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Review Article

The molecular machinery of meiotic recombination

Linda Chen and John R. Weir

Structural Biochemistry of Meiosis Group, Friedrich Miescher Laboratory, Max-Planck-Ring 9, 72076 Tübingen, Germany

Correspondence: John R. Weir (john.weir@tuebingen.mpg.de)

Meiotic recombination, a cornerstone of eukaryotic diversity and individual genetic identity, is essential for the creation of physical linkages between homologous chromosomes, facilitating their faithful segregation during meiosis I. This process requires that germ cells generate controlled DNA lesions within their own genome that are subsequently repaired in a specialised manner. Repair of these DNA breaks involves the modulation of existing homologous recombination repair pathways to generate crossovers between homologous chromosomes. Decades of genetic and cytological studies have identified a multitude of factors that are involved in meiotic recombination. Recent work has started to provide additional mechanistic insights into how these factors interact with one another, with DNA, and provide the molecular outcomes required for a successful meiosis. Here, we provide a review of the recent developments with a focus on protein structures and protein–protein interactions.

Introduction

Meiosis, a specialised form of cell division, is key to generating the diversity of life. This process, culminating in the generation of haploid gametes such as eggs, sperm, or spores, facilitates subsequent syngamy, the fusion of these gametes, during fertilisation to create a new euploid organism (Figure 1A). The reduction in genome size during meiosis is achieved through a unique sequence of events: a single round of DNA replication followed by two distinct rounds of chromosomal segregation. Meiosis I segregates homologous chromosomes, while meiosis II, akin to mitosis, segregates sister chromatids.

Physical linkages between chromosomes allow tension to be generated across the bivalent, facilitated by the forces generated by the spindle, and ultimately satisfy the spindle assembly checkpoint [1]. Therefore, such linkages are essential for the faithful segregation of chromosomes. Sister chromatids, segregated during mitosis and meiosis II, are linked by cohesive cohesin that is loaded during DNA replication. During meiosis I, homologous chromosomes do not have intrinsic linkages, and therefore inter-homologue connections must be established prior to the chromosome segregation event during meiosis I, in order that homologous chromosomes be properly sorted and segregated at anaphase I. This will ensure the formation of viable gametes, and subsequent healthy euploid offspring.

Most sexually reproducing species use recombination to link homologous chromosomes, initiated through the programmed formation of double-stranded DNA breaks (DSBs). This mechanism solves the mechanistic conundrum of how to organise homologous chromosomes in meiosis I and simultaneously introduces genetic diversity by reshuffling parental haplotypes. Interestingly, some organisms, like the model nematode *Caenorhabditis elegans*, have decoupled homologous pairing from recombination [2], while others, such as male fruit flies [3], eschew recombination entirely. However, this review will concentrate on meiotic recombination during 'canonical' meiosis I, a process common to fungi, plants, and vertebrates.

One defining feature of meiosis I is the formation of a distinct chromosomal architecture: a proteinaceous axis from which loops of chromatin emerge. DSBs, essential for recombination, are introduced in these DNA loops, with the break-forming machinery localised to the axis [4], initiating the process of pairing followed by synapsis. These breaks are repaired using the homologous chromosome rather than the sister chromatid, initiating the process of synapsis — defined by the progressive development of

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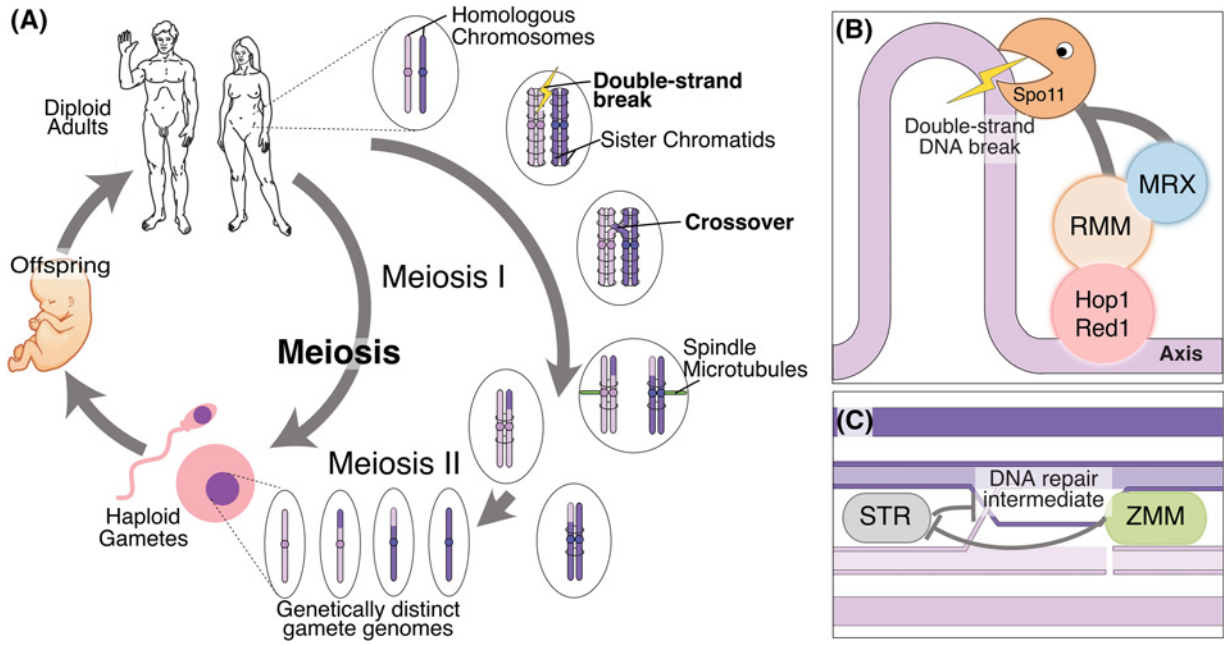

Figure 1. Overview of the key stages in meiosis.

(**A**) Cartoon overview of meiosis in the context of the generation and continuation of eukaryotic life. On the right-hand side, cartoon chromosomes are considered to be homologues. The stages of meiosis I are shown as DSB formation, crossover formation and the segregation of homologues. The outcome of meiosis II is shown at the bottom as four genetically distinct haploid gametes. (**B**) Inset of meiotic DSB formation. The axial proteins Hop1 and Red1 recruit the RMM complex proteins. The RMM proteins, together with the MRX, recruit and activate the Spo11 core complex that catalyses meiotic DSB formation in loops of chromatin emerging from the axis. (**C**) The ZMM group of proteins functions to promote meiotic crossover formation by antagonising the activity of anti-crossover factors such as the STR (Sgs1–Top3–Rmi1) complex.

zipper-like connections forming along the chromosome axis. Certain repair intermediates mature into crossovers (COs), the critical junctures where homologous chromosomes exchange arms [5]. Cohesive cohesin complexes between sister chromatids distal to COs sites then provide the necessary physical links between homologues.

This minireview aims to concisely delineate our current understanding of the molecular machinery with an emphasis on recent advances and, in particular, protein–protein interactions vital for meiotic recombination (summarised in Figure 2).

The meiotic axis

At the onset of meiotic prophase, chromosomes undergo a morphological change, as a proteinaceous axis forms along their length, from which chromatin loops emerge [13]. For instance, in *Saccharomyces cerevisiae* (budding yeast), loops are ~25 kb long [14], while in mice, they range from 1 to 2 Mb [15]. The precise structural organisation of the meiotic axis has not yet been fully elucidated, but it generally comprises at least Rec8-containing cohesin, condensin, a Red1-type axial filament protein (such as Red1 in budding yeast or SYCP2 in mice [16,17]), and one or more HORMA domain proteins such as Hop1 in yeast. The axis is believed to play a pivotal role in determining the proper placement and number of meiotic DSBs, modulating DNA repair, particularly in favouring inter-homologue bias, and in the formation of the synaptonemal complex (SC).

While the composition of meiotic cohesin varies between species, there seems to invariably exist at least one meiosis-specific kleisin variant — Rec8 [18]. It is thought that Rec8 cohesin contributes to the formation of chromatin loops, through loop extrusion activity [19], but that it also directly recruits Red1-type proteins. Red1 co-IPs with Rec8 [20], and co-localises with cohesin in ChIP-chip [4] and super-resolution microscopy [21], but formal proof of a direct interaction is lacking. Red1/SYCP2 contains an N-terminal globular domain (consisting of an ARM-like and PH domain [22]), of an unknown function (Figure 3A). The C-terminal region of Red1/SYCP2 contains a coiled-coil region with the ability to form both tetramers and higher-order filaments [17]. Red1 is presumed to recruit Hop1-like HORMA domain proteins.

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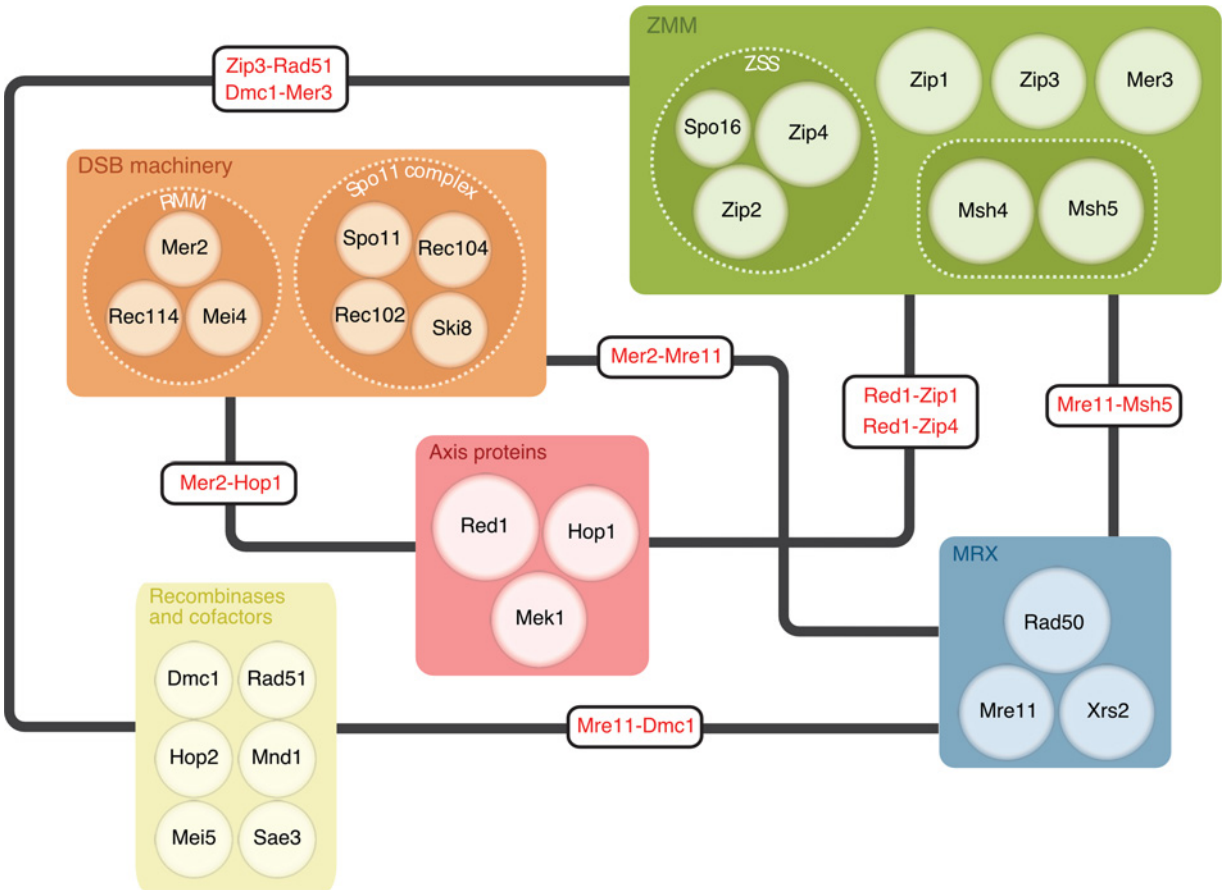

Figure 2. Summary of some key meiotic recombination factors and inter-complex physical interactions in early prophase I.
Protein complexes are defined according to the convention described in the main text. Citations for the inter-complex physical interactions are; Zip3–Rad51 [6], Mer2–Mre11 [7], Red1–Zip1 [8], Red1–Zip4 [9] Mer2–Hop1 [7], Mre11–Msh5 [10], Mer3–Dmc1 [11], Mre11–Dmc1 [12].

HORMA domains are dynamic domains that can adopt two topologically distinct conformations, open and closed. The transition to the energetically more stable closed state is catalysed by the interaction with a closure motif [27]. Unlike other HORMA domain proteins, the Hop1-like meiotic HORMA domains contain self-binding *cis* closure motifs in their C-terminal region (Figure 3A) [28]. Meiotic HORMAs can also interact with closure motif(s) in *trans* (for example, in Red1-like proteins, Figure 3A, right) but this presumably requires an active remodelling of the HORMA domain through the AAA + ATPase Pch2 (TRIP13 in mammals) [29]. Mammals have two meiotic HORMA domain proteins, HORMAD1 (Figure 3A, left) and HORMAD2 [30], and HORMAD2 has been shown to bind to the SYCP2 closure motif [17].

Hop1-like proteins in many species (though notably not in mammals) contain an additional chromatin binding domain (CBR) consisting of at least a winged-helix-turn helix domain, and in some cases combined with a PHD domain [31]. In yeast, this region can specifically bind to nucleosomes, which provides a second recruitment pathway for Hop1 and Red1 [31]. In budding yeast, one function of the CBR appears to be to enhance DSB formation on small chromosomes through localisation of Hop1 to nucleosome-rich islands [32]. Inversely, the removal of Hop1 is an important mechanism for the suppression of DSB formation in, for example, rDNA repeat regions [33,34]. Thus regulating levels of chromosomal Hop1 locally appears to be a fundamental mechanism for regulating DSB formation.

Meiotic DNA break formation and initial repair

DSBs, essential to initiate meiotic recombination, are catalysed by the topoisomerase-like enzyme Spo11. The complexity of DSB formation is underscored by its dependence on numerous additional factors; at least nine proteins (in addition to Spo11) in budding yeast are needed for DSB formation [35]. This regulatory framework

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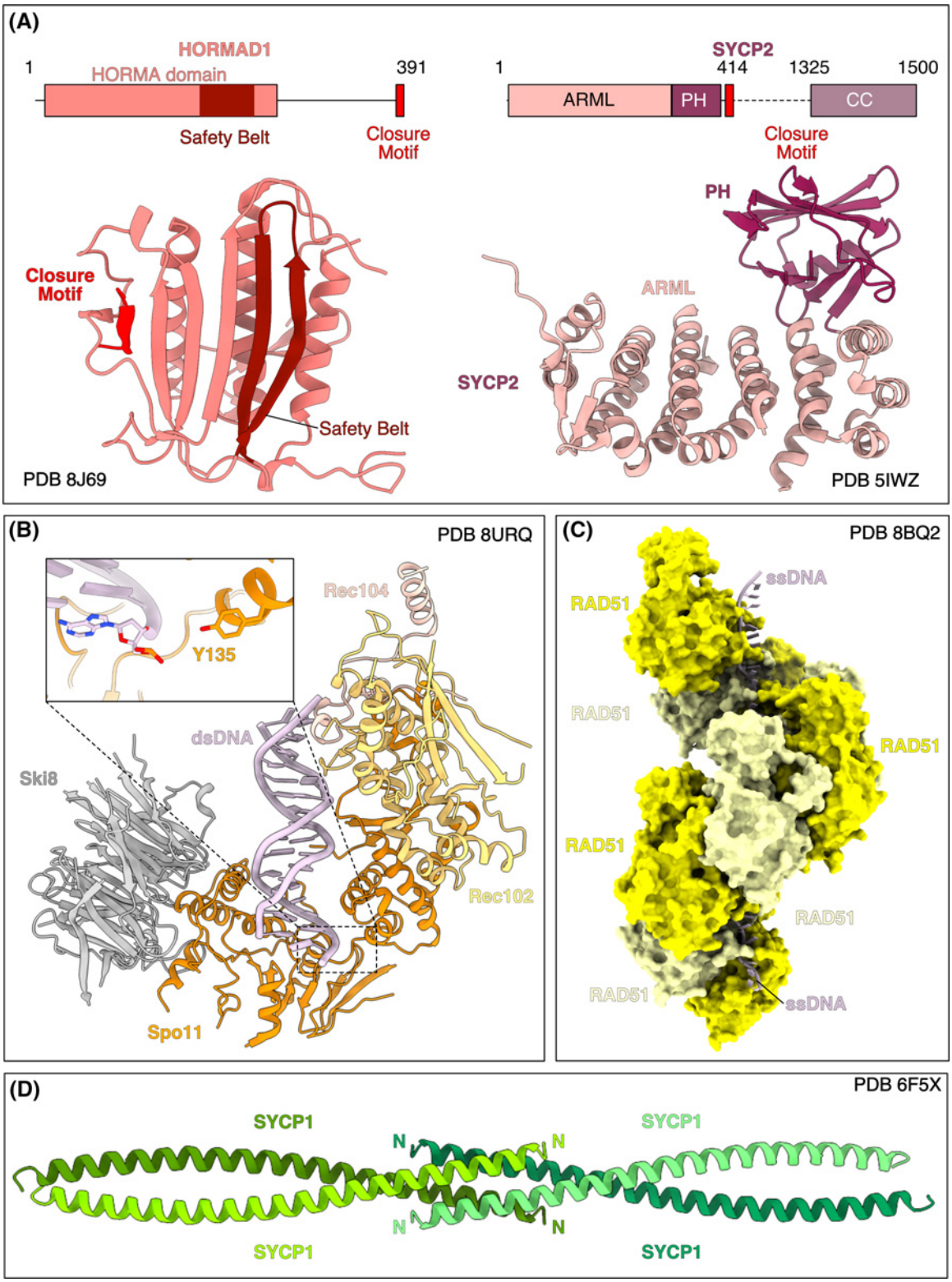

Figure 3. Examples of key experimental protein structures of the meiotic machinery. Part 1 of 2

(**A**) Structures of meiotic axis proteins. Left, X-ray structure of human HORMAD1 (Hop1 in budding yeast). The N-terminal HORMA domain of HORMAD1 physically entraps the C-terminal closure motif (red) due to the movement of the safety belt (maroon) [23]. Right, the crystal structure of mouse SYCP2 N-terminus consisting of the ARM-like (ARML) and PH domains

Figure 3. Examples of key experimental protein structures of the meiotic machinery. Part 2 of 2

[22], C-terminal to the PH domain is a closure motif [17]. (**B**) CryoEM structure of the *S. cerevisiae* Spo11 core complex (Spo11, orange; Rec102, pale orange; Rec104, pale yellow; Ski8, grey) in complex with dsDNA (pink). The catalytic tyrosine of Spo11 (Y135) is highlighted proximal to the sugar-phosphate backbone of the dsDNA [24]. (**C**) cryoEM structure of human RAD51 bound to single-stranded DNA (pink) [25]. (**D**) Crystal structure of the human SYCP1 (Zip1 in *S. cerevisiae*) αN-end head-to-head assembly region [26].

likely reflects a balance between preventing genome instability due to uncontrolled DSB formation and ensuring sufficient breaks for reliable homologue linkage. Spo11 is similar to the TopoVI family of type II DNA topoisomerases, which require an 'A' subunit (here, Spo11) and a 'B' subunit for full functionality [36]. DeMassy and co-workers discovered the Spo11 'B' subunit, TOPOVIBL, in mice [37], while at the same time the Grelon laboratory reported the discovery of the plant Spo11 'B' subunit — MTOPVIB — which was found to bind to both plant Spo11 proteins [38]. These discoveries allowed the realisation that a 'B' subunit in budding yeast is encoded in the Rec102 protein [37].

Recent work made use of recombinant yeast Spo11 'core complex' (Spo11, Rec102, Rec104, and Ski8), molecular modelling and mass spectrometry to confirm the role of Rec102 as a 'B' subunit that functions together with Rec104 [39]. Importantly, this work also showed that the Spo11 complex contains only one copy of the Spo11 subunit; two catalytically active Spo11 subunits would be required to break the backbone of double-stranded DNA. This is in line with the idea that a key role for the additional Spo11-associated factors is to accommodate the dimeriz (or multimerization) of Spo11 to activate it [40,41]. A recent breakthrough from the Keeney laboratory has taken the work with recombinant Spo11 complex a step further and revealed the cryoEM structure of the Spo11 core complex in complex with dsDNA (Figure 3B) [24]. Ski8 is canonically involved in regulating the RNA exosome 'moonlights' as part of the yeast Spo11 core complex, where it interacts with Spo11 through the same motif that is also found in Ski3 [42,43], but the role of Ski8 in the Spo11 complex is thought to be restricted to yeasts.

What types of DNA sequence are cleaved by Spo11 complexes? Several extrinsic factors guide the Spo11 machinery to DNA break 'hotspots'. This includes the concentration of axial proteins (see above), the chromatin state [44] and post-translational modifications on nucleosomes (reviewed in [45]). Recombinant Spo11 core complexes have a preference for binding to bent DNA [39]. Consistent with this, *in vivo* it was also observed that Spo11 has a preference for sequences that match a DNA bending site. Moreover, the periodicity of the break sites observed is consistent with Spo11 cutting on the same face of underwound DNA. Finally, DSB sites correlated with TopoII binding sites, strongly indicating a role for topological stress in DSB site preference [46]. Additional factors play a further role in modulating DSB site selection. The PHD domain protein Spp1, canonically part of the COMPASS methyltransferase complex [47], also targets the meiotic DSB forming machinery to promoter regions through an interaction with H3K4me3 nucleosomes and the Spo11 accessory factor Mer2 [48,49]. In vertebrates, the protein PRDM9 recognises certain DNA sequences via a C-terminal Zn-finger array and also targets the DSB machinery to these loci [50–52].

The association of the Spo11 core complex with the meiotic axis is a key aspect of its functionality (Figure 1C). This interaction is thought to be facilitated by Mer2, a protein capable of binding directly to Hop1 within the chromosome axis [7]. The mammalian ortholog of Mer2, IHO1, also binds directly to the axial protein HORMAD1 [53], and this is facilitated by DDK phosphorylation of the C-terminus of IHO1 [54], consistent with the previously described role of DKK phosphorylation of Mer2 [55–58]. Initially, Mer2 was identified as a component of a complex alongside Rec114 and Mei4, termed the RMM complex [59]. Rec114 and Mei4, including their mammalian counterparts REC114 and MEI4, form a stoichiometric 'RM' complex characterised by two Rec114 molecules bound to Mei4 [60]. In mice, the factor ANKRD31 was shown to be a direct interactor of REC114, necessary for normal DSB patterning and essential for recombination in the X/Y pseudoautosomal region (PAR) [61,62].

The interaction between Mer2 and the RM complex adds a layer of complexity to this system. Experiments have shown that in yeast, both Mer2 and the Rec114–Mei4 complex can independently form nucleoprotein condensates on DNA in the presence of a crowding agent [60]. Interestingly, mutations impairing Mer2's ability to bind DNA result in the loss of *in vivo* foci formation and a subsequent decrease in Spo11-induced DSBs [60]. Recent studies have demonstrated that in mice, IHO1 can bind directly to the REC114–MEI4

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complex, even in the absence of condensate formation [60,63]. This was also shown for yeast, but the assembly showed low affinity [60]. These discrepancies could come from the differing need for specific post-translational modifications in different species, or might indicate that the stoichiometric mouse RMM complex represents an intermediate stage in the formation of higher-order nucleoprotein condensates.

How is the Spo11 core complex recruited to the RMM complex? Rec102 and Rec104 are known to bind with Rec114, as established through yeast two-hybrid (Y2H) assays [43]. The importance of this interaction is underlined by the observation that mutations in Rec114's N-terminal PH domain disrupt its association with Rec102 and Rec104, as seen in Y2H assays. This disruption is associated with a decrease in Spo11-initiated DSB formation [60]. Further elucidating these interactions, De Massy, Robert, Kadlec, and colleagues have recently demonstrated a direct physical connection between the C-terminus of TOPOVIBL and the N-terminal PH domain of REC114 in mice. Disrupting this interaction results in a loss of DSB formation in female mice and a delayed formation in males [64].

Interestingly both ANKRD31 [61,62] and IHO1 [63] bind to the PH domain of REC114 in a mutually exclusive manner. This presents an apparent paradox for the function of the REC114 PH domain in mice. A more complex assembly might occur through a series of compatible or cooperative interactions. Considering that IHO1 and Mer2 both exist as tetramers and the REC114–MEI4 complex shows a 2:1 stoichiometry, a single IHO1 tetramer might ostensibly recruit four REC114–MEI4 complexes. This arrangement would leave the four PH domain binding sites available for ANKRD31 and TOPOVIBL.

MRX complex (Mre11, Rad50, Xrs2; Figure 3C) is required for the first steps in the DNA damage response and for telomere maintenance in mitotically dividing cells, but it is also required for the creation of meiotic DSBs in budding yeast [65,66] and in *C. elegans* [67], but not in plants [68] or fission yeast [69]. The physical connection between MRX and the Spo11 complex appears to also be mediated by Mer2. Mer2 was shown to interact with Xrs2 in a Y2H experiment [43], and Mer2 was recently shown to interact with Mre11 in a manner dependent on several conserved N-terminal residues in Mer2 [7]. Similarly, in *Arabidopsis*, Mer2 (PRD3) also interacts with Mre11 [70].

Regarding the regulation of the above-described interactions and their precise roles in Spo11 activation, our understanding, particularly of the latter, is still developing. It is anticipated that future structural studies, biochemical assays, and genetic analyses will provide deeper insights. We do have more information about the regulation of these interactions. For instance, Mer2 requires phosphorylation by both Cdk and DDK kinases at its N-terminal region to recruit Rec114 and Mei4, which is essential for DSB formation [4,56,71]. This phosphorylation might enhance Mer2's binding to the Rec114 PH domain. Additionally, the recent discovery that a Mer2 residue crucial for Mre11 interaction undergoes significant SUMOylation in meiosis [72] suggests that SUMOylation might be a key regulator of Mer2's interaction with the MRX complex.

DNA repair and inter-homologue bias

There are many excellent reviews on the detailed mechanisms of homologous recombination [73–76]. Briefly, once DSB resection has been initiated by Mre11 and Sae2 (CtIP), long-range resection occurs via Exo1 (EXO1), generating long tracts of ssDNA. This ssDNA is initially coated in RPA, before it is exchanged for one of two recombinases, Rad51, which is active in both the soma and the germline, or Dmc1, which is a germline-specific recombinase. ssDNA coated with recombinases are known as presynaptic filaments (Figure 3C), and these are competent to invade dsDNA (generating a displaced ssDNA) to interrogate these regions for sequence homology. In budding yeast, the meiosis-specific factors Mei5–Sae3 promote the exchange of RPA for Dmc [77]. Dmc1 seems to localise preferentially to the cut ends of resected DNA, and Rad51 to the opposite end [78]). Hop2–Mnd1 promotes the strand exchange activity of Dmc1/Rad51 [79,80].

In the mammalian germline, in addition to RPA, ssDNA is also coated with complexes of MEIOB/SPATA22, a heterodimer that forms an arrangement of DNA binding domains analogous to the heterotrimeric RPA complex [81–83]. Exchange of RPA or MEIOB/SPATA22 for RAD51/DMC1 requires BRCA2 [84]. A meiosis-specific binding partner of BRCA2, MEILB2 [85,86] is, together with BRME1 (also known as MEIOK21) [87–91], required for the proper loading of DMC1/RAD51. Intriguingly BRCA2 does not require MEILB2–BRME1 for loading RAD51 in the soma, suggesting that it might facilitate the BRCA2 loading of DMC1 or be required for the removal of MEIOB/SPATA22 in the germline. Indeed the latter might be more likely, since MEILB2–BRME1 binds directly to MEIOB/SPATA22 [86,89].

The replicated sister chromatid is an ideal template to repair DSBs, with repair from the sister in somatic cells being some 4-fold more frequent than from the homologue [92]. However, inter*sister* recombination

events are non-productive for the formation of inter-homologue COs and during meiosis repair from the homologue is ∼5-fold more frequent than from the sister [93,94]. This inversion of DNA repair frequency is known as inter-homologue bias.

The axial proteins play an important role in the establishment of inter-homologue bias. Removal of Red1 reverts the meiotic bias and gives rise to a mitotic-like DNA repair [95]. The S/T kinase Mek1 is recruited to the axis in response to DSB formation, by binding to the ATM/ATR phosphorylation site on Hop1 [96–99]. Mek1 phosphorylates both Rad54 and Hed1, which attenuate Rad51 activity [100,101]. How might this enable Mek1 to contribute to inter-homologue bias? One model proposes that Mek1 kinase activity is spatially restricted to the axis, and DNA repair is suppressed in a zone of influence around the initial break site. This zone of DNA repair suppression includes the proximal (and aligned) sister chromatid, but the homologous chromosome is presumably outside this Mek1 sphere of influence [102]. One issue with this model is that Mek1 also phosphorylates global targets, especially the transcription factor Ndt80, which prevents binding to target sequences and thus prevents progression through meiosis until DNA damage has been resolved [103,104].

ZMM proteins in crossover formation

The formation of germline COs is crucial in most organisms to establish the specific physical linkages between homologous chromosomes necessary for satisfying the spindle assembly checkpoint. However, COs are generally detrimental in somatic cells and are thus typically disfavoured [105]). Nascent DNA repair intermediates are often disassembled by the STR (Sgs1–Top3–Rm1) complex (Figure 1C). A group of meiosis-specific proteins, collectively known as ZMM, play a pivotal role in stabilising DNA repair intermediates and channelling them towards pathways more likely to result in COs (refer to Table 1 for details). These ZMM proteins were identified due to the shared impact of mutations on CO formation and synapsis [121,122]. We will briefly explore what is currently known about the different ZMM factors.

Zip2, Zip4, and Spo16 together form a complex known as ZZS [9]. Within this complex, Zip2 and Spo16 interact to form a heterodimer [116], structurally akin to the XPF–ERCC1 nuclease (Figure 3E), albeit lacking endonuclease activity [9,116]. *In vitro* studies reveal that the Zip2–Spo16 complex has an affinity for DNA, particularly structured or bent DNA forms. Zip4, characterised by its TPR repeat structure, binds to the N-terminal region of Zip2 [9]. TPR repeat proteins are often structural scaffolds that interact with a wide range of peptide motifs [123]. Consistent with this function, it was found that Zip4 not only interacts with the axial protein Red1 in Y2H assays but Red1 also shows strong enrichment in Zip4 IP-MS experiments [9]. Furthering our understanding, recent work has shown that Zip4 also directly binds to central element proteins of the SC, specifically through Ecm11 [124]. This study from the Borde laboratory is particularly significant as it for the first time elucidates the physical connection between ZMM proteins and the central element of the SC.

Mer3 is a helicase with many extra domains beyond its helicase core. It is most closely related to the spliceosomal RNA helicase Brr2 [11,125]. The helicase activity of Mer3 has been previously suggested to expand nascent D-loops, thus stabilising them. Indeed, *in vitro* Mer3 clearly has a strong preference for D-loop DNA [11,126]. The preference for D-loop DNA binding suggests that Mer3 may bind to early recombination intermediates. This is supported by *in vivo* data that shows Mer3 loci forming early in meiotic prophase [127] and with a higher number of foci than subsequent COs forming [128].

In vivo mutations that abrogate the helicase activity of Mer3 result in mild CO phenotypes, in contrast with the deletion of Mer3 [126,129]. In the spliceosome, the extra domains of Brr2 contribute to protein–protein interactions, and it seems likely to be similar for Mer3; the Ig-like domain of Mer3 contributes to the direct binding of Mlh1–Mlh2 (MutLβ) [126]. The Mer3–MutLβ complex functions to constrain D-loop extension through binding to, and inhibiting Pif1 helicase, thus reducing the size of gene conversion tracts [126,130]. We recently discovered that Mer3 can also bind to the meiotic recombinase Dmc1, and to the Top3–Rmi1 complex which is involved in the disassembly of DNA repair intermediates [11]. It is currently unclear whether Mer3 has further direct physical connections to the ZMM proteins, or if this is mediated through DNA substrates.

Msh4 and Msh5, collectively known as MutSγ, form a heterodimer that is structurally and functionally akin to the bacterial DNA mismatch repair factor MutS, which is characterised by its ring-like structure [118]. *In vitro,* studies demonstrate MutSγ's preference for binding to double Holliday junctions (dHJs), though it generally exhibits high affinity for a variety of DNA repair intermediates [119,120]. This binding is believed to physically entrap two duplexes of double-stranded DNA, thereby stabilising the recombination intermediate.

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Table 1. Core recombination proteins Part 1 of 2

Protein group	Protein name in			Structural description	Functional description
	S. cerevisiae	***M. musculus***	***A. thaliana***		
Axial proteins	Red1	SYCP2 (and SYCP3)	ASY3	N-terminal ARM domain followed by a PH domain [16,22]. Closure motif for interaction with Hop1 [106]. C-terminal coiled-coil region [17]	Speculated to interact with cohesin, may also interact with centromere proteins [22]. Forms a filament that likely is the basis of the axis and subsequent axial element of the SC [17]
	Hop1	HORMAD1 and HORMAD2	ASY2	N-terminal HORMA domain [107] with C-terminal closure motif [106]. Additional chromatin binding domain in some organisms	Involved in DSB formation. Involved in the activation of the meiotic checkpoint
	Mek1	?	?	N-terminal FHA domain, C-terminal S/T kinase domain	Meiotic checkpoint effector. Inhibits Rad51 via Rad54 and Hed1 phosphorylation. [101] Prevents progression through meiosis via Ndt80 phosphorylation [103]
RMM complex	Mer2	IHO1	PRD3	Coiled-coil forming a parallel homotetramer [108]	Binding to several factors including Spp1 [48,49], Rec114 and Mei4, Hop1, Mre11, and nucleosomes [7]
	Rec114	REC114	PHS1	N-terminal PH domain [61,109], C-terminal homodimerization region [60,108,110]	Phosphorylation of Rec114 down-regulates DSB formation [111]
	Mei4	MEI4	PRD2	N-terminus of Mei4 forms a globular structure, C-terminus consists of HEAT repeats [108]	N-term of Mei4 binds to two Rec114 DNA binding domains [63,108–110]
Spo11 complex	Spo11	SPO11	SPO11-1 and SPO11-2	Topoisomerase-like (Top6A) factor	Catalyses the formation of meiotic DSBs by cleavage of the phosphodiester backbone [112,113]
	Rec102 and Rec104	TOPOVIBL	MTOPIVB	Rec102 similar to the transducer domain of the B subunit, and Rec104 replaces the GHKL domain [24,39]	Presumably activates and regulates Spo11 activity. Likely forms further protein–protein interactions.
ZMM	Mer3	HFM1	MER3	Helicase core with additional domains, similar to Brr2 helicase [11]	Stabilises early DNA intermediates by D-loop extension [114]
	Zip11	SYCP1	ZYP1a and ZYP1b	Coiled-coil protein; tetramer that self-assembles at N- and C-terminal ends into a lattice [26]	Transverse filament component of SC. N-terminus associated with central element of SC, C-terminus with the meiotic axis [115]

Continued

Table 1. Core recombination proteins Part 2 of 2

Protein group	Protein name in			Structural description	Functional description
	S. cerevisiae	*M. musculus*	*A. thaliana*		
	Zip2	SHOC1/ZIP2	SHOC1	C-terminal is structurally similar to XPF [9,116]	Binding to structured DNAs
	Zip3	HEI10 and RNF212/ RNF212B	HEI10	N-terminal RING domain, C-terminal coiled-coil	SUMO or ubiquitin ligase. Plant HEI10 is the master regulator of crossover number and distribution [117]
	Zip4 (Spo22)	TEX11	ZIP4	TPR repeat protein	Likely interaction hub for the ZMM proteins and additional recombination components [9]
	Spo16	SPO16	PTD	Structurally similar to ERCC1 [9,116]	Exact function unknown, likely structured DNA binding [9]
	Msh4 Msh5	MSH4 MSH5	MSH4 MSH5	Structurally similar to bacterial MutS, i.e. a ring structure with a large central channel [118]	Binds to DNA repair intermediates and stabilises them [119,120]

The proteins discussed in this minireview are described here and, where known or present, the orthologous proteins from *S. cerevisiae*, *Mus musculus*, and *Arabidopsis thaliana* are shown.[1]As outlined in the text, Zip1 is functionally a 'ZMM' but also the major component of the transverse filament of the synaptonemal complex.

However, super-resolution microscopy data suggest that the Msh4/5 complex may only embrace one dsDNA in the recombination intermediate [131].

After they have been established, dHJs need to be resolved prior to the removal of cohesive cohesin from chromosomal arms at anaphase I. The resolution of dHJs can result in either non-crossover (NCO) or CO formation. In most model organisms the majority of meiotic COs are generated through the activity of the MutLγ endonuclease, a complex of Mlh1 and Mlh3, the activity of which exclusively generates COs [132]. MutLγ is not a structure-specific endonuclease [133], though it does preferentially bind Holliday Junctions [134]. How then does MutLγ only generate COs? Two recent studies from the Hunter and Cejka laboratories revealed that MutLγ endonuclease activity is stimulated *in vitro* by EXO1, PCNA, and RFC [135,136]. These findings lead to a model which proposes that the asymmetry of PCNA retained at joint molecules might provide a signal that stimulates MutLγ endonuclease to generate COs.

Significant gaps in our understanding of the function of ZMM proteins remain, leaving fundamental questions unanswered. Key among these are the mechanisms by which specific DSB sites are 'selected' by ZMM proteins, the exact order of binding events among these proteins, and the intricate details of how the temporal and spatial organisation of the ZMM interactome is controlled, particularly in relation to post-translational modifications.

Synapsis and crossover distribution

In the study of meiosis across a broad range of organisms, a common observation is the simultaneous occurrence of CO formation and the physical 'zippering' or synapsis of homologous chromosomes. This process is mediated by the SC, a structure integral to this pairing. Synapsis typically begins at DSB sites and progresses along the chromosomal axis [137]. The COs, as discussed earlier, occur within the SC, which connects to and forms the axial element of the SC. The intricate structure, function, and implications of the SC in disease have been comprehensively reviewed recently [115]. The SC is composed of three gross morphological elements, the central element, which runs along the midline of the SC, the axial element, which is a remodelled meiotic axis in the context of the SC, and the transverse filaments which link the axial and central elements. Numerous recent structural studies from the Davies laboratory have provided insight into the detailed organisation of the SC. Highlights include the revelation that part of the central element can polymerise by itself, forming intermediate filament-like structures [138], and details of the tetramerization regions of SYCP1 that form the gross structural arrangement of the transverse filaments [26] (Figure 3F).

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The distribution of COs, a topic of current interest in meiotic research, was thoroughly reviewed in this journal [139]. However, a brief summary is pertinent. In most organisms, CO distribution is not random. The occurrence of a CO at one locus typically reduces the probability of another CO nearby, a phenomenon termed 'crossover interference'. The ZMM proteins are primarily responsible for generating these interfering, or class I, COs. Among other factors, a group of key regulators in this process are RING E3 ligases belonging to two related families, Zip3 and HEI10. In *S. cerevisiae* only e Zip3 is present [6], whereas plants and *Sordaria macrospora* only have the HEI10 member [140]. Mammals have both HEI10 and the Zip3-related RNF212 [141,142] (and the paralog RNF212B) (Table 1). On synapsed chromosomes, HEI10 forms loci that exhibit 'coarsening,' where their size increases as their number decreases [117,143,144]. The mechanisms and regulatory processes behind HEI10 coarsening are currently under active investigation, promising to unveil further insights into the complex orchestration of CO distribution, and perhaps offering the possibility of exogenously manipulating CO numbers.

Conclusions and outlook

Meiotic recombination is an essential process, required at the organismal level to facilitate the proper segregation of homologous chromosomes, and at the species level to continually generate new allele combinations. The fundamental mechanism of meiosis — the breaking and subsequent modified repair of the genome — is a high-risk strategy. To ensure the necessary outcome, without compromising genome integrity, requires the temporal and spatial coordination of a variety of meiosis-specific factors that modify and act in consort with somatic factors.

One of the challenges of studying any cellular process is pleiotropic mutant effects, especially with the use of deletions. Thus one goal must be the generation of separation of function mutants. The recent protein structure prediction revolution, spearheaded by AlphaFold2 [145] has considerably lowered the barriers to high-resolution structural information necessary for point mutant design. From this, separation-of-function mutants can be used to study the details of meiotic recombination, as has been demonstrated recently [63,108,110]. At the time of writing, advanced prediction algorithms like AlphaFold2 do not yet possess the capability to model post-translational modifications, small molecule ligands, or nucleic acids. However, given the rapid advancements in this field, it's plausible to anticipate that these features will be integrated shortly. Far from rendering *in vitro* biophysical and biochemical studies obsolete, the advent of AlphaFold2 underscores their importance. These studies are crucial not only for validating the predictions of such algorithms but also for providing detailed input for complex components and stoichiometries, which are essential for accurate modelling.

Perspectives

- Meiotic recombination is at the very centre of the continuation and diversity of eukaryotic life.
- It will be necessary to explore the relationships between different subcomplexes of the meiotic machinery and understand the contributions made by various post-translational modifications.
- Large-scale biochemical reconstitutions will explore the role of each meiotic factor in a reductionist approach, while CryoET will provide detailed images of meiotic machines *in situ*.

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

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Abbreviations

CBR, chromatin binding domain; dHJs, double Holliday junctions; DSBs, double-stranded DNA breaks; SC, synaptonemal complex; Y2H, yeast two-hybrid.

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