Journal of Microbiology (2019) Vol. 57, No. 4, pp. 221–231
DOI 10.1007/s12275-019-8541-9

eISSN 1976-3794
pISSN 1225-8873

MINIREVIEW

The nature of meiotic chromosome dynamics and recombination in budding yeast

Soogil Hong, Jeong Hwan Joo, Hyeseon Yun, and Keunpil Kim*

Department of Life Science, Chung-Ang University, Seoul 06974, Republic of Korea

(Received Sep 28, 2018 / Revised Oct 24, 2018 / Accepted Oct 26, 2018)

During meiosis, crossing over allows for the exchange of genes between homologous chromosomes, enabling their segregation and leading to genetic variation in the resulting gametes. Spo11, a topoisomerase-like protein expressed in eukaryotes, and diverse accessory factors induce programmed double-strand breaks (DSBs) to initiate meiotic recombination during the early phase of meiosis after DNA replication. DSBs are further repaired via meiosis-specific homologous recombination. Studies on budding yeast have provided insights into meiosis and genetic recombination and have improved our understanding of higher eukaryotic systems. Cohesin, a chromosome-associated multiprotein complex, mediates sister chromatid cohesion (SCC), and is conserved from yeast to humans. Diverse cohesin subunits in budding yeast have been identified in DNA metabolic pathways, such as DNA replication, chromosome segregation, recombination, DNA repair, and gene regulation. During cell cycle, SCC is established by multiple cohesin subunits, which physically bind sister chromatids together and modulate proteins that involve in the capturing and separation of sister chromatids. Cohesin components include at least four core subunits that establish and maintain SCC: two structural maintenance chromosome subunits (Smc1 and Smc3), an α-kleisin subunit (Mcd1/Scc1 during mitosis and Rec8 during meiosis), and Scc3/Irr1 (SA1 and SA2). In addition, the cohesin-associated factors Pds5 and Rad61 regulate structural modifications and cell cycle-specific dynamics of chromatin to ensure accurate chromosome segregation. In this review, we discuss SCC and the recombination pathway, as well as the relationship between the two processes in budding yeast, and we suggest a possible conserved mechanism for meiotic chromosome dynamics from yeast to humans.

***Keywords*:** meiosis, yeast, recombination, sister chromatid cohesion, cohesin

*For correspondence. E-mail: kpkim@cau.ac.kr; Tel.: +82-2-820-5792
Copyright ⓒ 2019, The Microbiological Society of Korea

Introduction

During meiosis, diploid cells undergo two cycles of nuclear division and create four haploid cells in sexually reproducing organisms. Research on meiosis in diverse model organisms, including *Mus musculus*, *Drosophila melanogaster*, *Caenorhabditis elegans*, *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, and *Sordaria macrospora*, has substantially improved our understanding of genetic recombination and chromosome morphogenesis. In particular, the budding yeast *S. cerevisiae*, as a model of eukaryotic cells, has been widely used to study the meiotic cell cycle and genetic recombination. More than 50% of all yeast gene mutants can be complemented by their corresponding human homologs (Sekigawa *et al*., 2010; Laurent *et al*., 2016).

Budding yeast is an ideal model organism for studies of genetic recombination and chromosome dynamics during meiosis for several reasons. First, when diploid yeast cells are deficient in nutrients such as carbon and nitrogen, most yeast cells in the population undergo meiosis synchronously. This efficient synchronicity allows for time-course analysis of meiotic processes using biochemical, molecular, and cytological assays. Second, mutations in target genes can be easily created and isolated, since precise genetic manipulations and highly efficient transformation are possible in yeast cells. Moreover, artificial and synthetic gene constructs integrated into authentic chromosomes provide valuable tools for studying genetic recombination, chromosome pairing, and chromosome morphogenesis during meiosis.

Meiotic recombination is a type of homologous recombination (HR), in which nucleotide sequences are exchanged between two identical DNA molecules to repair broken chromosomes, maintain genome integrity, and enhance genome diversity in eukaryotes (Choi *et al*., 2013; Chung, 2014). The programmed repair of double-strand breaks (DSBs) via meiotic recombination provides a fundamental molecular mechanism of genetic diversity. The steps in this process are as follows: (1) introduction of a DSB, (2) resection of the DSB to produce tailed DSB ends with 3′-single-stranded (ss) DNA overhangs, (3) invasion of an ssDNA end into homologous double-stranded (ds) DNA, (4) subsequent annealing of the other processed end and DNA synthesis, (5) second-break end capture to form a double Holliday junction (dHJ), and (6) branch migration and resolution of the dHJ. For initial joint molecule formation-invasion of the 3′-ssDNA tail into the homologous template DNA-a nucleoprotein complex comprising recombinases and the ssDNA of the DSB is

required.

In *S. cerevisiae*, homolog search and DNA strand exchange are mediated by several recombination-associated DNA-binding proteins, i.e. Rad51, Dmc1 (meiosis-specific protein), Rad52, Rad55, Rad57, PCSS complex (Psy3, Csm2, Shu1, and Shu2), Mei5-Sae3, and Hop2-Mnd1 (Lao *et al*., 2008; Cloud *et al*., 2012; Hong *et al*., 2013; Sasanuma *et al*., 2013; Brown *et al*., 2015). Rad51 protein, a yeast homolog of the *Escherichia coli* RecA protein, catalyzes DNA strand exchange in the presence of ATP (Sung, 1994; Sugiyama *et al*., 1997). Replication protein-A (RPA), an ssDNA-binding protein in eukaryotes, is a heterotrimeric complex composed of Rpa1, Rpa2, and Rpa3 (Rfa1, Rfa2, and Rfa3 in budding yeast) and participates in all aspects of eukaryotic DNA metabolism involving ssDNA intermediates. During the early stages of HR, the ssDNA overhangs exposed at the DSB ends are coated by RPA (Cejka *et al*., 2010; Niu *et al*., 2010). RPA protects the ssDNA from enzymatic degradation, serves as a checkpoint signaling intermediate, and recruits specific proteins to the HR machinery (Cejka *et al*., 2010; Niu *et al*., 2010). Most importantly, when RPA protein is allowed to coat the ssDNA tail formed by the resection of DSB ends, it inhibits the formation of ssDNA secondary structures. Through this pathway, RPA facilitates presynaptic complex formation by eliminating DNA secondary structures (Sugiyama *et al*., 1997). RPA binds the ssDNA and is then displaced by Rad51 to form a uniform Rad51 nucleoprotein complex; this pathway is referred to as the RPA-first pathway (Wold, 1997; New *et al*., 1998).

Sister chromatid cohesion (SCC) is a cellular process that is essential for ensuring chromosome segregation and maintaining proper chromosome structure (Marston, 2014; Makrantoni and Marston, 2018). Without SCC, the chromosomes spread apart within the nucleus, making it difficult for the cell to stabilize chromosome structures for DNA metabolic processes, including normal gene regulation, accurate separation, DNA replication, and DNA repair. Thus, functional abnormalities in cohesin can induce genomic instability and aneuploidy, which are present in most cancers and genetic disorders (Brooker and Berkowitz, 2014). This linkage between sister chromatids allows chromosomal DNA to be properly aligned to support DSB repair by recombination. During meiotic S phase, DNA replication generates sister chromatids that are held together by a cohesin complex, consisting of cohesins and regulatory factors involved in capturing sister chromatids. SCC is then maintained until anaphase in the cell cycle, during which sister chromatid separation occurs. However, mutation of cohesin subunits in *S. cerevisiae* induces premature separation of sister chromatids in S phase of the cell cycle. In addition to their cohesion functions, cohesins and regulatory proteins are required for meiotic axis formation, meiotic DSB formation, homolog pairing, and meiotic recombination (Klein *et al*., 1999; Jin *et al*., 2009; Katis *et al*., 2010; Lin *et al*., 2011; Hong *et al*., 2013; Challa *et al*., 2016).

In this review, we discuss what is known regarding the molecular mechanisms underlying meiosis, genetic recombination, and SCC, with a particular focus on *S. cerevisiae*. Our review highlights the utility of unicellular organisms, like the budding yeast, in elucidating complex cell division pathways.

Mitosis and meiosis

Most eukaryotic cells undergo mitosis, in which chromosomes are separated to produce two daughter cells. To fully understand the meiotic cell cycle, it is essential to understand how mitotic cell cycle components are utilized and how they are substituted during the meiotic cell cycle. Both the mitotic and meiotic cell cycles are divided into G_1, S, G_2, and M (mitotic or meiotic) phases (Fig. 1). Haploid and diploid yeast cells undergo DNA replication to duplicate chromosomes before mitosis or meiosis. In diploid yeast cells, two parental chromosomes are present, and haploid cells can be crossed with those of the opposite mating type (a type and α type) to create diploid yeast cells. After DNA replication, when all chromosomes are duplicated, SCC is established by cohesin complexes. Spindle fibers pull the chromosomes to the spindle body, and chromosomes are then segregated to the opposite poles of the daughter cells. Thus, mitotic cells produce two daughter cells that possess the same parental DNA through one round of division (Fig. 1).

Unlike mitosis, meiosis involves two rounds of cell division composed of reductional division (meiosis I) and equational division (meiosis II) to form four haploid gametes that are each unique, as they contain recombined genetic materials and half the full complement of chromosomes. Thus, meiosis

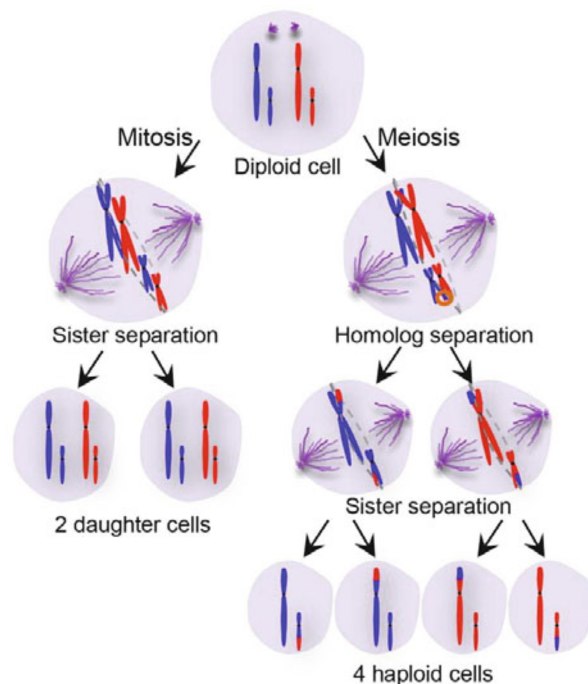

Fig. 1. The events of mitosis and meiosis. During S phase, chromosomes in a diploid cell are duplicated to initiate mitosis and meiosis. In G2 phase, cells, which include chromosomes consisting of a pair of identical sister chromatids after DNA replication, enter the division process. Mitosis is a cell division process that produces two identical daughter cells with the same genetic material. Meiosis is analogous to mitosis but produces four different haploid gametes after two rounds of cell division. During the prophase of meiosis I, genetic recombination occurs between homologous chromosomes. Then, separation of sister chromatids occurs to form haploid cells during meiosis II. Orange circle indicates the site of crossing over.

can be used to pass new genetic information on to the next generation (Fig. 1). Meiosis I is divided into prophase, metaphase, anaphase, and telophase. During prophase I, chromosomes are compacted into rod shapes, and homologs are paired. At this stage, crossover (CO)-which is an important feature of meiosis-occurs between homologous chromosomes. In metaphase, the chromosomes are aligned at the equatorial plane by spindle fibers. Aligned chromosomes, attached to spindle fibers, are pulled toward the poles during anaphase. The compacted chromosomes undergo decondensation and become visible in telophase. Meiosis II is the second round of meiotic division, during which sister chromatids are separated to opposite poles. In metaphase, both sister chromatids are aligned at the equatorial plane by spindle fibers. The sister chromatids, attached to spindle fibers, are then pulled to opposite poles during anaphase. Finally, four daughter cells, each containing half the number of diploid chromosomes, are generated. As a result of meiosis, cells produce four haploid gametes with genetic information that is distinct from that of either parent.

Meiotic chromosomes

During meiosis, homologous chromosomes exchange their genetic material through a recombination process that results in genetic diversity and occurs during prophase I (which is further divided into leptotene, zygotene, pachytene, diplotene, and diakinesis; Fig. 2A). By the end of premeiotic replication, chromosomes are duplicated, and cohesins hold sister chromatids together, thus forming a sister chromatid axis consisting of Red1, Hop1, cohesins, and condensin (Yu and Koshland, 2003; Sun *et al*., 2015; Markowitz *et al*., 2017). Prior to this, in the leptotene stage of prophase I, programmed DSB formation in preduplicated chromosomes occurs; during this stage, chromosomes can be observed using electron microscopy or high-resolution microscopy, and sister chromatids can be distinguished. In *S. cerevisiae*, meiosis-specific ZMM proteins (Zip1, Zip2, Zip3, Mer3, Msh4, Msh5, Spo22/Zip4, and Spo16) are expressed from early prophase I and are required for establishing synapsis between homologous chromosomes (Sym *et al*., 1993; Chua and Roeder, 1998; Agarwal and Roeder, 2000; Börner *et al*., 2004; Shinohara *et al*., 2008). Zygotene synapses are formed between homologous chromosomes, allowing for a number of contact points called synaptonemal complexes (SCs), which show a zipper-like structure due to the paired chromosomes (Fig. 2B). SCs promote synapses by maintaining proximity between the combined chromosomes (Fig. 2C). Once synapses are formed, CO can occur between pairs of homologous chromosomes. As a result, the exchange of genetic information that occurs through recombination increases significantly. During the diplotene phase, the two homologous chromosomes begin to separate as the SC dissolves between the two chromosome arms. The chiasma, which only appears in a small region of the chromosome after SC completion and enables crossing over, is visible at this stage.

Meiotic recombination

Meiotic recombination occurs during meiotic prophase I in budding yeast and is a dynamic process involving chromosomes and diverse proteins. This process is tightly regulated for the exchange of genetic materials and segregation of chromosomes into haploid spores (Fig. 3A). One important aspect in which meiotic and mitotic recombination differ is the repair template used in the process. Mitotic recombination occurs primarily upon spontaneous or induced damage, and sister chromatids act as preferred templates (this is known as "sister bias"; Moynahan and Jasin, 2010; Symington *et al*., 2014). In meiosis, however, recombination primarily occurs between homologs ("homolog bias") to provide genetic diversity to the progeny, i.e., sperm and eggs in animals, pollen and ovules in plants, and spores in yeasts. Thus, the mechanism conferring genetic variation to gametes is based on

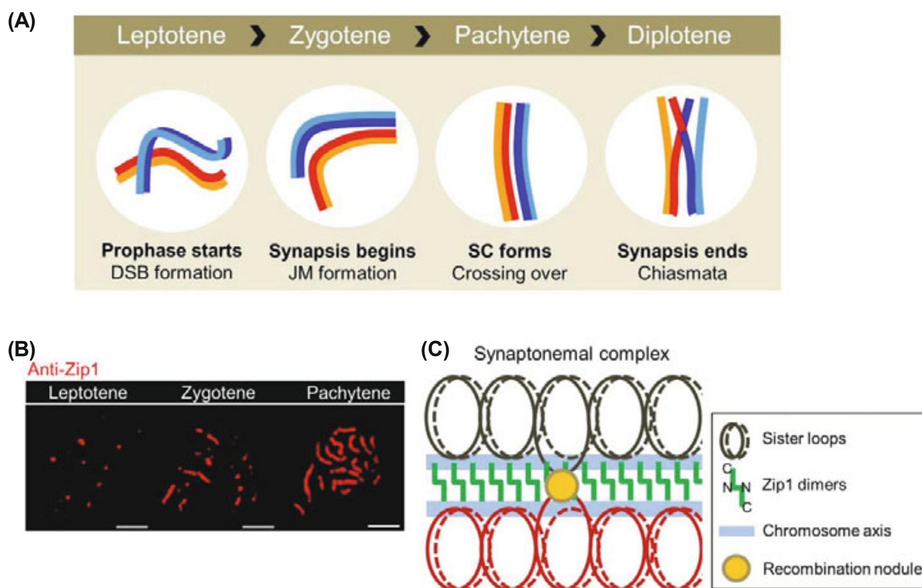

Fig. 2. Meiotic prophase I and synaptonemal complex formation. (A) Prophase I can be divided into the substages leptotene, zygotene, pachytene, and diplotene. During prophase I, homologs bind along their entire length, forming synapses via the synaptonemal complex (SC), and crossing over occurs between homologous chromosomes. DSB, double-strand break; JM, joint molecule. (B) Zip1 assembly in leptotene, zygotene, and pachytene. Zip1 proteins were immunostained using anti-Zip1 rabbit polyclonal antibodies on chromosome spreads. (C) SC formation. SC is a highly organized zipper-like structure that is assembled between homologous chromosomes by Zip1 proteins. Recombination nodules, which form multicomponent proteinaceous ellipsoids, can develop during meiotic prophase I. C, C-terminus of Zip1 protein; N, N-terminus of Zip1 protein.

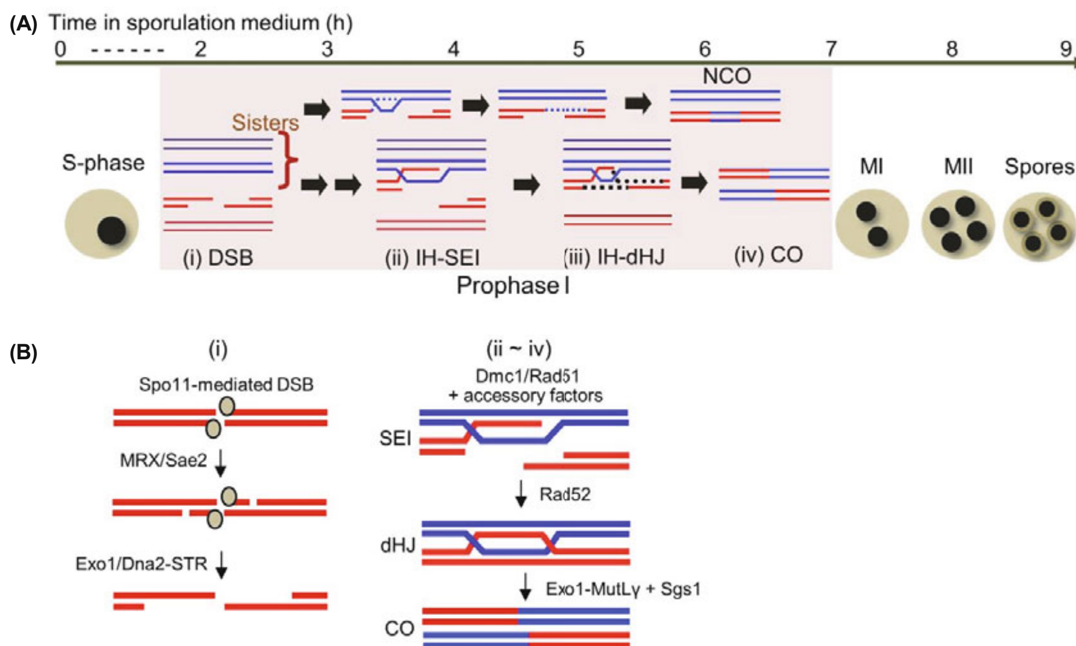

Fig. 3. Meiotic recombination and spore formation in budding yeast. (A and B) In the SK1 budding yeast strain, meiosis is coupled to the sporulation process. Meiosis is induced by transferring G_1-synchronized yeast cells to potassium acetate sporulation medium. (i) After premeiotic replication, DSBs are initiated by Spo11 and other accessory proteins. MRX (Mre11, Rad50, and Xrs2 in budding yeast; Mre11/Rad50/Nbs1 in mammals), Sae2, and Exo1 (or Dna2-Sgs1-Top3-Rmi1) proteins are involved in DSB-end resection to expose the 5′ ends. (ii, iii) Dmc1 and Rad51 then assemble on the single-stranded DNA and form joint molecules as single-end invasions give way to double-Holliday junctions. (iv) double-Holliday junction resolvases (Exo1-MutLγ-Sgs1) bind to the junctions and produce the majority of crossovers (COs). In contrast, the synthesis-dependent strand annealing pathway produces noncrossovers (NCOs). Yeast cells undergo meiosis I (MI) and II (MII), and diploid cells ultimately form four spores containing half the number of chromosomes.

crossing over, the process by which non-identical DNA between parental chromatids is exchanged (Marcon and Moens, 2005).

In the meiotic recombination pathway of *S. cerevisiae*, many proteins show complex interactions. To initiate meiotic recombination, programmed DSBs are generated by Spo11, a meiosis-specific topoisomerase-like protein (Keeney, 2001; Neale *et al*., 2005). Sites at which programmed DSBs are introduced are not randomly distributed but are instead located in intergenic promoter regions or GC-rich chromosomal domains (Longhese *et al*., 2009). The proportion of programmed DSBs is then communicated with its homologous partner (Hunter and Kleckner, 2001; Bishop and Zickler, 2004; Kim *et al*., 2010; Hong *et al*., 2013). Resection of DSBs occurs via the Exo1 protein, which digests DNA with 5′ to 3′ directionality (Zakharyevich *et al*., 2010). Exo1 belongs to the Rad2/*Xeroderma pigmentosum* complementation group G (XPG) nuclease family and plays a role in DSB end resection; it was initially discovered in fission yeast as a dsDNA exonuclease (Zakharyevich *et al*., 2010; Nanbu *et al*., 2015). Moreover, Exo1 has been identified as an important factor in DNA metabolic processes, including homologous recombination, telomere maintenance, mismatch repair, and cell cycle checkpoint signaling (Szankasi and Smith, 1995; Tran *et al*., 2004; Morin *et al*., 2008). Exo1 is also essential for promoting CO formation during meiotic recombination in *S. cerevisiae* (Tsubouchi and Ogawa, 2000; Zakharyevich *et al*., 2010). During the generation of CO products, Exo1 functions in conjunction with the Mlh1-Mlh3 heterodimer and Sgs1 (Zakharyevich *et al*., 2010; Rogacheva *et al*., 2014; Lukaszewicz *et al*., 2015).

Released DSB ends then seek a partner duplex and form stable D-loop structures called single-end invasions (SEIs; Fig. 3B). SEIs are extended by DNA polymerase and are engaged into dHJs. The search for homolog templates is required to build the dHJs and direct interactions between non-sister chromatids in the crossing over pathway. During *S. cerevisiae* meiosis, Dmc1 is a major component, along with Rad51, of the homolog search and strand invasion processes (Cloud *et al*., 2012; Hong *et al*., 2013; Lao *et al*., 2013). The partner choice for homologous chromosomes (homolog bias), which leads to interhomolog crossing over, is tightly regulated by a meiosis-specific mechanism involving recombinase proteins (Dmc1, Rad51, and accessory factors) and chromosome axis proteins, including Red1-Hop1-Mek1 (RMH) and cohesin (Kim *et al*., 2010; Kim and Mirkin, 2018). In meiotic recombination, RMH counteracts the cohesin-enforced sister bias, and the strand exchange activity of Rad51 is inhibited by Hed1, a meiosis-specific Rad51 regulatory protein, while Dmc1 and mediator proteins promote interhomolog joint molecules (Cloud *et al*., 2012; Hong *et al*., 2013; Lao *et al*., 2013). Interestingly, RMH is required for interhomolog recombination because Dmc1 can be activated in its presence; however, if cohesin is absent, RMH is dispensable for the homolog bias of recombination (Hong *et al*., 2013). ZMM proteins, which are major components located between homologous synapses, further promote CO recombination by stabilizing joint molecules (Agarwal and Roeder, 2000; Börner *et al*., 2004; Cheng *et al*., 2006; Serrentino *et al*., 2013). Most

Table 1. Cohesin complex in eukaryotes

		SMC subunit		Kleisin subunit	HEAT repeat subunit
Saccharomyces cerevisiae	Mitosis Meiosis	*SMC1*	*SMC3*	*MCD1/SCC1* *REC8*	*SCC3/IRR1*
Schizosaccharomyces pombe	Mitosis Meiosis	*psm1*$^{+}$	*psm3*$^{+}$	*rad21*$^{+}$ *rec8*$^{+}$	*psc3*$^{+}$ *rec11*$^{+}$
Drosophila melanogaster	Mitosis Meiosis	*SMC1*	*Cap*	*Rad21* *c(2)M*	*SA, SA-2*
Homo sapiens	Mitosis Meiosis	*SMC1A* *SMC1B*	*SMC3*	*RAD21* *REC8, RAD21L*	*STAG1, STAG2* *STAG3*

of these tight interactions between homologs are finally resolved into COs through strictly regulated pathways, while the remainder of the interactions mature into non-COs (NCOs), with no exchange of flanking regions (Fig. 3).

Cohesin complex: structures and interactions

As discussed above, the two sister chromatids must be accurately trapped during DNA replication for the chromosomes to duplicate and divide correctly (Fig. 4A). This is controlled by the cohesin complex. Previous studies have shown that the cohesin complex functions in capturing sister chromatids during mitosis and meiosis; in mitosis, the complex is composed of two structural maintenance chromosome proteins (Smc1 and Smc3), an α-kleisin subunit Scc1, and the non-SMC subunit sister chromatid cohesion 3 (Scc3) in *S. cerevisiae* (Table 1 and Fig. 4B; Nasmyth and Haering, 2009; Remeseiro and Losada, 2013). The SMC family proteins Smc1 and Smc3 are connected to each other by an ATP-binding cassette-like head domain and a hinge domain for SMC protein dimerization, resulting in the generation of a V-shaped SMC dimer. Scc1 and Scc3 bind to the ATPase domain of Smc1/3 and are stabilized, forming a ring structure (Kulemzina *et al*., 2012). In the ring structure, Scc1 stably binds to Smc1 and Smc3, while Scc3 binds to the C-terminus of Scc1 to establish SCC. Finally, when Scc1 is connected to both SMC proteins, the cohesin ring structure is closed. In addition, the cohesion-associated factors precocious dissociation of sisters (Pds5) and Rad61 form a heterodimer and regulate cohesin function (Table 2 and Fig. 4B; Kueng *et al*., 2006; Rowland *et al*., 2009; Sutani *et al*., 2009).

SCC enables faithful chromosome segregation in mitosis and meiosis. The meiotic cohesin complex and its roles differ from those of the mitotic cohesin complex. The meiosis-specific cohesin complex plays roles in not only SCC but also chromosome dynamics and meiotic recombination. Specifically, the Scc1 subunit is largely replaced by the α-kleisin subunit Rec8, which is phosphorylated by the Dbf4-dependent Cdc7 kinase and casein kinase 1δ/ε. The phosphorylation of Rec8 is involved in CO-designated recombination (Katis *et al*., 2010; Yoon *et al*., 2016). During meiosis, the cohesin complex modulates chromosome morphogenesis, including chromosome axis formation, condensation, and homolog pairing. Further, Pds5, a cohesin-associated factor, is required for the maintenance of SCC during mitosis but is involved in homolog pairing and interhomolog recombination during yeast meiosis (Jin *et al*., 2009). SCC-independent roles for cohesin have also been reported; cohesin complexes are involved in gene regulation, including promoter-enhanced interactions and transcription termination (Lara-Pezzi *et al*., 2004; Gullerova and Proudfoot, 2008; DeMare *et al*., 2013). However, gene regulation by the cohesin complex will not be discussed further in this review.

Smc1 and Smc3

The SMC family of cohesin complex proteins was originally identified through a genetic screen and was reported to have roles in proper chromosome segregation (Larionov *et al*., 1985; Strunnikov *et al*., 1993). Cohesins Smc1 and Smc3 form a heterodimer and function in SCC establishment (Haering *et al*., 2002; Gruber *et al*., 2003). These proteins are composed of several domains, i.e., the Walker A/B ATP-binding motif, coiled-coil region 1/2, and hinge domain. Smc1 and Smc3 form a coiled-coil shape and contain a hinge domain-head domain, with a hinge-to-head length of approximately 45 nm (Melby *et al*., 1998; Hirano and Hirano, 2002). The coiled-coil Smc1 and Smc3 proteins are connected through the hinge domain and form a V-shaped structure (Haering *et al*., 2004; Gligoris *et al*., 2014).

α-Kleisin subunits

Mitotic chromosome determinant 1 (Mcd1) is a major subunit of the cohesin complex that is required for SCC during mitosis (Guacci *et al*., 1993). Mcd1 (or Scc1) in budding yeast is essential for cell viability and chromosome structure (Guacci *et al*., 1993). Moreover, Mcd1/Scc1 is cleaved by separase (Esp1 in budding yeast) during anaphase initiation (Nasmyth *et al*., 2000). The α-kleisins Mcd1/Scc1, Smc1, and Smc3, containing 50-nm-long coiled-coil regions with a hinge domain at one end, form a ring-shaped structure (Haering *et al*., 2002,

Table 2. Cohesion accessory factors in eukaryotes

	Cohesin loading complex		Cohesion establishment/release		Cohesion maintenance	Securin	Separase
Saccharomyces cerevisiae	*SCC2*	*SCC4*	*ECO1*	*RAD61*	*PDS5*	*PDS1*	*ESP1*
Schizosaccharomyces pombe	*mis4*$^{+}$	*ssl3*$^{+}$	*eso1*$^{+}$	*wpl1*$^{+}$	*pds5*$^{+}$	*cut2*$^{+}$	*cut1*$^{+}$
Drosophila melanogaster	*Nipped-B*	*Mau2*	*eco*	*wapl*	*pds5*	*pim*	*Sse*
Homo sapiens	*NIPBL*	*SCC4*	*ESCO1/2*	*WAPAL*	*PDS5A, PDS5B*	*PTTG1*	*ESPL1*

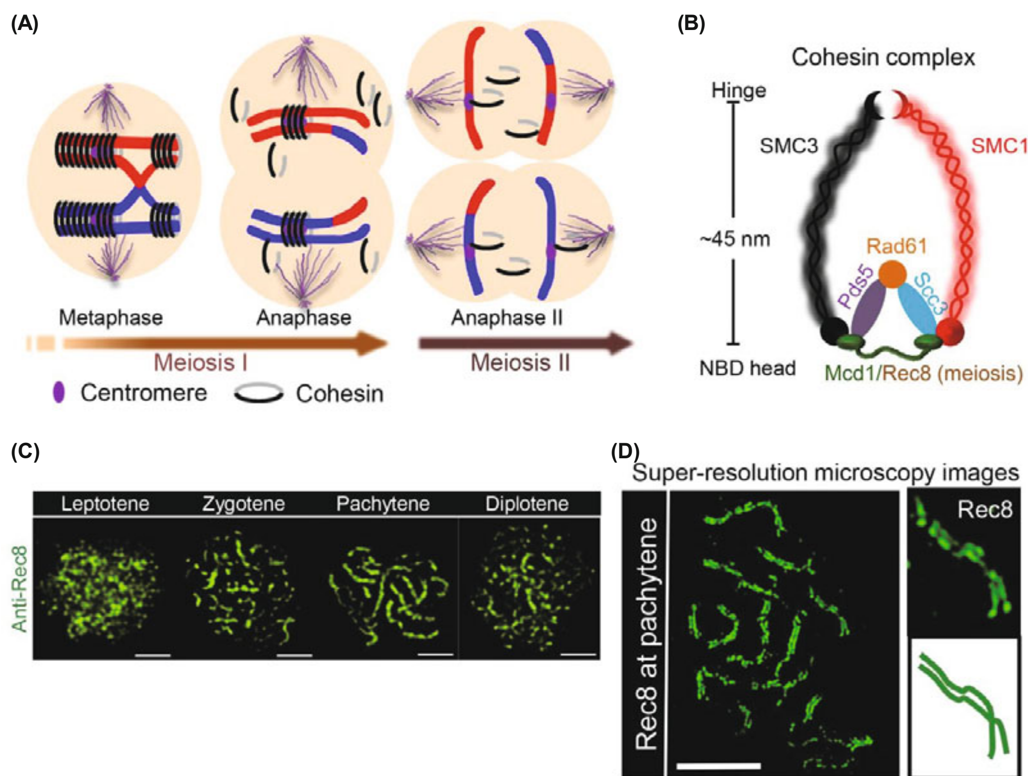

Fig. 4. Cohesin complex in budding yeast. (A) Cohesion and dissociation of the cohesin complex on chromosomes during meiosis I and II. (B) Cohesin complex of budding yeast (Kulemzina *et al*., 2012). (C) Chromosomal axis formation during prophase I in budding yeast. Chromosome spread was stained with anti-Rec8 antibodies, and images were acquired by fluorescence microscopy. Scale bars: 2.5 µm. (D) Super-resolution microscopy images of chromosomal axes at pachytene. Chromosome spread was stained with anti-Rec8 antibodies, and images were acquired by structured illumination microscopy. Scale bar: 2.5 µm.

2008). Mcd1/Scc1 connects Scc3 and the Smc1/3 heterodimer and directly interacts with Pds5 (Haering *et al*., 2002; Chan *et al*., 2013). During meiosis, Rec8, an α-kleisin subunit, mediates SCC and chromosome organization in a manner similar to that of Mcd1 in mitosis (Brar *et al*., 2006; Lee *et al*., 2006; Kim *et al*., 2010). In addition, Rec8 plays diverse meiotic roles through its involvement in chromosomal axis formation, synaptonemal complex assembly, and maintenance of homolog bias in CO-designated DSB repair during prophase (Fig. 4C and D; Molnar *et al*., 1995; Klein *et al*., 1999). Interestingly, Mcd1 expression during the meiotic cell cycle modestly rescues the progression of meiotic intermediates (Kim *et al.*, 2010; Hong *et al*., 2013).

Scc3

Scc3-also referred to as irregular cell behavior protein 1/Stag/SA1/SA2-is a subunit of the cohesin complex and requires cohesin to be loaded onto the chromosomes. Moreover, Scc3 is essential for cell viability (Kulemzina *et al*., 2012; Orgil *et al*., 2015; Kowalec *et al*., 2017; Li *et al*., 2018). Like other cohesin subunits, Scc3 interacts with Pds5 and Rad61/Wapl-cohesin-associated factors that regulate SCC functions. Interestingly, Scc3 plays a role in chromosome morphogenesis and REC8 gene expression during yeast meiosis (Lin *et al*., 2011).

Pds5

S. cerevisiae Pds5 is a homolog of Spo76/BIMD, which is conserved in most eukaryotes and is a prominent chromosomal axis component that mediates the establishment/maintenance of SCC and chromosome morphogenesis (Denison *et al*., 1993; van Heemst *et al*., 1999; Hartman *et al*., 2000; Zhang *et al*., 2005). After cohesion is established, maintenance is facilitated by Pds5/Spo76/BIMD (Denison *et al*., 1993; Hartman *et al*., 2000; Panizza *et al*., 2000; Sumara *et al*., 2000; Tanaka *et al*., 2001). Pds5, a regulatory subunit of the cohesin complex, has been well studied in the mitotic pathway. The mitotic cell cycle essentially requires Pds5, as it affects cohesion and condensation. X-ray crystal structure analysis demonstrated that Pds5 directly interacts with Mcd1 (Muir *et al*., 2016). Moreover, Pds5 interacts and colocalizes with cohesin on chromosomes in cohesin-associated regions (Hartman *et al*., 2000; Panizza *et al*., 2000). Despite this colocalization, Pds5 and cohesin clearly exhibit distinct roles, as they are not mutually dependent for chromosomal binding (Hartman *et al*., 2000; Tanaka *et al*., 2001; Losada and Hirano, 2005; Zhang *et al*., 2005). During meiosis, Pds5 limits chromosomal compaction; therefore, loss of Pds5 function results in hypercompaction of chromosomes. Additionally, Rec8 has been shown to be a key chromosome-loading factor for Pds5 (Zhang *et al*., 2005; Jin *et al*., 2009). Furthermore, Pds5 mediates homolog interactions that facilitate SC formation and meiotic recombination in a timely manner, demonstrating

a role for chromosome structural dynamics in DNA metabolism (Zhang *et al*., 2005; Storlazzi *et al*., 2008; Jin *et al*., 2009).

Rad61/Wapl

In yeast cells, Rad61 (Wapl in *D. melanogaster*) forms a complex with Pds5 and supports the association of cohesin with chromosomes (Sutani *et al*., 2009). The acetyltransferase Eco1/Ctf7 promotes dissociation of the Rad61-Pds5 complex from cohesin (Sutani *et al*., 2009). While absence of Rad61 is not essential for cohesion in budding yeast, it is related to hypercompaction of the rDNA region during the mitotic cell cycle (Lopez-Serra *et al*., 2013). The absence of Rad61 is also not essential for Rec8 loading on the chromosomal axis during meiosis. Instead, Rad61 limits hypercondensation of the chromosomal axis and is required for efficient DSB and SC formation, as well as telomere dynamics (Challa *et al*., 2016). The relationships between Rad61 and Rec8 or other cohesion-associated factors (e.g., Pds5 and Scc3) are not well understood in meiosis.

The relationship between cohesins and recombination during meiosis

The biochemical events comprising meiotic recombination occur in the context of developing and developed chromosome structural axes, from the time of DSB formation onward, with functional interplay between DNA events and structural events. During meiosis, recombination is specifically directed to occur between homologs rather than between sisters. In budding yeast, prominent components of the chromosomal axis, i.e., cohesins and meiosis-specific RHM, modulate chromosome morphogenesis, recombination, and homolog bias (Kim *et al*., 2010; Hong *et al*., 2013; Lao *et al*., 2013; Yoon *et al*., 2016). The dominant meiotic cohesin complex uniquely includes Rec8, a meiosis-specific α-kleisin subunit. Many studies on cohesins have focused on the roles of Rec8 in chromosome segregation and the pathway through which cohesins are removed from chromosomes. Furthermore, the cohesin-associated protein Spo76/Pds5 and cohesin modulator Rad61/Wapl are present all along the meiotic chromosome axes and are functionally implicated in local events at the recombinosome/structure/sister interface. Consistent with the intimate functional interplay between DNA biochemistry and structure, previous studies have documented important roles for Rec8 in the recombination process (Fig. 5). Physical analysis of recombination in *rec8*-deleted cells has revealed a modest deficit in the number of DSBs and a tendency for recombination to proceed through ensuing steps with significant delays (Klein *et al*., 1999; Kim *et al*., 2010). Additionally, *rec8*-deleted cells exhibit defects in CO-specific maintenance of bias at the SEI-to-dHJ transition (Fig. 5). It has been suggested that Rec8 is phosphorylated by Dbf4-dependent Cdc7 kinase and casein kinase 1δ/ε (Hrr25 in yeast); this phosphorylation event is specifically required for the maintenance of homolog bias during CO recombination and does not involve Rec8 cleavage by separase (Katis *et al*., 2010; Yoon *et al*., 2016). Thus, the role of Rec8 during prophase, independently of cohesin cleavage, contributes to CO-fate recombination, specifically in the maintenance of homolog bias during meiotic prophase.

Cohesin in human disease

The cohesin complex and its regulatory proteins are conserved among almost all eukaryotes, from yeast to humans, and participate in genomic integrity, gene expression, and development during mitosis and meiosis (Tables 1 and 2). Thus, research on the cohesin complex in a yeast model sys-

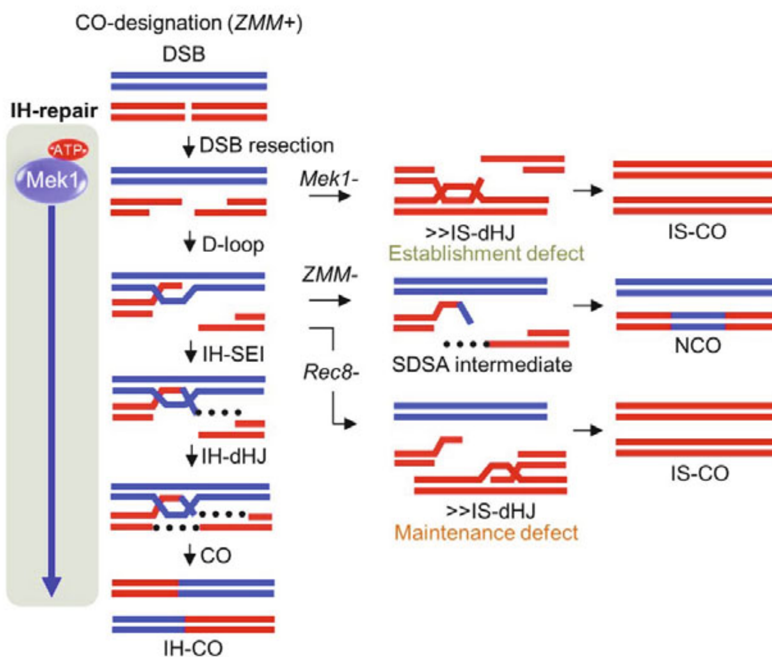

Fig. 5. Cohesin-mediated modulation of meiotic recombination. In the budding yeast *S. cerevisiae*, DSBs occur during leptotene; DSBs designated to become crossovers (COs) are converted to SEIs and dHJs. The nascent D-loop molecules are processed to the non-crossover (NCO) fate via the synthesis-dependent strand annealing (SDSA) pathway. Rec8 plays an important role during CO-designated recombination in the *ZMM+* pathway. *rec8*-deleted cells are impaired in terms of homolog bias maintenance. The absence of ZMM proteins leads to defects in the repair of CO-fated DSBs and abrogates SC formation. Mek1 kinase mediates recombination processes through interhomolog interactions.

tem can provide strategies for treating cohesin-related human diseases. Most importantly, cohesins play a role in holding the sister chromatids together during DNA replication in mitosis and meiosis. Cell cycle SCC is very important for proper segregation and for creating new daughter cells. Mutations in *RAD21* or *STAG1* result in a phenotype consistent with cohesinopathy, a cohesin-related developmental disorder in humans that results in abnormalities of cohesin complex regulation (Deardorff *et al*., 2012). Cohesinopathies include Cornelia de Lange syndrome (CdLS; Krantz *et al*., 2004; Tonkin *et al*., 2004) and Roberts syndrome (Xu *et al*., 2014). CdLS is generated by heterozygous mutations in *SMC1*, *SMC3*, or *NIPBL* (the vertebrate homolog of yeast Scc2), which are also involved in the transcriptional regulation of cohesins (Krantz *et al*., 2004; Tonkin *et al*., 2004; Musio *et al*., 2006). The estimated incidence of CdLS is approximately 1 in 10,000 live births, and the condition is often accompanied by mental and genetic abnormalities, as well as physical anomalies (Horsfield *et al*., 2012). In CdLS patients, there are no abnormalities in cohesin complex formation (Horsfield *et al*., 2012), although changes in gene expression levels have been noted (Liu *et al*., 2009; Remeseiro *et al*., 2013); thus, CdLS is closely related to cohesin gene expression. *RAD21* mutations have also been linked to developmental disorders (Deardorff *et al*., 2012). Previous studies have shown that mice lacking two copies of the *PDS5* gene, *PDS5A* and *PDS5B*, did not exhibit cohesin defects but showed various developmental defects, including growth retardation and congenital heart defects, suggesting that Pds5 may regulate gene expression or have other related functions. For example, Pds5 has been shown to interact with breast cancer type 2 susceptibility protein (Zhang *et al*., 2007, 2009; Misulovin *et al*., 2018). A homozygous mutation in the *ESCO2* gene (*ECO1* in yeast) causes Roberts syndrome (Vega *et al*., 2005). Both CdLS and Roberts syndrome are associated with chromosomal aneuploidy and tumorigenesis, which are promoted by chromosomal nonsegregation (Monnich *et al*., 2011; Remeseiro and Losada, *et al*., 2013).

Cohesin may be closely related to the maternal age effect, caused by chromosome aneuploidy and genomic instability (Mannini *et al*., 2010). Recent studies have suggested that loss of cohesin function during meiosis causes this aneuploidy-related maternal age effect in humans (Tsutsumi *et al*., 2014). Although the underlying cause of the maternal age effect has not been determined, oocyte aging has been shown to result in loss of SCC, leading to premature separation of chromosomes and ultimately to aneuploidy. Although the regulation and mechanisms of the cohesin complex have not yet been fully elucidated, research employing yeast as a model system has yielded rapid progress.

Conclusion

For many decades, SCC and recombination have been extensively studied at the cellular and biochemical levels in many model organisms. Owing to several recent studies on yeast meiosis, we now have a molecular model of changes in chromosomal structures and recombination processes that have been observed via microscopic and physical analyses. SCC ensures accurate chromosomal segregation and facilitates the regulation of genes and specific types of DNA repair. In addition, experiments have suggested that the regulatory roles of cohesin and separase are critical for chromosome dynamics during yeast meiosis. The meiosis-specific isoforms of several cohesin subunits are also expressed and interact with the meiotic cohesin complex. Cohesins appear to contribute to not only chromosome dynamics but also interactions between meiotic chromosome structure and the meiotic cell cycle. They also play roles in genetic recombination independent of DNA replication-related processes. However, the functions and molecular modifications of these meiosis-specific cohesins in modulating recombination and chromosome dynamics are not yet fully understood. For these delicate mechanistic studies, yeast remains an important model organism.

Acknowledgements

We apologize to several colleagues for their excellent work, which could not be cited here due to space constraints. This work was supported by grants from the Chung-Ang University Graduate Research Scholarship in 2017 and the Next-Generation BioGreen21 Program (SSAC;PJ01322801), Rural Development Administration, Republic of Korea.

References

Agarwal, S. and Roeder, G.S. 2000. Zip3 provides a link between recombination enzymes and synaptonemal complex proteins. *Cell* **102**, 245–255.

Bishop, D.K. and Zickler, D. 2004. Early decision: Meiotic crossover interference prior to stable strand exchange and synapsis. *Cell* **117**, 9–15.

Börner, G.V., Kleckner, N., and Hunter, N. 2004. Crossover/non-crossover differentiation, synaptonemal complex formation, and regulatory surveillance at the leptotene/zygotene transition of meiosis. *Cell* **117**, 29–45.

Brar, G.A., Kiburz, B.M., Zhang, Y., Kim, J.E., White, F., and Amon, A. 2006. Rec8 phosphorylation and recombination promote the step-wise loss of cohesins in meiosis. *Nature* **441**, 532–536.

Brooker, A.S. and Berkowitz, K.M. 2014. The roles of cohesins in mitosis, meiosis, and human health and disease. *Methods Mol. Biol.* **1170**, 229–266.

Brown, M.S., Grubb, J., Zhang, A., Rust, M.J., and Bishop, D.K. 2015. Small Rad51 and Dmc1 complexes often co-occupy both ends of a meiotic DNA double strand break. *PLoS Genet.* **11**, e1005653.

Cejka, P., Cannavo, E., Polaczek, P., Masuda-Sasa, T., Pokharel, S., Campbell, J.L., and Kowalczykowski, S.C. 2010. DNA end resection by Dna2-Sgs1-RPA and its stimulation by Top3-Rmi1 and Mre11-Rad50-Xrs2. *Nature* **467**, 112–116.

Challa, K., Lee, M.S., Shinohara, M., Kim, K.P., and Shinohara, A. 2016. Rad61/Wpl1 (Wapl), a cohesin regulator, controls chromosome compaction during meiosis. *Nucleic Acids Res.* **44**, 3190–3203.

Chan, K.L., Gligoris, T., Upcher, W., Kato, Y., Shirahige, K., Nasmyth, K., and Beckouët, F. 2013. Pds5 promotes and protects cohesin acetylation. *Proc. Natl. Acad. Sci. USA* **110**, 13020–13025.

Cheng, C.H., Lo, Y.H., Liang, S.S., Ti, S.C., Lin, F.M., Yeh, C.H., Huang, H.Y., and Wang, T.F. 2006. SUMO modifications control assembly of synaptonemal complex and polycomplex in

meiosis of *Saccharomyces cerevisiae*. *Genes Dev.* **20**, 2067–2081.

Choi, D.H., Lee, R., Kwon, S.H., and Bae, S.H. 2013. Hrq1 functions independently of Sgs1 to preserve genome integrity in *Saccharomyces cerevisiae*. *J. Microbiol.* **51**, 105–112.

Chua, P.R. and Roeder, G.S. 1998. Zip2, a meiosis-specific protein required for the initiation of chromosome synapsis. *Cell* **93**, 349–359.

Chung, W.H. 2014. To peep into Pif1 helicase: Multifaceted all the way from genome stability to repair-associated DNA synthesis. *J. Microbiol.* **52**, 89–98.

Cloud, V., Chan, Y.L., Grubb, J., Budke, B., and Bishop, D.K. 2012. Rad51 is an accessory factor for Dmc1-mediated joint molecule formation during meiosis. *Science* **337**, 1222–1225.

Deardorff, M.A., Wilde, J.J., Albrecht, M., Dickinson, E., Tennstedt, S., Braunholz, D., Mönnich, M., Yan, Y., Xu, W., Gil-Rodríguez, M.C., *et al.* 2012. RAD21 mutations cause a human cohesinopathy. *Am. J. Hum. Genet.* **90**, 1014–1027.

DeMare, L.E., Leng, J., Cotney, J., Reilly, S.K., Yin, J., Sarro, R., and Noonan, J.P. 2013. The genomic landscape of cohesin-associated chromatin interactions. *Genome Res.* **23**, 1224–1234.

Denison, S.H., Käfer, E., and May, G.S. 1993. Mutation in the *bimD* gene of *Aspergillus nidulans* confers a conditional mitotic block and sensitivity to DNA damaging agents. *Genetics* **134**, 1085–1096.

Gligoris, T.G., Scheinost, J.C., Bürmann, F., Petela, N., Chan, K.L., Uluocak, P., Beckouët, F., Gruber, S., Nasmyth, K., and Löwe, J. 2014. Closing the cohesin ring: structure and function of its Smc3-kleisin interface. *Science* **346**, 963–967.

Gruber, S., Haering, C.H., and Nasmyth, K. 2003. Chromosomal cohesin forms a ring. *Cell* **112**, 765–777.

Guacci, V., Yamamoto, A., Strunnikov, A., Kingsbury, J., Hogan, E., Meluh, P., and Koshland, D. 1993. Structure and function of chromosomes in mitosis of budding yeast, pp. 677–685. *In* Cold spring harbor symposia on quantitative biology Vol. 58. Cold Spring Harbor Laboratory Press.

Gullerova, M. and Proudfoot, N.J. 2008. Cohesin complex promotes transcriptional termination between convergent genes in *S. pombe*. *Cell* **132**, 983–995.

Haering, C.H., Farcas, A.M., Arumugam, P., Metson, J., and Nasmyth, K. 2008. The cohesin ring concatenates sister DNA molecules. *Nature* **454**, 297–301.

Haering, C.H., Löwe, J., Hochwagen, A., and Nasmyth, K. 2002. Molecular architecture of SMC proteins and the yeast cohesin complex. *Mol. Cell* **9**, 773–788.

Haering, C.H., Schoffnegger, D., Nishino, T., Helmhart, W., Nasmyth, K., and Löwe, J. 2004. Structure and stability of cohesin's Smc1-kleisin interaction. *Mol. Cell* **15**, 951–964.

Hartman, T., Stead, K., Koshland, D., and Guacci, V. 2000. Pds5p is an essential chromosomal protein required for both sister chromatid cohesion and condensation in *Saccharomyces cerevisiae*. *J. Cell Biol.* **151**, 613–626.

Hirano, M. and Hirano, T. 2002. Hinge-mediated dimerization of SMC protein is essential for its dynamic interaction with DNA. *EMBO J.* **21**, 5733–5744.

Hong, S., Sung, Y., Yu, M., Lee, M., Kleckner, N., and Kim, K.P. 2013. The logic and mechanism of homologous recombination partner choice. *Mol. Cell* **51**, 440–453.

Horsfield, J.A., Print, C.G., and Mönnich, M. 2012. Diverse developmental disorders from the one ring: distinct molecular pathways underlie the cohesinopathies. *Front. Genet.* **3**, 171.

Hunter, N. and Kleckner, N. 2001. The single-end invasion: an asymmetric intermediate at the double-strand break to double-Holliday junction transition of meiotic recombination. *Cell* **106**, 59–70.

Jin, H., Guacci, V., and Yu, H.G. 2009. Pds5 is required for homologue pairing and inhibits synapsis of sister chromatids during yeast meiosis. *J. Cell Biol.* **186**, 713–725.

Katis, V.L., Lipp, J.J., Imre, R., Bogdanova, A., Okaz, E., Habermann, B., Mechtler, K., Nasmyth, K., and Zachariae, W. 2010. Rec8 phosphorylation by casein kinase 1 and Cdc7-Dbf4 kinase regulates cohesin cleavage by separase during meiosis. *Dev. Cell* **18**, 397–409.

Keeney, S. 2001. Mechanism and control of meiotic recombination initiation. *Curr. Top. Dev. Biol.* **52**, 1–53.

Kim, K.P. and Mirkin, E.V. 2018. So similar yet so different: The two ends of a double strand break. *Mutat. Res.* **809**, 70–80.

Kim, K.P., Weiner, B.M., Zhang, L., Jordan, A., Dekker, J., and Kleckner, N. 2010. Sister cohesion and structural axis components mediate homolog bias of meiotic recombination. *Cell* **143**, 924–937.

Klein, F., Mahr, P., Galova, M., Buonomo, S.B., Michaelis, C., Nairz, K., and Nasmyth, K. 1999. A central role for cohesins in sister chromatid cohesion, formation of axial elements, and recombination during yeast meiosis. *Cell* **98**, 91–103.

Kowalec, P., Fronk, J., and Kurlandzka, A. 2017. The Irr1/Scc3 protein implicated in chromosome segregation in *Saccharomyces cerevisiae* has a dual nuclear-cytoplasmic localization. *Cell Div.* **12**, 1.

Krantz, I.D., McCallum, J., DeScipio, C., Kaur, M., Gillis, L.A., Yaeger, D., Jukofsky, L., Wasserman, N., Bottani, A., Morris, C.A., *et al.* 2004. Cornelia de Lange syndrome is caused by mutations in *NIPBL*, the human homolog of *Drosophila melanogaster* Nipped-B. *Nat. Genet.* **36**, 631–635.

Kueng, S., Hegemann, B., Peters, B.H., Lipp, J.J., Schleiffer, A., Mechtler, K., and Peters, J.M. 2006. Wapl controls the dynamic association of cohesin with chromatin. *Cell* **127**, 955–967.

Kulemzina, I., Schumacher, M.R., Verma, V., Reiter, J., Metzler, J., Failla, A.V., Lanz, C., Sreedharan, V.T., Rätsch, G., and Ivanov, D. 2012. Cohesin rings devoid of Scc3 and Pds5 maintain their stable association with the DNA. *PLoS Genet.* **8**, e1002856.

Lao, J.P., Cloud, V., Huan, C.C., Grubb, J., Thacker, D., Lee, C.Y., Dresser, M.E., Hunter, N., and Bishop, D.K. 2013. Meiotic crossover control by concerted action of Rad51-Dmc1 in homolog template bias and robust homeostatic regulation. *PLoS Genet.* **9**, e1003978.

Lao, O., Lu, T.T., Nothnagel, M., Junge, O., Freitag-Wolf, S., Caliebe, A., Balascakova, M., Bertranpetit, J., Bindoff, L.A., Comas, D., *et al.* 2008. Correlation between genetic and geographic structure in Europe. *Curr. Biol.* **18**, 1241–1248.

Lara-Pezzi, E., Pezzi, N., Prieto, I., Barthelemy, I., Carreiro, C., Martínez, A., Maldonado-Rodríguez, A., López-Cabrera, M., and Barbero, J.L. 2004. Evidence of a transcriptional co-activator function of cohesin STAG/SA/Scc3. *J. Biol. Chem.* **279**, 6553–6559.

Larionov, V., Karpova, T., Kouprina, N., and Jouravleva, G. 1985. A mutant of *Saccharomyces cerevisiae* with impaired maintenance of centromeric plasmids. *Curr. Genet.* **10**, 15–20.

Laurent, J.M., Young, J.H., Kachroo, A.H., and Marcotte, E.M. 2016. Efforts to make and apply humanized yeast. *Brief Funct. Genomics* **15**, 155–163.

Lee, J., Okada, K., Ogushi, S., Miyano, T., Miyake, M., and Yamashita, M. 2006. Loss of Rec8 from chromosome arm and centromere region is required for homologous chromosome separation and sister chromatid separation, respectively, in mammalian meiosis. *Cell Cycle* **5**, 1448–1455.

Li, Y., Muir, K.W., Bowler, M.W., Metz, J., Haering, C.H., and Panne, D. 2018. Structural basis for Scc3-dependent cohesin recruitment to chromatin. *Elife* **7**, e38356.

Lin, W., Jin, H., Liu, X., Hampton, K., and Yu, H.G. 2011. Scc2 regulates gene expression by recruiting cohesin to the chromosome as a transcriptional activator during yeast meiosis. *Mol. Biol. Cell* **22**, 1985–1996.

Liu, J., Feldman, R., Zhang, Z., Deardorff, M.A., Haverfield, E.V., Kaur, M., Li, J.R., Clark, D., Kline, A.D., Waggoner, D.J., *et al.* 2009. *SMC1A* expression and mechanism of pathogenicity in probands with X-linked Cornelia de Lange syndrome. *Hum. Mutat.* **30**, 1535–1542.

Longhese, M.P., Bonetti, D., Guerini, I., Manfrini, N., and Clerici, M. 2009. DNA double-strand breaks in meiosis: checking their formation, processing and repair. *DNA Repair (Amst.)* **8**, 1127–1138.

Lopez-Serra, L., Lengronne, A., Borges, V., Kelly, G., and Uhlmann, F. 2013. Budding yeast Wapl controls sister chromatid cohesion maintenance and chromosome condensation. *Curr. Biol.* **23**, 64–69.

Losada, A. and Hirano, T. 2005. Dynamic molecular linkers of the genome: the first decade of SMC proteins. *Genes Dev.* **19**, 1269–1287.

Lukaszewicz, A., Shodhan, A., and Loidl, J. 2015. Exo1 and Mre11 execute meiotic DSB end resection in the protist *Tetrahymena*. *DNA Repair* **35**, 137–143.

Makrantoni, V. and Marston, A.L. 2018. Cohesin and chromosome segregation. *Curr. Biol.* **28**, R688–R693.

Mannini, L., Liu, J., Krantz, I.D., and Musio, A. 2010. Spectrum and consequences of SMC1A mutations: the unexpected involvement of a core component of cohesin in human disease. *Hum. Mutat.* **31**, 5–10.

Marcon, E. and Moens, P.B. 2005. The evolution of meiosis: recruitment and modification of somatic DNA-repair proteins. *Bioessays* **27**, 795–808.

Markowitz, T.E., Suarez, D., Blitzblau, H.G., Patel, N.J., Markhard, A.L., MacQueen, A.J., and Hochwagen, A. 2017. Reduced dosage of the chromosome axis factor Red1 selectively disrupts the meiotic recombination checkpoint in *Saccharomyces cerevisiae. PLoS Genet.* **13**, e1006928.

Marston, A.L. 2014. Chromosome segregation in budding yeast: sister chromatid cohesion and related mechanisms. *Genetics* **196**, 31–63.

Melby, T.E., Ciampaglio, C.N., Briscoe, G., and Erickson, H.P. 1998. The symmetrical structure of structural maintenance of chromosomes (SMC) and MukB proteins: long, antiparallel coiled coils, folded at a flexible hinge. *J. Cell Biol.* **142**, 1595–1604.

Misulovin, Z., Pherson, M., Gause, M., and Dorsett, D. 2018. Brca2, Pds5 and Wapl differentially control cohesin chromosome association and function. *PLoS Genet.* **14**, e1007225.

Molnar, M., Bahler, J., Sipiczki, M., and Kohli, J. 1995. The *rec8* gene of *Schizosaccharomyces pombe* is involved in linear element formation, chromosome pairing and sister-chromatid cohesion during meiosis. *Genetics* **141**, 61–73.

Monnich, M., Kuriger, Z., Print, C.G., and Horsfield, J.A. 2011. A zebrafish model of Roberts syndrome reveals that Esco2 depletion interferes with development by disrupting the cell cycle. *PLoS One* **6**, e20051.

Morin, I., Ngo, H.P., Greenall, A., Zubko, M.K., Morrice, N., and Lydall, D. 2008. Checkpoint-dependent phosphorylation of Exo1 modulates the DNA damage response. *EMBO J.* **27**, 2400–2410.

Moynahan, M.E. and Jasin, M. 2010. Mitotic homologous recombination maintains genomic stability and suppresses tumorigenesis. *Nat. Rev. Mol. Cell Biol.* **11**, 196–207.

Muir, K.W., Kschonsak, M., Li, Y., Metz, J., Haering, C.H., and Panne, D. 2016. Structure of the Pds5-Scc1 complex and implications for cohesin function. *Cell Rep.* **14**, 2116–2126.

Musio, A., Selicorni, A., Focarelli, M.L., Gervasini, C., Milani, D., Russo, S., Vezzoni, P., and Larizza, L. 2006. X-linked Cornelia de Lange syndrome owing to *SMC1L1* mutations. *Nat. Genet.* **38**, 528–530.

Nanbu, T., Nguyễn, L.C., Habib, A.G., Hirata, N., Ukimori, S., Tanaka, D., Masuda, K., Takahashi, K., Yukawa, M., Tsuchiya, E., *et al.* 2015. Fission yeast Exo1 and Rqh1-Dna2 redundantly contribute to resection of uncapped telomeres. *PLoS One* **10**, e0140456.

Nasmyth, K. and Haering, C.H. 2009. Cohesin: its roles and mechanisms. *Annu. Rev. Genet.* **43**, 525–558.

Nasmyth, K., Peters, J.M., and Uhlmann, F. 2000. Splitting the chromosome: Cutting the ties that bind sister chromatids. *Science* **288**, 1379–1385.

Neale, M.J., Pan, J., and Keeney, S. 2005. Endonucleolytic processing of covalent protein-linked DNA double-strand breaks. *Nature* **436**, 1053–1057.

New, J.H., Sugiyama, T., Zaitseva, E., and Kowalczykowski, S.C. 1998. Rad52 protein stimulates DNA strand exchange by Rad51 and replication protein A. *Nature* **391**, 407–410.

Niu, H., Chung, W.H., Zhu, Z., Kwon, Y., Zhao, W., Chi, P., Prakash, R., Seong, C., Liu, D., Lu, L., *et al.* 2010. Mechanism of the ATP-dependent DNA end-resection machinery from *Saccharomyces cerevisiae*. *Nature* **467**, 108–111.

Orgil, O., Matityahu, A., Eng, T., Guacci, V., Koshland, D., and Onn, I. 2015. A conserved domain in the Scc3 subunit of cohesin mediates the interaction with both Mcd1 and the cohesin loader complex. *PLoS Genet.* **11**, e1005036.

Panizza, S., Tanaka, T., Hochwagen, A., Eisenhaber, F., and Nasmyth, K. 2000. Pds5 cooperates with cohesin in maintaining sister chromatid cohesion. *Curr. Biol.* **10**, 1557–1564.

Remeseiro, S., Cuadrado, A., Kawauchi, S., Calof, A.L., Lander, A.D., and Losada, A. 2013. Reduction of Nipbl impairs cohesin loading locally and affects transcription but not cohesion-dependent functions in a mouse model of Cornelia de Lange Syndrome. *Biochim. Biophys. Acta* **1831**, 2097–2102.

Remeseiro, S. and Losada, A. 2013. Cohesin, a chromatin engagement ring. *Curr. Opin. Cell Biol.* **25**, 63–71.

Rogacheva, M.V., Manhart, C.M., Chen, C., Guarne, A., Surtees, J., and Alani, E. 2014. Mlh1-Mlh3, a meiotic crossover and DNA mismatch repair factor, is a Msh2-Msh3-stimulated endonuclease. *J. Biol. Chem.* **289**, 5664–5673.

Rowland, B.D., Roig, M.B., Nishino, T., Kurze, A., Uluocak, P., Mishra, A., Beckouët, F., Underwood, P., Metson, J., Imre, R., *et al.* 2009. Building sister chromatid cohesion: Smc3 acetylation counteracts an antiestablishment activity. *Mol. Cell* **33**, 763–774.

Sasanuma, H., Tawaramoto, M.S., Lao, J.P., Hosaka, H., Sanda, E., Suzuki, M., Yamashita, E., Hunter, N., Shinohara, M., Nakagawa, A., *et al.* 2013. A new protein complex promoting the assembly of Rad51 filaments. *Nat. Commun.* **4**, 1676.

Sekigawa, M., Kunoh, T., Wada, S., Mukai, Y., Ohshima, K., Ohta, S., Goshima, N., Sasaki, R., and Mizukami, T. 2010. Comprehensive screening of human genes with inhibitory effects on yeast growth and validation of a yeast cell-based system for screening chemicals. *J. Biomol. Screen* **15**, 368–378.

Serrentino, M.E., Chaplais, E., Sommermeyer, V., and Borde, V. 2013. Differential association of the conserved SUMO ligase Zip3 with meiotic double-strand break sites reveals regional variations in the outcome of meiotic recombination. *PLoS Genet.* **9**, e1003416.

Shinohara, M., Oh, S.D., Hunter, N., and Shinohara, A. 2008. Crossover assurance and crossover interference are distinctly regulated by the ZMM proteins during yeast meiosis. *Nat. Genet.* **40**, 299–309.

Storlazzi, A., Tesse, S., Ruprich-Robert, G., Gargano, S., Pöggeler, S., Kleckner, N., and Zickler, D. 2008. Coupling meiotic chromosome axis integrity to recombination. *Genes Dev.* **22**, 796–809.

Strunnikov, A.V., Larionov, V.L., and Koshland, D. 1993. SMC1: An essential yeast gene encoding a putative head-rod-tail protein is required for nuclear division and defines a new ubiquitous family. *J. Cell Biol.* **123**, 1635–1648.

Sugiyama, T., Zaitseva, E.M., and Kowalczykowski, S.C. 1997. A single-stranded DNA-binding protein is needed for efficient presynaptic complex formation by the *Saccharomyces cerevisiae* Rad51 protein. *J. Biol. Chem.* **272**, 7940–7945.

Sumara, I., Vorlaufer, E., Gieffers, C., Peters, B.H., and Peters, J.M. 2000. Characterization of vertebrate cohesin complexes and their regulation in prophase. *J. Cell Biol.* **151**, 749–762.

Sun, X., Huang, L., Markowitz, T.E., Blitzblau, H.G., Chen, D., Klein, F., and Hochwagen, A. 2015. Transcription dynamically patterns the meiotic chromosome-axis interface. *Elife* **10**, 4.

Sung, P. 1994. Catalysis of ATP-dependent homologous DNA pairing and strand exchange by yeast RAD51 protein. *Science* **265**, 1241–1243.

Sutani, T., Kawaguchi, T., Kanno, R., Itoh, T., and Shirahige, K. 2009. Budding yeast Wpl1(Rad61)-Pds5 complex counteracts sister chromatid cohesion-establishing reaction. *Curr. Biol.* **19**, 492–427.

Sym, M., Engebrecht, J.A., and Roeder, G.S. 1993. ZIP1 is a synaptonemal complex protein required for meiotic chromosome synapsis. *Cell* **72**, 365–378.

Symington, L.S., Rothstein, R., and Lisby, M. 2014. Mechanisms and regulation of mitotic recombination in *Saccharomyces cerevisiae. Genetics* **198**, 795–835.

Szankasi, P. and Smith, G.R. 1995. A role for exonuclease I from *S. pombe* in mutation avoidance and mismatch correction. *Science* **267**, 1166–1169.

Tanaka, K., Hao, Z., Kai, M., and Okayama, H. 2001. Establishment and maintenance of sister chromatid cohesion in fission yeast by a unique mechanism. *EMBO J.* **20**, 5779–5790.

Tonkin, E.T., Wang, T.J., Lisgo, S., Bamshad, M.J., and Strachan, T. 2004. NIPBL, encoding a homolog of fungal Scc2-type sister chromatid cohesion proteins and fly Nipped-B, is mutated in Cornelia de Lange syndrome. *Nat. Genet.* **36**, 636–641.

Tran, P.T., Erdeniz, N., Symington, L.S., and Liskay, R.M. 2004. EXO1-A multi-tasking eukaryotic nuclease. *DNA Repair* **3**, 1549–1559.

Tsubouchi, H. and Ogawa, H. 2000. Exo1 roles for repair of DNA double-strand breaks and meiotic crossing over in *Saccharomyces cerevisiae*. *Mol. Biol. Cell* **11**, 2221–2233.

Tsutsumi, M., Fujiwara, R., Nishizawa, H., Ito, M., Kogo, H., Inagaki, H., Ohye, T., Kato, T., Fujii, T., and Kurahashi, H. 2014. Age-related decrease of meiotic cohesins in human oocytes. *PLoS One* **9**, e96710.

van Heemst, D., James, F., Pöggeler, S., Berteaux-Lecellier, V., and Zickler, D. 1999. Spo76p is a conserved chromosome morphogenesis protein that links the mitotic and meiotic programs. *Cell* **98**, 261–271.

Vega, H., Waisfisz, Q., Gordillo, M., Sakai, N., Yanagihara, I., Yamada, M., van Gosliga, D., Kayserili, H., Xu, C., Ozono, K., *et al.* 2005. Roberts syndrome is caused by mutations in ESCO2, a human homolog of yeast ECO1 that is essential for the establishment of sister chromatid cohesion. *Nat. Genet.* **37**, 468–470.

Wold, M.S. 1997. Replication protein A: a heterotrimeric, single-stranded DNA-binding protein required for eukaryotic DNA metabolism. *Annu. Rev. Biochem.* **66**, 61–92.

Xu, B., Lu, S., and Gerton, J.L. 2014. A deficit in acetylated cohesin leads to nucleolar dysfunction. *Rare Dis.* **2**, e27743.

Yoon, S.W., Lee, M.S., Xaver, M., Zhang, L., Hong, S.G., Kong, Y.J., Cho, H.R., Kleckner, N., and Kim, K.P. 2016. Meiotic prophase roles of Rec8 in crossover recombination and chromosome structure. *Nucleic Acids Res.* **44**, 9296–9314.

Yu, H.G. and Koshland, D.E. 2003. Meiotic condensin is required for proper chromosome compaction, SC assembly, and resolution of recombination-dependent chromosome linkages. *J. Cell Biol.* **163**, 937–947.

Zakharyevich, K., Ma, Y., Tang, S., Hwang, P.Y., Boiteux, S., and Hunter, N. 2010. Temporally and biochemically distinct activities of Exo1 during meiosis: double-strand break resection and resolution of double holliday junctions. *Mol. Cell* **40**, 1001–1015.

Zhang, B., Chang, J., Fu, M., Huang, J., Kashyap, R., Salavaggione, E., Jain, S., Shashikant, K., Deardorff, M.A., Uzielli, M.L., *et al.* 2009. Dosage effects of cohesin regulatory factor PDS5 on mammalian development: implications for cohesinopathies. *PLoS One* **4**, e5232.

Zhang, B., Jain, S., Song, H., Fu, M., Heuckeroth, R.O., Erlich, J.M., Jay, P.Y., and Milbrandt, J. 2007. Mice lacking sister chromatid cohesion protein PDS5B exhibit developmental abnormalities reminiscent of Cornelia de Lange syndrome. *Development* **134**, 3191–3201.

Zhang, Z., Ren, Q., Yang, H., Conrad, M.N., Guacci, V., Kateneva, A., and Dresser, M.E. 2005. Budding yeast PDS5 plays an important role in meiosis and is required for sister chromatid cohesion. *Mol. Microbiol.* **56**, 670–680.