004). The *Drosophila* meiotic kleisin C(2)M functions before the meiotic divisions. *Chromosoma*, *113*(4), 177–187.

Herbert, M., Kalleas, D., Cooney, D., Lamb, M., & Lister, L. (2015). Meiosis and maternal aging: Insights from aneuploid oocytes and trisomy births. *Cold Spring Harbor Perspectives in Biology*, *7*(4), a017970. https://doi.org/10.1101/cshperspect.a017970

Herran, Y., Gutierrez-Caballero, C., Sanchez-Martin, M., Hernandez, T., Viera, A., Barbero, J. L., … Pendás, A. M. (2011). The cohesin subunit RAD21L functions in meiotic synapsis and exhibits sexual dimorphism in fertility. *EMBO Journal*, *30*(15), 3091–3105. https://doi.org/10.1038/emboj.2011.222

Hiraoka, Y., & Dernburg, A. F. (2009). The SUN rises on meiotic chromosome dynamics. *Developmental Cell*, *17*(5), 598–605. https://doi.org/10.1016/j.devcel.2009.10.014

Hodges, C. A., Revenkova, E., Jessberger, R., Hassold, T. J., & Hunt, P. A. (2005). SMC1beta-deficient female mice provide evidence that cohesins are a missing link in age-related nondisjunction. *Nature Genetics*, *37*(12), 1351–1355. https://doi.org/10.1038/ng1672

Hopkins, J., Hwang, G., Jacob, J., Sapp, N., Bedigian, R., Oka, K., … Jordan, P. W. (2014). Meiosis-specific cohesin component, Stag3 is essential for maintaining centromere chromatid cohesion, and required for DNA repair and synapsis between homologous chromosomes. *PLoS Genetics*, *10*(7), e1004413. https://doi.org/10.1371/journal.pgen.1004413

Horn, H. F., Kim, D. I., Wright, G. D., Wong, E. S., Stewart, C. L., Burke, B., & Roux, K. J. (2013). A mammalian KASH domain protein coupling meiotic chromosomes to the cytoskeleton. *Journal of Cell Biology*, *202*(7), 1023–1039. https://doi.org/10.1083/jcb.201304004

Horsfield, J. A., Print, C. G., & Monnich, M. (2012). Diverse developmental disorders from the one ring: Distinct molecular pathways underlie the cohesinopathies. *Frontiers in Genetics*, *3*, 171.

Ishiguro, T., Tanaka, K., Sakuno, T., & Watanabe, Y. (2010). Shugoshin-PP2A counteracts casein-kinase-1-dependent cleavage of Rec8 by separase. *Nature Cell Biology*, *12*(5), 500–506. https://doi.org/10.1038/ncb2052

Ishiguro, K., Kim, J., Fujiyama-Nakamura, S., Kato, S., & Watanabe, Y. (2011). A new meiosis-specific cohesin complex implicated in the cohesin code for homologous pairing. *EMBO Reports*, *12*(3), 267–275. https://doi.org/10.1038/embor.2011.2

Ishiguro, K., Kim, J., Shibuya, H., Hernandez-Hernandez, A., Suzuki, A., Fukagawa, T., … Watanabe, Y. (2014). Meiosis-specific cohesin mediates homolog recognition in mouse spermatocytes. *Genes and Development*, *28*(6), 594–607. https://doi.org/10.1101/gad.237313.113

Ishiguro, K., & Watanabe, Y. (2016). The cohesin REC8 prevents illegitimate inter-sister synaptonemal complex assembly. *EMBO Reports*, *17*(6), 783–784. https://doi.org/10.15252/embr.201642544

Ivanov, D., Schleiffer, A., Eisenhaber, F., Mechtler, K., Haering, C. H., & Nasmyth, K. (2002). Eco1 is a novel acetyltransferase that can acetylate proteins involved in cohesion. *Current Biology*, *12*(4), 323–328. https://doi.org/10.1016/S0960-9822(02)00681-4

Jin, H., Guacci, V., & Yu, H. G. (2009). Pds5 is required for homologue pairing and inhibits synapsis of sister chromatids during yeast meiosis. *Journal of Cell Biology*, *186*(5), 713–725. https://doi.org/10.1083/jcb.200810107

Jones, K. T. (2008). Meiosis in oocytes: Predisposition to aneuploidy and its increased incidence with age. *Human Reproduction Update*, *14*(2), 143–158. https://doi.org/10.1093/humupd/dmm043

Jordan, P. W., Eyster, C., Chen, J., Pezza, R. J., & Rankin, S. (2017). Sororin is enriched at the central region of synapsed meiotic chromosomes. *Chromosome Research*, *25*(2), 115–128. https://doi.org/10.1007/s10577-016-9542-8

Kagey, M. H., Newman, J. J., Bilodeau, S., Zhan, Y., Orlando, D. A., van Berkum, N. L., … Young, R. A. (2010). Mediator and cohesin connect gene expression and chromatin architecture. *Nature*, *467*(7314), 430–435. https://doi.org/10.1038/nature09380

Kaitna, S., Pasierbek, P., Jantsch, M., Loidl, J., & Glotzer, M. (2002). The aurora B kinase AIR-2 regulates kinetochores during mitosis and is required for separation of homologous chromosomes during meiosis. *Current Biology*, *12*(10), 798–812. https://doi.org/10.1016/S0960-9822(02)00820-5

Katis, V. L., Galova, M., Rabitsch, K. P., Gregan, J., & Nasmyth, K. (2004). Maintenance of cohesin at centromeres after meiosis I in budding yeast requires a kinetochore-associated protein related to MEI-S332. *Current Biology*, *14*(7), 560–572. https://doi.org/10.1016/j.cub.2004.03.001

Katis, V. L., Matos, J., Mori, S., Shirahige, K., Zachariae, W., & Nasmyth, K. (2004). Spo13 facilitates monopolin recruitment to kinetochores and regulates maintenance of centromeric cohesion during yeast meiosis. *Current Biology*, *14*(24), 2183–2196. https://doi.org/10.1016/j.cub.2004.12.020

Katis, V. L., Lipp, J. J., Imre, R., Bogdanova, A., Okaz, E., Habermann, B., … Zachariae, W. (2010). Rec8 phosphorylation by casein kinase 1 and Cdc7-Dbf4 kinase regulates cohesin cleavage by separase during meiosis. *Developmental Cell*, *18*(3), 397–409. https://doi.org/10.1016/j.devcel.2010.01.014

Keeney, S., Lange, J., & Mohibullah, N. (2014). Self-organization of meiotic recombination initiation: General principles and molecular pathways. *Annual Review of Genetics*, *48*, 187–214. https://doi.org/10.1146/annurev-genet-120213-092304

Kenna, M. A., & Skibbens, R. V. (2003). Mechanical link between cohesion establishment and DNA replication: Ctf7p/Eco1p, a cohesion establishment factor, associates with three different replication factor C complexes. *Molecular and Cellular Biology*, *23*(8), 2999–3007. https://doi.org/10.1128/MCB.23.8.2999-3007.2003

Kerrebrock, A. W., Miyazaki, W. Y., Birnby, D., & Orr-Weaver, T. L. (1992). The *Drosophila* mei-S332 gene promotes sister-chromatid cohesion in meiosis following kinetochore differentiation. *Genetics*, *130*(4), 827–841.

Khetani, R. S., & Bickel, S. E. (2007). Regulation of meiotic cohesion and chromosome core morphogenesis during pachytene in *Drosophila* oocytes. *Journal of Cell Science*, *120*(Pt 17), 3123–3137. https://doi.org/10.1242/jcs.009977

Kim, K. P., Weiner, B. M., Zhang, L., Jordan, A., Dekker, J., & Kleckner, N. (2010). Sister cohesion and structural axis components mediate homolog bias of meiotic recombination. *Cell*, *143*(6), 924–937. https://doi.org/10.1016/j.cell.2010.11.015

Kim, J., Ishiguro, K., Nambu, A., Akiyoshi, B., Yokobayashi, S., Kagami, A., … Watanabe, Y. (2015). Meikin is a conserved regulator of meiosis-I-specific kinetochore function. *Nature*, *517*(7535), 466–471. https://doi.org/10.1038/nature14097

Kitajima, T. S., Miyazaki, Y., Yamamoto, M., & Watanabe, Y. (2003). Rec8 cleavage by separase is required for meiotic nuclear divisions in fission yeast. *EMBO Journal*, *22*(20), 5643–5653. https://doi.org/10.1093/emboj/cdg527

Kitajima, T. S., Yokobayashi, S., Yamamoto, M., & Watanabe, Y. (2003). Distinct cohesin complexes organize meiotic chromosome

domains. *Science*, *300*(5622), 1152–1155. https://doi.org/10.1126/science.1083634

Kitajima, T. S., Kawashima, S. A., & Watanabe, Y. (2004). The conserved kinetochore protein shugoshin protects centromeric cohesion during meiosis. *Nature*, *427*(6974), 510–517. https://doi.org/10.1038/nature02312

Kitajima, T. S., Sakuno, T., Ishiguro, K., Iemura, S., Natsume, T., Kawashima, S. A., & Watanabe, Y. (2006). Shugoshin collaborates with protein phosphatase 2A to protect cohesin. *Nature*, *441*(7089), 46–52. https://doi.org/10.1038/nature04663

Kogo, H., Tsutsumi, M., Inagaki, H., Ohye, T., Kiyonari, H., & Kurahashi, H. (2012). HORMAD2 is essential for synapsis surveillance during meiotic prophase via the recruitment of ATR activity. *Genes to Cells*, *17*(11), 897–912. https://doi.org/10.1111/gtc.12005

Kogo, H., Tsutsumi, M., Ohye, T., Inagaki, H., Abe, T., & Kurahashi, H. (2012). HORMAD1-dependent checkpoint/surveillance mechanism eliminates asynaptic oocytes. *Genes to Cells*, *17*(6), 439–454. https://doi.org/10.1111/j.1365-2443.2012.01600.x

Koszul, R., & Kleckner, N. (2009). Dynamic chromosome movements during meiosis: A way to eliminate unwanted connections? *Trends in Cell Biology*, *19*(12), 716–724. https://doi.org/10.1016/j.tcb.2009.09.007

Kouznetsova, A., Novak, I., Jessberger, R., & Hoog, C. (2005). SYCP2 and SYCP3 are required for cohesin core integrity at diplotene but not for centromere cohesion at the first meiotic division. *Journal of Cell Science*, *118*(Pt 10), 2271–2278. https://doi.org/10.1242/jcs.02362

Krishnan, B., Thomas, S. E., Yan, R., Yamada, H., Zhulin, I. B., & McKee, B. D. (2014). Sisters unbound is required for meiotic centromeric cohesion in *Drosophila melanogaster*. *Genetics*, *198*(3), 947–965. https://doi.org/10.1534/genetics.114.166009

Kudo, N. R., Wassmann, K., Anger, M., Schuh, M., Wirth, K. G., Xu, H., … Nasmyth, K. (2006). Resolution of chiasmata in oocytes requires separase-mediated proteolysis. *Cell*, *126*(1), 135–146. https://doi.org/10.1016/j.cell.2006.05.033

Kudo, N. R., Anger, M., Peters, A. H., Stemmann, O., Theussl, H. C., Helmhart, W., … Nasmyth, K. (2009). Role of cleavage by separase of the Rec8 kleisin subunit of cohesin during mammalian meiosis I. *Journal of Cell Science*, *122*(Pt 15), 2686–2698. https://doi.org/10.1242/jcs.035287

Kueng, S., Hegemann, B., Peters, B. H., Lipp, J. J., Schleiffer, A., Mechtler, K., & Peters, J. M. (2006). Wapl controls the dynamic association of cohesin with chromatin. *Cell*, *127*(5), 955–967. https://doi.org/10.1016/j.cell.2006.09.040

Kuleszewicz, K., Fu, X., & Kudo, N. R. (2013). Cohesin loading factor Nipbl localizes to chromosome axes during mammalian meiotic prophase. *Cell Division*, *8*(1), 12. https://doi.org/10.1186/1747-1028-8-12

Kumar, R., Ghyselinck, N., Ishiguro, K., Watanabe, Y., Kouznetsova, A., Hoog, C., … de Massy, B. (2015). MEI4 – A central player in the regulation of meiotic DNA double-strand break formation in the mouse. *Journal of Cell Science*, *128*(9), 1800–1811. https://doi.org/10.1242/jcs.165464

Lam, I., & Keeney, S. (2015). Mechanism and regulation of meiotic recombination initiation. *Cold Spring Harbor Perspectives in Biology*, *7*(1), a016634. https://doi.org/10.1101/cshperspect.a016634

Lee, B. H., Amon, A., & Prinz, S. (2002). Spo13 regulates cohesin cleavage. *Genes and Development*, *16*(13), 1672–1681. https://doi.org/10.1101/gad.989302

Lee, B. H., & Amon, A. (2003). Role of Polo-like kinase CDC5 in programming meiosis I chromosome segregation. *Science*, *300*(5618), 482–486. https://doi.org/10.1126/science.1081846

Lee, J., Iwai, T., Yokota, T., & Yamashita, M. (2003). Temporally and spatially selective loss of Rec8 protein from meiotic chromosomes during mammalian meiosis. *Journal of Cell Science*, *116*(Pt 13), 2781–2790. https://doi.org/10.1242/jcs.00495

Lee, J. Y., Dej, K. J., Lopez, J. M., & Orr-Weaver, T. L. (2004). Control of centromere localization of the MEI-S332 cohesion protection protein. *Current Biology*, *14*(14), 1277–1283. https://doi.org/10.1016/j.cub.2004.07.023

Lee, B. H., Kiburz, B. M., & Amon, A. (2004). Spo13 maintains centromeric cohesion and kinetochore coorientation during meiosis I. *Current Biology*, *14*(24), 2168–2182. https://doi.org/10.1016/j.cub.2004.12.033

Lee, J., Kitajima, T. S., Tanno, Y., Yoshida, K., Morita, T., Miyano, T., & Watanabe, Y. (2008). Unified mode of centromeric protection by shugoshin in mammalian oocytes and somatic cells. *Nature Cell Biology*, *10*(1), 42–52. https://doi.org/10.1038/ncb1667

Lee, J., & Hirano, T. (2011). RAD21L, a novel cohesin subunit implicated in linking homologous chromosomes in mammalian meiosis. *Journal of Cell Biology*, *192*(2), 263–276. https://doi.org/10.1083/jcb.201008005

Lister, L. M., Kouznetsova, A., Hyslop, L. A., Kalleas, D., Pace, S. L., Barel, J. C., … Herbert, M. (2010). Age-related meiotic segregation errors in mammalian oocytes are preceded by depletion of cohesin and Sgo2. *Current Biology*, *20*(17), 1511–1521. https://doi.org/10.1016/j.cub.2010.08.023

Liu, L., & Keefe, D. L. (2008). Defective cohesin is associated with age-dependent misaligned chromosomes in oocytes. *Reproductive BioMedicine Online*, *16*(1), 103–112. https://doi.org/10.1016/S1472-6483(10)60562-7

Llano, E., Gomez, R., Gutierrez-Caballero, C., Herran, Y., Sanchez-Martin, M., Vazquez-Quinones, L., … Pendás, A. M. (2008). Shugoshin-2 is essential for the completion of meiosis but not for mitotic cell division in mice. *Genes and Development*, *22*(17), 2400–2413. https://doi.org/10.1101/gad.475308

Llano, E., Herran, Y., Garcia-Tunon, I., Gutierrez-Caballero, C., de Alava, E., Barbero, J. L., … Pendás, A. M. (2012). Meiotic cohesin complexes are essential for the formation of the axial element in mice. *Journal of Cell Biology*, *197*(7), 877–885. https://doi.org/10.1083/jcb.201201100

Llano, E., Gomez, H. L., Garcia-Tunon, I., Sanchez-Martin, M., Caburet, S., Barbero, J. L., … Pendas, A. M. (2014). STAG3 is a strong candidate gene for male infertility. *Human Molecular Genetics*, *23*(13), 3421–3431. https://doi.org/10.1093/hmg/ddu051

Losada, A., & Hirano, T. (2005). Dynamic molecular linkers of the genome: The first decade of SMC proteins. *Genes and Development*, *19*(11), 1269–1287. https://doi.org/10.1101/gad.1320505

Losada, A., Yokochi, T., & Hirano, T. (2005). Functional contribution of Pds5 to cohesin-mediated cohesion in human cells and Xenopus egg extracts. *Journal of Cell Science*, *118*(Pt 10), 2133–2141. https://doi.org/10.1242/jcs.02355

Manheim, E. A., & McKim, K. S. (2003). The Synaptonemal complex component C(2)M regulates meiotic crossing over in *Drosophila*. *Current Biology*, *13*(4), 276–285. https://doi.org/10.1016/S0960-9822(03)00050-2

Marston, A. L., Tham, W. H., Shah, H., & Amon, A. (2004). A genome-wide screen identifies genes required for centromeric

cohesion. *Science*, *303*(5662), 1367–1370. https://doi.org/10.1126/science.1094220

Matos, J., Lipp, J. J., Bogdanova, A., Guillot, S., Okaz, E., Junqueira, M., … Zachariae, W. (2008). Dbf4-dependent CDC7 kinase links DNA replication to the segregation of homologous chromosomes in meiosis I. *Cell*, *135*(4), 662–678. https://doi.org/10.1016/j.cell.2008.10.026

McGuinness, B. E., Hirota, T., Kudo, N. R., Peters, J. M., & Nasmyth, K. (2005). Shugoshin prevents dissociation of cohesin from centromeres during mitosis in vertebrate cells. *PLoS Biology*, *3*(3), e86. https://doi.org/10.1371/journal.pbio.0030086

Minamino, M., Ishibashi, M., Nakato, R., Akiyama, K., Tanaka, H., Kato, Y., … Shirahige, K. (2015). Esco1 acetylates cohesin via a mechanism different from that of Esco2. *Current Biology*, *25*(13), 1694–1706. https://doi.org/10.1016/j.cub.2015.05.017

Miyazaki, W. Y., & Orr-Weaver, T. L. (1994). Sister-chromatid cohesion in mitosis and meiosis. *Annual Review of Genetics*, *28*, 167–187. https://doi.org/10.1146/annurev.ge.28.120194.001123

Miyoshi, T., Ito, M., Kugou, K., Yamada, S., Furuichi, M., Oda, A., … Ohta, K. (2012). A central coupler for recombination initiation linking chromosome architecture to S phase checkpoint. *Molecular Cell*, *47*(5), 722–733. https://doi.org/10.1016/j.molcel.2012.06.023

Morimoto, A., Shibuya, H., Zhu, X., Kim, J., Ishiguro, K., Han, M., & Watanabe, Y. (2012). A conserved KASH domain protein associates with telomeres, SUN1, and dynactin during mammalian meiosis. *Journal of Cell Biology*, *198*(2), 165–172. https://doi.org/10.1083/jcb.201204085

Murdoch, B., Owen, N., Stevense, M., Smith, H., Nagaoka, S., Hassold, T., … Hunt, P. (2013). Altered cohesin gene dosage affects Mammalian meiotic chromosome structure and behavior. *PLoS Genetics*, *9*(2), e1003241. https://doi.org/10.1371/journal.pgen.1003241

Nabeshima, K., Villeneuve, A. M., & Colaiacovo, M. P. (2005). Crossing over is coupled to late meiotic prophase bivalent differentiation through asymmetric disassembly of the SC. *Journal of Cell Biology*, *168*(5), 683–689. https://doi.org/10.1083/jcb.200410144

Nagaoka, S. I., Hassold, T. J., & Hunt, P. A. (2012). Human aneuploidy: Mechanisms and new insights into an age-old problem. *Nature Reviews Genetics*, *13*(7), 493–504. https://doi.org/10.1038/nrg3245

Nakajima, M., Kumada, K., Hatakeyama, K., Noda, T., Peters, J. M., & Hirota, T. (2007). The complete removal of cohesin from chromosome arms depends on separase. *Journal of Cell Science*, *120*(Pt 23), 4188–4196. https://doi.org/10.1242/jcs.011528

Nasmyth, K., & Haering, C. H. (2009). Cohesin: Its roles and mechanisms. *Annual Review of Genetics*, *43*, 525–558. https://doi.org/10.1146/annurev-genet-102108-134233

Nishiyama, T., Ladurner, R., Schmitz, J., Kreidl, E., Schleiffer, A., Bhaskara, V., … Peters, J. M. (2010). Sororin mediates sister chromatid cohesion by antagonizing Wapl. *Cell*, *143*(5), 737–749. https://doi.org/10.1016/j.cell.2010.10.031

Nishiyama, T., Sykora, M. M., Huis in 't Veld, P. J., Mechtler, K., & Peters, J. M. (2013). Aurora B and Cdk1 mediate Wapl activation and release of acetylated cohesin from chromosomes by phosphorylating Sororin. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(33), 13404–13409. https://doi.org/10.1073/pnas.1305020110

Novak, I., Wang, H., Revenkova, E., Jessberger, R., Scherthan, H., & Hoog, C. (2008). Cohesin Smc1beta determines meiotic chromatin axis loop organization. *Journal of Cell Biology*, *180*(1), 83–90. https://doi.org/10.1083/jcb.200706136

Ortiz, R., Kouznetsova, A., Echeverria-Martinez, O. M., Vazquez-Nin, G. H., & Hernandez-Hernandez, A. (2016). The width of the lateral element of the synaptonemal complex is determined by a multilayered organization of its components. *Experimental Cell Research*, *344*(1), 22–29. https://doi.org/10.1016/j.yexcr.2016.03.025

Page, S. L., & Hawley, R. S. (2004). The genetics and molecular biology of the synaptonemal complex. *Annual Review of Cell and Developmental Biology*, *20*, 525–558. https://doi.org/10.1146/annurev.cellbio.19.111301.155141

Panizza, S., Mendoza, M. A., Berlinger, M., Huang, L., Nicolas, A., Shirahige, K., & Klein, F. (2011). Spo11-accessory proteins link double-strand break sites to the chromosome axis in early meiotic recombination. *Cell*, *146*(3), 372–383. https://doi.org/10.1016/j.cell.2011.07.003

Parisi, S., McKay, M. J., Molnar, M., Thompson, M. A., van der Spek, P. J., van Drunen-Schoenmaker, E., … Kohli, J. (1999). Rec8p, a meiotic recombination and sister chromatid cohesion phosphoprotein of the Rad21p family, conserved from fission yeast to humans. *Molecular and Cellular Biology*, *19*, 3515–3528. https://doi.org/10.1128/MCB.19.5.3515

Parra, M. T., Viera, A., Gomez, R., Page, J., Benavente, R., Santos, J. L., … Suja, J. A. (2004). Involvement of the cohesin Rad21 and SCP3 in monopolar attachment of sister kinetochores during mouse meiosis I. *Journal of Cell Science*, *117*(Pt 7), 1221–1234. https://doi.org/10.1242/jcs.00947

Pelttari, J., Hoja, M. R., Yuan, L., Liu, J. G., Brundell, E., Moens, P., … Höög, C. (2001). A meiotic chromosomal core consisting of cohesin complex proteins recruits DNA recombination proteins and promotes synapsis in the absence of an axial element in mammalian meiotic cells. *Molecular and Cellular Biology*, *21*(16), 5667–5677. https://doi.org/10.1128/MCB.21.16.5667-5677.2001

Peoples, T. L., Dean, E., Gonzalez, O., Lambourne, L., & Burgess, S. M. (2002). Close, stable homolog juxtaposition during meiosis in budding yeast is dependent on meiotic recombination, occurs independently of synapsis, and is distinct from DSB-independent pairing contacts. *Genes and Development*, *16*(13), 1682–1695. https://doi.org/10.1101/gad.983802

Peoples-Holst, T. L., & Burgess, S. M. (2005). Multiple branches of the meiotic recombination pathway contribute independently to homolog pairing and stable juxtaposition during meiosis in budding yeast. *Genes and Development*, *19*(7), 863–874. https://doi.org/10.1101/gad.1293605

Phadnis, N., Cipak, L., Polakova, S., Hyppa, R. W., Cipakova, I., Anrather, D., … Gregan, J. (2015). Casein kinase 1 and phosphorylation of cohesin subunit Rec11 (SA3) promote meiotic recombination through linear element formation. *PLoS Genetics*, *11*(5), e1005225. https://doi.org/10.1371/journal.pgen.1005225

Prieto, I., Suja, J. A., Pezzi, N., Kremer, L., Martinez, A. C., Rufas, J. S., & Barbero, J. L. (2001). Mammalian STAG3 is a cohesin specific to sister chromatid arms in meiosis I. *Nature Cell Biology*, *3*(8), 761–766. https://doi.org/10.1038/35087082

Prieto, I., Pezzi, N., Buesa, J. M., Kremer, L., Barthelemy, I., Carreiro, C., … Barbero, J. L. (2002). STAG2 and Rad21 mammalian mitotic cohesins are implicated in meiosis. *EMBO Reports*, *3*(6), 543–550. https://doi.org/10.1093/embo-reports/kvf108

Prieto, I., Tease, C., Pezzi, N., Buesa, J. M., Ortega, S., Kremer, L., … Barbero, J. L. (2004). Cohesin component dynamics during meiotic prophase I in mammalian oocytes. *Chromosome Research*, *12*(3), 197–213. https://doi.org/10.1023/B:CHRO.0000021945.83198.0e

Rabitsch, K. P., Gregan, J., Schleiffer, A., Javerzat, J. P., Eisenhaber, F., & Nasmyth, K. (2004). Two fission yeast homologs of *Drosophila* Mei-S332 are required for chromosome segregation during meiosis I and II. *Current Biology*, *14*(4), 287–301. https://doi.org/10.1016/j.cub.2004.01.051

Revenkova, E., Eijpe, M., Heyting, C., Gross, B., & Jessberger, R. (2001). Novel meiosis-specific isoform of mammalian SMC1. *Molecular and Cellular Biology*, *21*(20), 6984–6998. https://doi.org/10.1128/MCB.21.20.6984-6998.2001

Revenkova, E., Eijpe, M., Heyting, C., Hodges, C. A., Hunt, P. A., Liebe, B., … Jessberger, R. (2004). Cohesin SMC1 beta is required for meiotic chromosome dynamics, sister chromatid cohesion and DNA recombination. *Nature Cell Biology*, *6*(6), 555–562. https://doi.org/10.1038/ncb1135

Revenkova, E., Herrmann, K., Adelfalk, C., & Jessberger, R. (2010). Oocyte cohesin expression restricted to predictyate stages provides full fertility and prevents aneuploidy. *Current Biology*, *20*(17), 1529–1533. https://doi.org/10.1016/j.cub.2010.08.024

Riedel, C. G., Katis, V. L., Katou, Y., Mori, S., Itoh, T., Helmhart, W., … Nasmyth, K. (2006). Protein phosphatase 2A protects centromeric sister chromatid cohesion during meiosis I. *Nature*, *441*(7089), 53–61. https://doi.org/10.1038/nature04664

Rogers, E., Bishop, J. D., Waddle, J. A., Schumacher, J. M., & Lin, R. (2002). The aurora kinase AIR-2 functions in the release of chromosome cohesion in *Caenorhabditis elegans* meiosis. *Journal of Cell Biology*, *157*(2), 219–229. https://doi.org/10.1083/jcb.200110045

Sakakibara, Y., Hashimoto, S., Nakaoka, Y., Kouznetsova, A., Hoog, C., & Kitajima, T. S. (2015). Bivalent separation into univalents precedes age-related meiosis I errors in oocytes. *Nature Communications*, *6*, 7550. https://doi.org/10.1038/ncomms8550

Sakuno, T., Tada, K., & Watanabe, Y. (2009). Kinetochore geometry defined by cohesion within the centromere. *Nature*, *458*(7240), 852–858. https://doi.org/10.1038/nature07876

Sakuno, T., Tanaka, K., Hauf, S., & Watanabe, Y. (2011). Repositioning of aurora B promoted by chiasmata ensures sister chromatid mono-orientation in meiosis I. *Developmental Cell*, *21*(3), 534–545. https://doi.org/10.1016/j.devcel.2011.08.012

Sakuno, T., & Watanabe, Y. (2015). Phosphorylation of cohesin Rec11/SA3 by casein kinase 1 promotes homologous recombination by assembling the meiotic chromosome axis. *Developmental Cell*, *32*(2), 220–230. https://doi.org/10.1016/j.devcel.2014.11.033

Salic, A., Waters, J. C., & Mitchison, T. J. (2004). Vertebrate shugoshin links sister centromere cohesion and kinetochore microtubule stability in mitosis. *Cell*, *118*(5), 567–578. https://doi.org/10.1016/j.cell.2004.08.016

Scherthan, H. (2001). A bouquet makes ends meet. *Nature Reviews Molecular Cell Biology*, *2*(8), 621–627. https://doi.org/10.1038/35085086

Schmitz, J., Watrin, E., Lenart, P., Mechtler, K., & Peters, J. M. (2007). Sororin is required for stable binding of cohesin to chromatin and for sister chromatid cohesion in interphase. *Current Biology*, *17*(7), 630–636. https://doi.org/10.1016/j.cub.2007.02.029

Severson, A. F., Ling, L., van Zuylen, V., & Meyer, B. J. (2009). The axial element protein HTP-3 promotes cohesin loading and meiotic axis assembly in *C. elegans* to implement the meiotic program of chromosome segregation. *Genes and Development*, *23*(15), 1763–1778. https://doi.org/10.1101/gad.1808809

Severson, A. F., & Meyer, B. J. (2014). Divergent kleisin subunits of cohesin specify mechanisms to tether and release meiotic chromosomes. *Elife*, *3*, e03467. https://doi.org/10.7554/eLife.03467

Shibuya, H., Ishiguro, K., & Watanabe, Y. (2014). The TRF1-binding protein TERB1 promotes chromosome movement and telomere rigidity in meiosis. *Nature Cell Biology*, *16*(2), 145–156. https://doi.org/10.1038/ncb2896

Shibuya, H., & Watanabe, Y. (2014). The meiosis-specific modification of mammalian telomeres. *Cell Cycle*, *13*(13), 2024–2028. https://doi.org/10.4161/cc.29350

Shibuya, H., Hernandez-Hernandez, A., Morimoto, A., Negishi, L., Hoog, C., & Watanabe, Y. (2015). MAJIN links telomeric DNA to the nuclear membrane by exchanging telomere cap. *Cell*, *163*(5), 1252–1266. https://doi.org/10.1016/j.cell.2015.10.030

Shin, Y. H., Choi, Y., Erdin, S. U., Yatsenko, S. A., Kloc, M., Yang, F., … Rajkovic, A. (2010). Hormad1 mutation disrupts synaptonemal complex formation, recombination, and chromosome segregation in mammalian meiosis. *PLoS Genetics*, *6*(11), e1001190. https://doi.org/10.1371/journal.pgen.1001190

Shintomi, K., & Hirano, T. (2009). Releasing cohesin from chromosome arms in early mitosis: Opposing actions of Wapl-Pds5 and Sgo1. *Genes and Development*, *23*(18), 2224–2236. https://doi.org/10.1101/gad.1844309

Shonn, M. A., McCarroll, R., & Murray, A. W. (2002). Spo13 protects meiotic cohesin at centromeres in meiosis I. *Genes and Development*, *16*(13), 1659–1671. https://doi.org/10.1101/gad.975802

Skibbens, R. V., Corson, L. B., Koshland, D., & Hieter, P. (1999). Ctf7p is essential for sister chromatid cohesion and links mitotic chromosome structure to the DNA replication machinery. *Genes and Development*, *13*(3), 307–319. https://doi.org/10.1101/gad.13.3.307

Storlazzi, A., Tesse, S., Gargano, S., James, F., Kleckner, N., & Zickler, D. (2003). Meiotic double-strand breaks at the interface of chromosome movement, chromosome remodeling, and reductional division. *Genes and Development*, *17*(21), 2675–2687. https://doi.org/10.1101/gad.275203

Strom, L., Karlsson, C., Lindroos, H. B., Wedahl, S., Katou, Y., Shirahige, K., & Sjögren, C. (2007). Postreplicative formation of cohesion is required for repair and induced by a single DNA break. *Science*, *317*(5835), 242–245. https://doi.org/10.1126/science.1140649

Suja, J. A., Antonio, C., Debec, A., & Rufas, J. S. (1999). Phosphorylated proteins are involved in sister-chromatid arm cohesion during meiosis I. *Journal of Cell Science*, *112*(Pt 17), 2957–2969.

Sumara, I., Vorlaufer, E., Stukenberg, P. T., Kelm, O., Redemann, N., Nigg, E. A., & Peters, J. M. (2002). The dissociation of cohesin from chromosomes in prophase is regulated by Polo-like kinase. *Molecular Cell*, *9*(3), 515–525. https://doi.org/10.1016/S1097-2765(02)00473-2

Tachibana-Konwalski, K., Godwin, J., van der Weyden, L., Champion, L., Kudo, N. R., Adams, D. J., & Nasmyth, K. (2010). Rec8-containing cohesin maintains bivalents without turnover during the growing phase of mouse oocytes. *Genes and Development*, *24*(22), 2505–2516. https://doi.org/10.1101/gad.605910

Tachibana-Konwalski, K., Godwin, J., Borsos, M., Rattani, A., Adams, D. J., & Nasmyth, K. (2013). Spindle assembly checkpoint of oocytes depends on a kinetochore structure determined by cohesin in meiosis I. *Current Biology*, *23*(24), 2534–2539. https://doi.org/10.1016/j.cub.2013.10.052

Takada, Y., Naruse, C., Costa, Y., Shirakawa, T., Tachibana, M., Sharif, J., … Koseki, H. (2011). HP1gamma links histone methylation marks to meiotic synapsis in mice. *Development*, *138*(19), 4207–4217. https://doi.org/10.1242/dev.064444

Takeo, S., Lake, C. M., Morais-de-Sa, E., Sunkel, C. E., & Hawley, R. S. (2011). Synaptonemal complex-dependent centromeric clustering and the initiation of synapsis in *Drosophila* oocytes. *Current Biology*, *21*(21), 1845–1851. https://doi.org/10.1016/j.cub.2011.09.044

Tanaka, K., Chang, H. L., Kagami, A., & Watanabe, Y. (2009). CENP-C functions as a scaffold for effectors with essential kinetochore functions in mitosis and meiosis. *Developmental Cell*, *17*(3), 334–343. https://doi.org/10.1016/j.devcel.2009.08.004

Tang, Z., Shu, H., Qi, W., Mahmood, N. A., Mumby, M. C., & Yu, H. (2006). PP2A is required for centromeric localization of Sgo1 and proper chromosome segregation. *Developmental Cell*, *10*(5), 575–585. https://doi.org/10.1016/j.devcel.2006.03.010

Tanneti, N. S., Landy, K., Joyce, E. F., & McKim, K. S. (2011). A pathway for synapsis initiation during zygotene in *Drosophila* oocytes. *Current Biology*, *21*(21), 1852–1857. https://doi.org/10.1016/j.cub.2011.10.005

Tanno, Y., Kitajima, T. S., Honda, T., Ando, Y., Ishiguro, K., & Watanabe, Y. (2010). Phosphorylation of mammalian Sgo2 by Aurora B recruits PP2A and MCAK to centromeres. *Genes and Development*, *24*(19), 2169–2179. https://doi.org/10.1101/gad.1945310

Toth, A., Rabitsch, K. P., Galova, M., Schleiffer, A., Buonomo, S. B., & Nasmyth, K. (2000). Functional genomics identifies monopolin: A kinetochore protein required for segregation of homologs during meiosis i. *Cell*, *103*(7), 1155–1168. https://doi.org/10.1016/S0092-8674(00)00217-8

Trelles-Sticken, E., Adelfalk, C., Loidl, J., & Scherthan, H. (2005). Meiotic telomere clustering requires actin for its formation and cohesin for its resolution. *Journal of Cell Biology*, *170*(2), 213–223. https://doi.org/10.1083/jcb.200501042

Tsutsumi, M., Fujiwara, R., Nishizawa, H., Ito, M., Kogo, H., Inagaki, H., … Kurahashi, H. (2014). Age-related decrease of meiotic cohesins in human oocytes. *PLoS One*, *9*(5), e96710. https://doi.org/10.1371/journal.pone.0096710

Uhlmann, F., Wernic, D., Poupart, M. A., Koonin, E. V., & Nasmyth, K. (2000). Cleavage of cohesin by the CD clan protease separin triggers anaphase in yeast. *Cell*, *103*(3), 375–386. https://doi.org/10.1016/S0092-8674(00)00130-6

Unal, E., Heidinger-Pauli, J. M., & Koshland, D. (2007). DNA double-strand breaks trigger genome-wide sister-chromatid cohesion through Eco1 (Ctf7). *Science*, *317*(5835), 245–248. https://doi.org/10.1126/science.1140637

Visnes, T., Giordano, F., Kuznetsova, A., Suja, J. A., Lander, A. D., Calof, A. L., & Ström, L. (2014). Localisation of the SMC loading complex Nipbl/Mau2 during mammalian meiotic prophase I. *Chromosoma*, *123*(3), 239–252. https://doi.org/10.1007/s00412-013-0444-7

Waizenegger, I. C., Hauf, S., Meinke, A., & Peters, J. M. (2000). Two distinct pathways remove mammalian cohesin from chromosome arms in prophase and from centromeres in anaphase. *Cell*, *103*(3), 399–410. https://doi.org/10.1016/S0092-8674(00)00132-X

Ward, A., Hopkins, J., McKay, M., Murray, S., & Jordan, P. W. (2016). Genetic interactions between the meiosis-specific cohesin components, STAG3, REC8, and RAD21L. *G3 (Bethesda)*, *6*(6), 1713–1724. https://doi.org/10.1534/g3.116.029462

Watanabe, Y., & Nurse, P. (1999). Cohesin Rec8 is required for reductional chromosome segregation at meiosis. *Nature*, *400*(6743), 461–464. https://doi.org/10.1038/22774

Watanabe, Y., Yokobayashi, S., Yamamoto, M., & Nurse, P. (2001). Premeiotic S phase is linked to reductional chromosome segregation and recombination. *Nature*, *409*(6818), 359–363. https://doi.org/10.1038/35053103

Watanabe, Y. (2012). Geometry and force behind kinetochore orientation: Lessons from meiosis. *Nature Reviews Molecular Cell Biology*, *13*(6), 370–382. https://doi.org/10.1038/nrm3349

Watrin, E., Schleiffer, A., Tanaka, K., Eisenhaber, F., Nasmyth, K., & Peters, J. M. (2006). Human Scc4 is required for cohesin binding to chromatin, sister-chromatid cohesion, and mitotic progression. *Current Biology*, *16*(9), 863–874. https://doi.org/10.1016/j.cub.2006.03.049

Weiner, B. M., & Kleckner, N. (1994). Chromosome pairing via multiple interstitial interactions before and during meiosis in yeast. *Cell*, *77*(7), 977–991. https://doi.org/10.1016/0092-8674(94)90438-3

Wendt, K. S., Yoshida, K., Itoh, T., Bando, M., Koch, B., Schirghuber, E., … Peters, J. M. (2008). Cohesin mediates transcriptional insulation by CCCTC-binding factor. *Nature*, *451*(7180), 796–801. https://doi.org/10.1038/nature06634

Wendt, K. S., & Peters, J. M. (2009). How cohesin and CTCF cooperate in regulating gene expression. *Chromosome Research*, *17*(2), 201–214. https://doi.org/10.1007/s10577-008-9017-7

Wendt, K. S. (2017). Resolving the genomic localization of the kollerin cohesin-loader complex. *Methods in Molecular Biology*, *1515*, 115–123. https://doi.org/10.1007/978-1-4939-6545-8

Winters, T., McNicoll, F., & Jessberger, R. (2014). Meiotic cohesin STAG3 is required for chromosome axis formation and sister chromatid cohesion. *EMBO Journal*, *33*(11), 1256–1270.

Wojtasz, L., Daniel, K., Roig, I., Bolcun-Filas, E., Xu, H., Boonsanay, V., … Toth, A. (2009). Mouse HORMAD1 and HORMAD2, two conserved meiotic chromosomal proteins, are depleted from synapsed chromosome axes with the help of TRIP13 AAA-ATPase. *PLoS Genetics*, *5*(10), e1000702.

Wolf, P. G., Cuba Ramos, A., Kenzel, J., Neumann, B., & Stemmann, O. (2018). Studying meiotic cohesin in somatic cells reveals that Rec8-containing cohesin requires Stag3 to function and is regulated by Wapl and sororin. *Journal of Cell Science*, *131*(11), jcs212100. https://doi.org/10.1242/jcs.212100

Wutz, G., Varnai, C., Nagasaka, K., Cisneros, D. A., Stocsits, R. R., Tang, W., … Peters, J. M. (2017). Topologically associating domains and chromatin loops depend on cohesin and are regulated by CTCF, WAPL, and PDS5 proteins. *EMBO Journal*, *36*(24), 3573–3599. https://doi.org/10.15252/embj.201798004

Xu, H., Beasley, M., Verschoor, S., Inselman, A., Handel, M. A., & McKay, M. J. (2004). A new role for the mitotic RAD21/SCC1 cohesin in meiotic chromosome cohesion and segregation in the mouse. *EMBO Reports*, *5*(4), 378–384. https://doi.org/10.1038/sj.embor.7400121

Xu, H., Beasley, M. D., Warren, W. D., van der Horst, G. T., & McKay, M. J. (2005). Absence of mouse REC8 cohesin promotes synapsis of sister chromatids in meiosis. *Developmental Cell*, *8*(6), 949–961. https://doi.org/10.1016/j.devcel.2005.03.018

Yan, R., Thomas, S. E., Tsai, J. H., Yamada, Y., & McKee, B. D. (2010). SOLO: A meiotic protein required for centromere cohesion, coorientation, and SMC1 localization in *Drosophila melanogaster*. *Journal of Cell Biology*, *188*(3), 335–349. https://doi.org/10.1083/jcb.200904040

Yan, R., & McKee, B. D. (2013). The cohesion protein SOLO associates with SMC1 and is required for synapsis, recombination, homolog bias and cohesion and pairing of centromeres in *Drosophila*

Meiosis. *PLoS Genetics*, *9*(7), e1003637. https://doi.org/10.1371/journal.pgen.1003637

Yang, F., De La Fuente, R., Leu, N. A., Baumann, C., McLaughlin, K. J., & Wang, P. J. (2006). Mouse SYCP2 is required for synaptonemal complex assembly and chromosomal synapsis during male meiosis. *Journal of Cell Biology*, *173*(4), 497–507. https://doi.org/10.1083/jcb.200603063

Yokobayashi, S., Yamamoto, M., & Watanabe, Y. (2003). Cohesins determine the attachment manner of kinetochores to spindle microtubules at meiosis I in fission yeast. *Molecular and Cellular Biology*, *23*(11), 3965–3973. https://doi.org/10.1128/MCB.23.11.3965-3973.2003

Yokobayashi, S., & Watanabe, Y. (2005). The kinetochore protein Moa1 enables cohesion-mediated monopolar attachment at meiosis I. *Cell*, *123*(5), 803–817. https://doi.org/10.1016/j.cell.2005.09.013

Yu, H.-G., & Dawe, R. K. (2000). Functional redundancy in the maize meiotic kinetochore. *Journal of Cell Biology*, *151*(1), 131–141. https://doi.org/10.1083/jcb.151.1.131

Yuan, L., Liu, J. G., Zhao, J., Brundell, E., Daneholt, B., & Hoog, C. (2000). The murine SCP3 gene is required for synaptonemal complex assembly, chromosome synapsis, and male fertility. *Molecular Cell*, *5*(1), 73–83. https://doi.org/10.1016/S1097-2765(00)80404-9

Yuan, L., Yang, X., Ellis, J. L., Fisher, N. M., & Makaroff, C. A. (2012). The *Arabidopsis* SYN3 cohesin protein is important for early meiotic events. *The Plant Journal*, *71*(1), 147–160. https://doi.org/10.1111/j.1365-313X.2012.04979.x

Zhang, J., Hakansson, H., Kuroda, M., & Yuan, L. (2008). Wapl localization on the synaptonemal complex, a meiosis-specific proteinaceous structure that binds homologous chromosomes, in the female mouse. *Reproduction in Domestic Animals*, *43*(1), 124–126.

Zhang, J., Shi, X., Li, Y., Kim, B. J., Jia, J., Huang, Z., … Qin, J. (2008). Acetylation of Smc3 by Eco1 is required for S phase sister chromatid cohesion in both human and yeast. *Molecular Cell*, *31*(1), 143–151. https://doi.org/10.1016/j.molcel.2008.06.006

Zhang, J., Tu, Z., Watanabe, Y., & Shibuya, H. (2017). Distinct TERB1 domains regulate different protein interactions in meiotic telomere movement. *Cell Reports*, *21*(7), 1715–1726. https://doi.org/10.1016/j.celrep.2017.10.061

Zickler, D., & Kleckner, N. (1999). Meiotic chromosomes: Integrating structure and function. *Annual Review of Genetics*, *33*, 603–754. https://doi.org/10.1146/annurev.genet.33.1.603

Zickler, D., & Kleckner, N. (2015). Recombination, pairing, and synapsis of homologs during meiosis. *Cold Spring Harbor Perspectives in Biology*, *7*(6), a016626. https://doi.org/10.1101/cshperspect.a016626

Zielinska, A. P., Holubcova, Z., Blayney, M., Elder, K., & Schuh, M. (2015). Sister kinetochore splitting and precocious disintegration of bivalents could explain the maternal age effect. *Elife*, *4*, e11389. https://doi.org/10.7554/eLife.11389

Zuin, J., Dixon, J. R., van der Reijden, M. I., Ye, Z., Kolovos, P., Brouwer, R. W., … Wendt, K. S. (2014). Cohesin and CTCF differentially affect chromatin architecture and gene expression in human cells. *Proceedings of the National Academy of Sciences of the United States of America*, *111*(3), 996–1001. https://doi.org/10.1073/pnas.1317788111

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