The cohesin complex in mammalian meiosis

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Funding information
Yamada Science Foundation; KAKENHI, Grant/Award Number: #16H01257, #16H01221, #17H03634 and #18K19304

Communicated by: Eisuke Nishida

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), synopsis (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, 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 synopsis, 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...
same daughter cell, a process named monopolar kinetochore orientation. In meiosis II, pairs of 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.

### 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.

#### 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 evolutionarily 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,
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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). Ecol 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 cohesion 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, & Stoccsits, 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, Cuaba 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 homologe synopsis, 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, & Kourovetsova, 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, 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, Oyster, 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).
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, 2016).

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.
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, Ghyseleinck, 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-phosphorylable will answer the question.

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

Homologous chromosomes undergo pairing, synopsis, 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 synopsis, 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 synopsis (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/zygote 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 zygote-like arrest, suggesting that some recombination process is initiated...
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 synopsis 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; Treles-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.

**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 synopsis. 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.
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<sup>TEV/TEV</sup> and Rad21/Scc1<sup>TEV/TEV</sup> knock-in mice, 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 M I-arrested oocytes from Rec8<sup>TEV/TEV</sup> and Rad21/Scc1<sup>TEV/TEV</sup> knocked-in females, all the bivalent chromosomes are converted into single chromatids in Rec8<sup>TEV/TEV</sup>, while they remain intact in Rad21/Scc1<sup>TEV/TEV</sup>. 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 KO, 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 KO, super-resolution microscopic analyses showed that the chromosome axis is regionally separated in hypomorphic Stag3 mutants and Smc1β KO’s, 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 Smc1β 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. Separate 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 (Kitajima, Sakuno, Ishiguro, Iemura, & Natsume, 2006; Riedel, Katis, Katou, Mori, & Itoh, 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 that contains B56 subunit (Kitajima, Sakuno, Ishiguro, Iemura, & Natsume, 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
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 (bipolar attachment). In meiosis I, sister kinetochores on 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). 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
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, 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.

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 diplo‐tene 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, Carroll, & 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 homologe synopsis 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 stromalain/SA subunits (Heidmann, Horn, Heidmann, Schleiffer, & Nasmuth, 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 stromalain/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 stromalain/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 stromalain/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). 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 homologous 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 & McKe, 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 synopsis. Instead, Drosophila oocytes exhibit centromere clustering as a prerequisite for homologue synopsis, 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 synopsis initiation, while synopsis is also initiated at the interstitial sites along the chromosomal arms at the later stage. Centromere clustering and synopsis 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 synopsis 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 kleinsins 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 mis-segregation 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 cohesin 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, Holubcová, 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 Smc1β 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 chiasma 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 meioiotic 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 de-synapsing 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 Rec8TEV/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 Rec8TEV/TEV females, all the bivalent chromosomes are converted into single chromatids, indicating that cohesion is lost completely after REC8TEV depletion. However, when TEV-resistant REC8 is exogenously expressed from a conditionally activated Rec8 transgene in Rec8TEV/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 REC8TEV. However, it is important to note, that when TEV-resistant REC8 is expressed in Rec8TEV/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 Smc1β 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.
ACKNOWLEDGMENT

This review is devoted to the Molecular Biology Society of Japan for the recommendation to Yamada Science Foundation.

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How to cite this article: Ishiguro K-i. The cohesin complex in mammalian meiosis. Genes Cells. 2019;24:6–30. https://doi.org/10.1111/gtc.12652