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Review

Meiotic chromosome behavior in *Saccharomyces cerevisiae* and (mostly) mammals

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1. Foreword

In diploid organisms meiosis is required to haploidize the genome prior to spore or gamete formation. The high fidelity of chromosome segregation during meiosis requires that pairs of homologous chromosomes be oriented toward separate poles at the first meiotic division. Proper orientation of each pair depends on their forming attachments termed chiasmata, whose formation in turn depends on a series of interdependent meiosis-specific processes, which reorganize nuclear architecture while recombining the chromosomes. The most obvious manifestations of these events are synaptonemal complexes (SCs) and crossing over.The intent here mainly is to review what is known of meiotic chromosome behavior from *Saccharomyces cerevisiae* and to make a brief comparison with what is known from mammals. For more detail, see recent reviews of meiosis in *Sac. cerevisiae* [1–3].

2. Meiosis in *Sac. cerevisiae*

2.1. Meiosis is both non-essential and conditional in Sac. cerevisiae

Haploid and diploid strains can be maintained indefinitely and only enter meiosis under appropriate nutrient conditions (Fig. 1). Thus, meiotic mutants, even those which die upon entry to meiosis, are easily maintained. This allows examination of phenotypes caused by targetted complete deletion mutations of meiosis-specific genes, ''perfect'' nulls, whose effects are simpler to interpret than, e.g., temperature-conditional mutations. A culture of *Sac. cerevisiae* can be induced to undergo a semi-synchronous meiosis, providing a nearly pure population without the need for separating meiocytes from surrounding cell types.

2.2. Meiotic recombination and haploidization are not required for sporulation

This surprising and important observation was made relatively early in the genetic analysis of meiosis in *Sac. cerevisiae* [4] where a diploid strain unable to initiate meiotic recombination (*rad50*) and undergoing only a single meiotic division (*spo13*) formed viable, diploid, spores. On the other hand, mutants, which remain able to initiate recombination by forming DNA double-strand breaks (DSBs) but cannot repair the breaks, do generally block in meiosis (see below). In such mutants, it is possible to select for further mutations that eliminate the initiation of recombination, as these defects actually rescue the strains to allow production of viable spores, an approach that has led to the isolation of a class of

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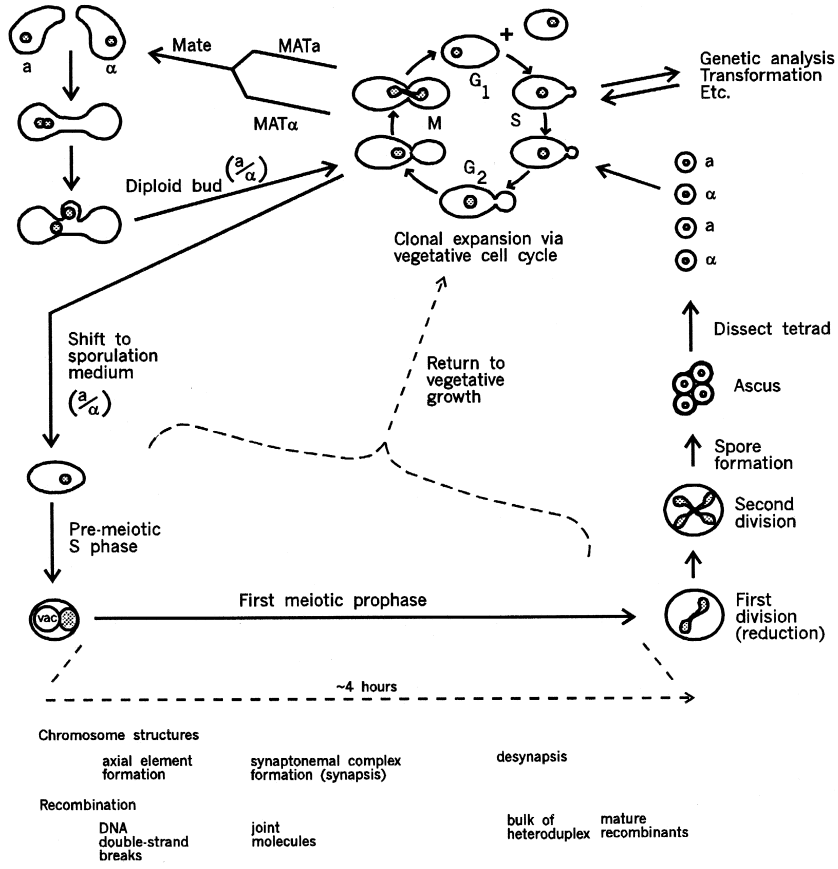

Fig. 1. The *Sac. cerevisiae* yeast life cycle. Haploid cells of opposite mating types, *MAT***a** and *MATα*, can mate to form diploids. On transfer to medium lacking a nitrogen source and containing a non-fermentable carbon source, diploid cells (or any cells functionally heterozygous at *MAT*) begin sporulation. Cells can be returned to vegetative growth as diploids until late in first meiotic prophase by transfer back to rich medium, providing for assays of meiotic recombination in cells unable to complete sporulation. The approximate times of appearance of several landmark events during first meiotic prophase are listed across the bottom of the figure.

genes termed ''early'' recombination genes [5]. These early recombination genes are useful in epistasis analysis, as they suppress the lethality of mutations in later steps in recombination.

2.3. Ascus formation following meiosis allows detailed genetic analysis of meiotic recombination

Tetrad analysis — analysis of the (normally) haploid products of a single meiosis by separating the four spores from a single ascus and examining each resulting clonal population genetically (Fig. 1) — is a significant strength of the *Sac. cerevisiae* model. Analysis of the four products of each meiosis allows all of the products of a single recombination event to be identified and, with appropriate markers, crossovers along a given chromosome can be detected, allowing measurement of crossover interference.

2.4. Meiotic chromosome behavior in Sac. cerevisiae follows the general plan observed in larger eukaryotes

In spite of the small size of the 16 pairs of chromosomes and the absence of extensive chromo-

some condensation at the divisions, *Sac. cerevisiae* chromosomes pair, form SCs and recombine as do those in larger organisms. Even though the level of recombination is remarkably high, with crossing over occurring at levels of ~0.3 to 1.5 cM/kb of DNA (depending on chromosome length, [6]), chromosome rearrangement can nevertheless reduce the level of crossing over [7]. Crossing over in translocations influences segregation in the same manner as described for other species [8], indicating that although chiasmata have not been visualized directly, the concept remains useful (and as structural proteins are identified, chiasmata are likely to be visualized using, e.g., fluorescent tags). In the absence of crossing over, chromosomes fail to be properly oriented at the first meitoic division, resulting in aneuploidy and inviability [9]. Finally, crossovers show positive interference [10], occur at least once per meiosis on even the shortest of the chromosomes [11,12] and are relatively infrequent near the centromeres and telomeres [6,13,14], all as described in larger organisms.

3. Chromosome pairing and synapsis

Synaptonemal complex formation is the culmination of a series of steps. Chromosomes, which have paired and have elaborated proteinaceous axes (axial elements, or AEs), finally become joined together along their lengths by transverse filaments which lie in the central region between the two axes. This final event is termed synapsis, or more specifically homosynapsis to distinguish it from SC formation between non-homologous chromosomes (heterosynapsis). In molecular terms, the SC is a huge structure with sufficient mass and density to be obvious at relatively low magnification in isolated, flattened nuclei, using phase-contrast light microscopy. Generally, the SC appears homogeneous in structure along its length, with clear modifications at centromeres and telomeres, but there are further modifications interstitially which reflect regional variations in chromosome composition and, presumably, structure.

One of the technical problems in *Sac. cerevisiae* is to manage penetration of the fixative through the cell wall in order to preserve SC structure, and it remains a concern that some structural detail may be lost in preparation. The main practical drawback of using embedded, sectioned material at the electron microscope has been that to view the entire contents of a single nucleus requires laborious serial section reconstruction. Nevertheless, certain features of meiotic nuclear architecture, e.g., approach of the ends of the SCs to the nuclear envelope, are so far best appreciated in this type of preparation. Cytological analysis can be more efficient using isolated, flattened nuclei (or ''spread preparations''), where soluble proteins are removed and SC structures can be contrasted for light and electron microscopy by silver-staining (Fig. 2) or can be immunolabeled to determine the presence and location of specific proteins ([15–18], and many variations since). Preservation of detailed structure is not the major goal of such preparations and, even without the relatively harsh silver-staining, this approach provides relatively low-resolution results. Disagreement in immunolocalizations between spread and sectioned preparations have been reported [19,20]. Even so, the rapidity with which localization and colocalization data can be collected in spread preparations has led to wide-spread use of this approach.

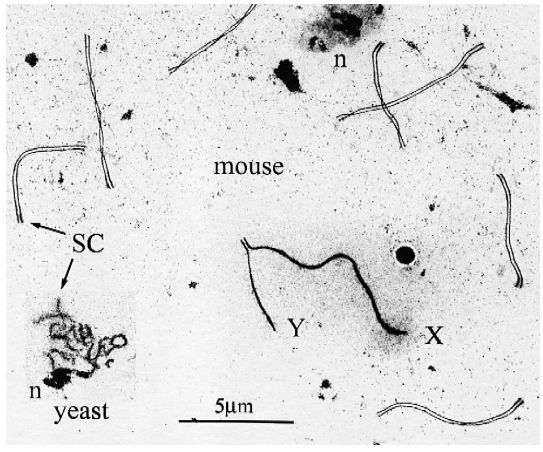

Fig. 2. Electron micrographs of silver-stained meiotic prophase nucleus from *Sac. cerevisiae* (yeast) and partial nucleus from male mouse showing synaptonemal complexes (SCs), nucleoli (n), and the partially synapsed axes of the X and Y chromosomes of the mouse. Image from mouse provided by M.J. Moses. The magnification bar refers to both images.

3.1. Synaptonemal complex structure and formation in Sac. cerevisiae follows the conserved program

The first descriptions of the SC in *Sac. cerevisiae* came from observations of meiotic nuclei in thin-sectioned samples at the electron microscope [21–25] and demonstrated, as have numerous subsequent studies employing spread preparations [16], that the SC forms by the general series of steps outlined above. In fact, synapsis is not required universally for successful meiosis and is absent, e.g., in *Schizosaccharomyces pombe* even though formation of AE-like structures does coincide with evident chromosome pairing [26]. It is not clear why in many disparate organisms SC architecture has been so well preserved (though susceptible to much apparent variation) while SCs are not required in other species, or even in only one sex of the two as in *Drosophila* [27,28]. These observations have led to discussions of whether (at least some features of) meiosis are conserved or represent convergent evolution, and, in this regard it is interesting that there is little sequence similarity between proteins with potentially similar functions in synapsis in *Sac. cerevisiae* and mouse [29].

3.2. Chromosome pairing may depend on interactions which are found even in vegetative cells

For normal SC formation, homologous chromosomes must align in close proximity before synapsing exclusive of the other chromosomes in the nucleus. In situ hybridization has been used to assess the locations of the chromosomes prior to synapsis in wild-type strains [30,31] and in mutants where synapsis never occurs [32–35]. These studies have been carried out in spread preparations of nuclei where spreading forces may help to ''dissect'' apart non-interacting sites as well as in unflattened preparations, and in addition have allowed description of the condensation state of the chromosomes at critical times in the meiotic pairing process [30,36,37]. Remarkably, *Sac. cerevisiae* chromosomes engage in pairing interactions even in vegetative cells [38] and clearly do not require recombination functions (e.g., *SPO11*, see below) to pair in early meiotic cells [31,32,39]. However, in many recombination mutants, the pairing associations are lost during meiotic prophase, possibly because of the absence of stabilization by synapsis in the face of (as yet undefined) forces which drive the chromosomes apart [31]. Nevertheless, heterologous chromosomes which lack homologous partners associate during prophase [40].

Even in the absence of crossing over, heterologs tend to disjoin from one another at the first meiotic division, a phenomenon termed distributive segregation (or achiasmate segregation, or distributive disjunction). In distributive segregation, small artificial chromosomes [41] or circular plasmids can also be engaged [42] and can even compete with normal, relatively large heterologous chromosomes [43] for a segregation partner, although crossing over between two members of a trio usually ensures their disjunction [41]. Numerous suggestions have been made concerning how pairing might occur between homologs even in vegetative/somatic cells [44]; the mechanism(s) for heterolog association would presumably be quite different. Pairing remains poorly understood.

Failure of homologs to pair may result in heterosynapsis by default, at least in some circumstances. Deletion of the *HOP2* gene in *Sac. cerevisiae* prevents homosynapsis in spite of essentially normal levels of recombination initiation events and allows heterosynapsis after some delay even in diploids [45]. This phenotype could be explained by a defect in a critical late step in homologous pairing that leads to homosynapsis, with no defect in SC formation per se, but it may be that Hop2p serves a regulatory role, preventing heterosynapsis under normal circumstances [45]. Lifting of an early prophase restriction to homosynapsis, to allow heterosynapsis later in prophase, was first proposed by Moses and Poorman [46] to account for observations of synaptic adjustment in mouse.

3.3. Chromosome pairing is facilitated by bouquet formation via meiosis-specific telomere functions

In vegetative cells of *Sac. cerevisiae*, telomeres form clusters near the nuclear envelope [17,47] while centromeres form a separate group [48]. Early in meiotic prophase, the telomeres replace the centromere group near the spindle pole body, forming the meitoic ''bouquet'' arrangement [49], a well-conserved feature of early meiotic prophase [3,50]. Bouquet formation occurs in mice and humans [51]

and is perturbed in mice by deletion of the *ATM* gene ([52], and see below). Bouquet formation may facilitate pairing by arranging an initial rough alignment of the chromosomes, reducing much of the homology search to a two-dimensional problem [53]. If the volume through which chromosomal DNA can diffuse is limited, as indicated by recent cytological results [54], then bouquet formation presumably would provide the required, larger scale chromosome movements. In *Sac. cerevisiae*, there is good evidence that circular chromosomes do not engage in pairing with the efficiency of linear chromosomes [55] and further that the *NDJ1 / TAM1* protein, presumably via a telomere-mediated function [56,57], is intimately involved in bringing chromosome ends together into an association that satisfies an as-yet undefined checkpoint for pairing [55]. A relatively high efficiency of ectopic recombination between sequences near the chromosome ends supports the idea that there is some special arrangement of these sequences in the nucleus at the time partners in recombination are established [58]. Not all strains of *Sac. cerevisiae* seem to form the bouquet to the same degree, or perhaps at all [59], but there is no reason a priori that all telomeres need to be clustered at once for the associations to have the proposed effects. The forces which bring about this reorganization of nuclear architecture have not been defined but clues are available from *Sch. pombe*, where telomeres cluster adjacent to the spindle pole to lie at the leading edges of meiotic prophase nuclei as they are swept from one end of the cell to the other during meiotic prophase [60–62]. The importance of the telomere clustering [63–65] and of the nuclear movements [66] to meiotic recombination in *Sch. pombe* indicate a role for the cytoskeleton, in particular for microtubules, in the chromosomal events of meiotic prophase [62,66,67]. The kinesin-related gene *KAR3* in *Sac. cerevisiae* also is required for normal levels of meiotic recombination [68].

3.4. Immunocytological localization of proteins in the meiotic nucleus has provided the foundation for most of the studies aimed at the molecular structure of the SC

In mammals, immunocytology in spread preparations ([69,70]) has provided the critical first step in analysis, the most significant contributions having begun with monoclonal antibodies raised against preparations enriched in isolated SCs [71] or with antibodies against defined candidate proteins, e.g., topoisomerase II ([18] and see below). In *Sac. cerevisiae*, immunocytological results generally have followed genetic starting points. Genetic support is an important consideration for the obvious reasons — visible accumulation of a protein may not reflect its function (and certainly not the timing of its function), just as the absence of detectable accumulation does not signify an absence of function. For example, accumulation of the *ZIP1* protein in *Sac. cerevisiae* is easily visualized only along synapsed regions as a major component of the central region [72,73], but Zip1p apparently influences recombination at an early step, independent of synapsis [74].

3.5. Axial elements form independently of pairing and synapsis

Although axial element (AE) formation and synapsis coincide in some *Sac. cerevisiae* strains, the existence of mutants delayed in or never engaging in synapsis demonstrate the independence of these events [75], as does AE formation in haploid strains [76,77]. Mutations in most genes required early in the initiation of recombination do not prevent AE formation [34,78–80], *SPO11* being an apparent exception.

Axial element structure depends on underlying chromosome organization. Early in the study of the SC it was suggested, based on observations of polycomplexes (extrachromosomal assemblies of SC components) that AEs are elaborated along a pre-existing chromosome axis, thus establishing the general features of SC architecture [81]. After or during assembly the AE components could in turn act on the chromosome axes, certainly in the course of synapsis, but potentially also at earlier stages [1].

In mouse, a given segment of DNA can exhibit differences in the length of the loop it makes depending on where along the chromosome/SC it is integrated [82], and observations have been made of variations in AE thickness and length associated with euchromatin vs. heterochromatin and with dark vs. light G-bands (e.g., in human, [83]). Underlying

chromosome/chromatin structure appears to be an important factor in the recombinational activities in a region and investigations of heterogeneities in structure and activities along the paired chromosomes/SCs is likely to be a fertile field in the near future. In this regard, it is interesting that there are data to suggest an *Sac. cerevisiae*-like organization and activity of mammalian DNA in *Sac. cerevisiae* meiosis [84,85], even though chromatin loops along the SC are considerably shorter than in mammals (~20 kb vs. ~120 kb, respectively [86]). This is in contrast to non-eukaryotic DNA which behaves quite differently, in *Sac. cerevisiae* [87] and in mouse [88]. The origins of these differences necessarily lie in the molecular organization of the SC.

SCP2 [89] and *SCP3/COR1* [90–92] (and *SCP1/SYN1*, see below) are mammalian SC genes isolated by using monoclonal antibodies to identify clones in cDNA expression libraries [93]. Scp2p, which shows some similarity to *Sac. cerevisiae* Red1p [89], and Scp3p/Cor1p are located in the AEs [20,91]. Cor1p also interacts homotypically in the two-hybrid assay, and Cor1p (and Syn1p) were found to interact with Ubc9p, a ubiquitin-conjugation enzyme [94] which also has been localized to the SC [95]. *SCP3* −/− mice fail to make AEs and fail to synapse [96], as also is seen in *Sac. cerevisiae* deleted for the AE-associated Red1p [97,98].

3.6. Axial element formation depends on sister chromatid cohesion functions

Recent observations made in three fungi, *Sac. cerevisiae*, *Sch. pombe* and *Sordaria macrospora*, indicate the importance of proteins required for sister chromatid cohesion early in meiotic prophase [99]. Mutations in the *SPO76* gene in *S. macrospora* [100,101], in the *Rec8* gene in *Sch. pombe* [102–104] and in the *SPO69/REC8* gene of *Sac. cerevisiae* [105] cause defects in sister chromatid cohesion, in formation of axial elements (''linear elements'' in *Sch. pombe*) and in recombination. The Spo76p cohesion protein functions in mitotic as well as in meiotic cells, and in meiotic prophase appears in a ''supraaxial'' position as compared with topoII [101], suggesting a physical distinction between structures involved in cohesion vs. synapsis per se (the molecular architecture of the SC remains relatively unexplored). Regional differences in chromosome and SC structure in the *spo76* mutant are reminiscent of the patchy localizations of Red1p and related proteins, and of the *SPO69/REC8*-related, mitotic (and perhaps meiotic) cohesin Mcd1p/Scc1p (which also is required for normal chromosome condensation [106]) described recently for mitotic cells by chromatin precipitation [107]. Another cohesin, the *SMC3* protein, localizes to the AEs in mouse [108] as it does in *Sac. cerevisiae* where it is required for meiotic recombination as well as for sister chromatid cohesion [105]. These findings are consistent with the observation that a hot spot for the initiation of recombination increases sister chromatid cohesion in meiosis (in human DNA within an *Sac. cerevisiae* artificial chromosome, [109]) and with a model for meiotic chromosome behavior which emphasizes the role of sister chromatid interactions [1].

3.7. Axial element structure is dynamic

In some mammals there occurs a consistent series of morphological changes during pachytene in the unsynapsed regions of the X and Y chromosome axes (and in nucleoli). In practical terms, these changes provide internal timing markers that allow division of pachytene into finer substages (for mouse and human spermatocytes, [110,111] and [83], respectively). Similar but more modest changes may occur in the synapsed portions of AEs (which following synapsis are termed lateral elements (LEs); [112]. Such modifications have not been described in *Sac. cerevisiae* but studies of semi-synchronous cultures with immunocytological reagents, in conjunction with high-resolution time-lapse microscopy of fluorescent protein-tagged proteins, may reveal similar changes. In mouse, ''accomodation'' occurs to equalize the lengths of AEs/LEs of homologs which begin pachytene with different lengths because of heterozygosity, for example for a tandem duplication [46]. This activity provides evidence for plasticity in the association between chromatin and these SC structures. Also in mouse, synaptic adjustment of homologously synapsed regions occurs in inversion heterozygotes during pachytene, to give straight but non-homologously synapsed regions in the SCs by late pachytene [113]. This observation provides evi-

dence of adaptations in the synaptic associations of the chromosomes [28] and suggests that DNA involved in recombination might become detached from close association with the LEs without disrupting overall SC morphology (or recombination) during pachytene [113]. Developmental changes in the association between the sister chromatids and the AEs/LEs may also occur, manifested by the obvious splitting of the LEs of autosomes into two strands during pachytene in (some) mammals [112].

3.8. Central region components function in concert with AEs to bring about synapsis

The *ZIP1* protein in *Sac. cerevisiae*, together with Zip2p [114], is required for synapsis [75]. Zip1p and the *SCP1/SYN1* protein of mammals (mouse, rat, hamster and human) are major components of the central region of the SC, are similarly oriented in SC structure (COOH-termini in the chromosome axes, NH_2-termini near the middle of the central region) and have common physical characteristics and homotypic interactions but nevertheless have very little sequence similarity outside respective domains predicted to form α-helical coiled coils (*ZIP1* — [29,73]; *SCP1/SYN1* — [19,91,115,116]). Each of these proteins has been observed to accumulate along the chromosome axes in the absence of normal AE formation (as judged from silver staining of spread preparations) following deletion of AE-associated proteins (in *Sac. cerevisiae*, deletion of *RED1* [98]; in mouse, deletion of *SCP3* [96]) but synapsis still fails to occur in these mutants. Clearly the series of molecular interactions required to foster appropriate recombination and chiasma formation are more complex than can be supported by the simple structural model where chromosome axes organize AEs which in turn anchor synaptic proteins.

4. Recombination

4.1. Initiation of recombination does not depend on prior homosynapsis

Careful correlation of cytological and biochemical results from samples taken at closely spaced timepoints in *Sac. cerevisiae* meiosis demonstrates that DSBs which initiate meiotic recombination appear when axial elements are forming, in advance of synapsis, and that the DSBs are processed into further recombination intermediates as synapsis proceeds ([117,118], Fig. 1). This is the reverse of what was long thought to be the case, i.e., that the prior occurrence of homologous SC formation assured that only properly located sequences would engage in (or even initiate) recombination leading to crossing over. However, early steps in recombination are in fact dependent on genes which also function early in SC morphogenesis.

Haploid *MAT***a**/*MAT*α strains enter meiosis, form (by definition) heterosynaptic SCs [76], and generate altered chromosomes by various ectopic recombination events [119]. Even in diploids, ectopic crossing over occurs [120,121] and can influence chromosomes to disjoin [122]. Nevertheless, homosynapsis and the events leading to it presumably influence partner choice in crossing over, perhaps by limiting or directing the volume searched for identification of the appropriate partner.

4.2. Meiotic recombination in Sac. cerevisiae occurs at very high but well-regulated levels

Relative to the small size of the *Sac. cerevisiae* chromosomes and genome, meiotic recombination occurs at extremely high levels, on the order of 260 events per nucleus per meiosis [123,124]. As in other organisms, there clearly are tight controls on the number and locations of crossovers, the longest chromosome pairs having numerous ''well-spaced'' (positively interfering) crossovers and the smallest chromosome pairs having at least one crossover per meiosis. Nevertheless, this high level of activity and the presence of hot spots for the initiation of recombination facilitates physical detection and analysis of recombination intermediates [125,126].

4.3. Meiotic recombination is initiated by DSBs

This seminal observation has been made directly only in *Sac. cerevisiae* where hot spots for DSB formation were first demonstrated at sites with ex-

ceptionally high crossover activities [127,128]. It is clear that prior DSB formation is required for gene conversion and crossing over in meiosis as both are eliminated by mutations in early recombination genes required to make the DSBs (for models and reviews, see [125,126]). Consistent with the essential role of the DSBs, defeating endogenous DSB formation by mutation of an early recombination gene but then supplying DSBs, by ionizing radiation [129] or by an endonuclease [130,131], partially restores recombination and ameliorates the effects following from the defects in meiotic recombination.

It is possible to assay genetically for the initiation of recombination (which coincides with DSB formation) even in mutants that cause a block in meiotic prophase, by restoring properly marked *Sac. cerevisiae* cells to vegetative growth medium before they become committed to sporulation (Fig. 1) [132]. However, the resolution of meiotic recombination intermediates in vegetative conditions is certainly non-meiotic. Physical methods of detection of recombination intermediates and final products circumvent this problem.

Methods for analysis of DNA from whole and broken *Sac. cerevisiae* chromosomes in Southern blots were quickly adopted to questions of meiotic chromosome behavior, first allowing the measurement of sister chromatid exchange using a circular chromosome [133]. Early on it was recognized that 5′-to-3′ resection at the break leaves 3′ overhangs which can invade homologous duplexes, and that specific mutations in the *RAD50* gene, designated *rad50S*, prevent this resection [128,134] (as do mutations in *SAE2 / COM1* [35,135] and *MRE11* [136,137]). Because DSBs accumulate in unprocessed form and thus run in discrete bands on gels, the *rad50S* mutation has been used extensively to demonstrate that DSBs occur in preferred locations [138], in hot spots along the chromosomes [139,140]. Finer mapping along the ~315-kb chromosome *III* reveals 76 regions favoring formation of DSBs, typically in GC-rich zones [141], though there are regions lacking obvious DSBs which nevertheless undergo significant levels of crossing over. It is possible that DSBs are not visualized in these regions because they are distributed evenly across these ''cold'' regions but this has not been demonstrated directly.

Finer mapping at hot spots for DSB formation reveals a cluster of breakpoints [142–145] indicating that specific sequence recognition is not involved. In fact, non-eukaryotic segments of DNA [128,146] and transplanted *Sac. cerevisiae* telomeric repeat sequences [145] can promote high levels of DSB formation. Also, the DSB activity of natural hot spot sequences can be reduced when the sequences are inserted into chromosome regions that are less frequently broken, without obvious changes in their chromatin structure [147], indicating the importance of neighboring chromatin and/or chromosome structure.

4.4. Joint molecules containing two Holliday structures and non-crossover strands are recombination intermediates which persist through pachytene

These intermediates are detected using two-dimensional DNA gels [148,149] and appear as DSBs disappear. The joint molecules contain double Holliday joins [150], confirming an inference based on electron microscopy of DNA isolated from meiotic cells [151], and such intermediates are predicted by the DSB model for recombination [152] (for additional models see [126]). Conversion is found for a marker at the DSB hot spot in ~25% of joint molecule strands [150], indicating an early role for mismatch repair genes. The joint molecules persist until the end of pachytene before being processed into mature recombinants.

4.5. The homolog rather than the sister chromatid is used preferentially in homologous repair during meiosis

This is one of the more interesting ''rules'' of meiotic recombination, as it is the opposite of the case in vegetative cells [153]. Several groups have provided evidence that heterologies at DSB hot spots reduce the level of DSBs, suggesting homolog–homolog interactions prior to (stable) DSB formation [144,154–156]. This would be a ''sensible'' mechanism, insuring that a homolog is available for repair before making the DSB, but meiotic DSB formation occurs during meiosis in haploid *Sac. cerevisiae*

strains (functionally heterozygous at the *MAT* locus) at roughly the same time as seen for diploid strains [157,158]. Whether the sister chromatid plays a different role in haploids than in diploids is not known.

4.6. Meiotic prophase is delayed to allow DSB repair

This is likely due to checkpoint activities (reviewed in [3]). Several of the checkpoint genes required in vegetative cells for response to DNA damage, *MEC1*, *RAD17* and *RAD24*, are also required for the meiotic arrest seen in *dmc1* and *zip1* mutants [159]. Similarly, perhaps, the meiotic prophase block in male *ATM* $-/-$ mice occurs later when cells also lack p21 function [160]. The meiosis-specific genes *PCH2* (and *DOT1* [161]), *RED1* and *MEK1* [162] of *Sac. cerevisiae* also seem specifically involved in this delay. Consistent with a DSB-mediated checkpoint delay in normal meiosis, the duration of the first meiotic prophase (that is, the time until the first meiotic division commences) is reduced by deletion of several early recombination genes where DSBs are not made [163]. However, the first meiotic division is advanced to different degrees in different mutants, suggesting that the usual ''delay'' may not be due simply to DSB formation and processing [131].

4.7. The DSB pathway for meiotic recombination appears to be conserved

One of the early recombination genes, *SPO11*, encodes a topoisomerase II-related protein which is found covalently linked to the DNA broken ends in *rad50S* mutants [164,165] and is required for DSB formation and recombination in *Sac. cerevisiae* [128]. Mutations in homologs of *SPO11* in *C. elegans* [166] and in *Drosophila melanogaster* [167] similarly eliminate meiotic recombination in these organisms, indicating conservation of the DSB pathway in meiosis. However, although *SPO11* is required for SC formation in *Sac. cerevisiae* (as are other early recombination genes, [2]), it is not required for SC formation in *C. elegans* [166] or in *D. melanogaster* [167]. Thus, the extent to which SC formation and recombination are interdependent in the different organisms remains an open question.

4.8. Meiosis-specific proteins with defined interactions are required for proper assembly of SCs and initiation of recombination, perhaps through an influence on sister chromatid associations

RED1, *HOP1* and *MEK1* are meiosis-specific genes which (a) are required for normal SC formation and recombination, (b) interact genetically and physically, and (c) encode proteins that have been immunolocalized to coincident locations along the chromosome axes early in prophase [45,97,98,168–175]. Red1p binding to sites along the chromosomes is independent of early recombination genes [98] or of Hop1p or Mek1p [175]. Red1p is phosphorylated dependent on Mek1p, a putative serine/threonine kinase [174,175]. Hop1p can bind DNA directly and inhibit exonucleolytic degradation [176] but accumulates along the chromosomes dependent on and at sites of Red1p [175]. Hop1p dissociates from the chromosomes before Red1p dissociation, with a delay in this turnover in *mek1Δ* [175]. Mek1p also accumulates along the chromosomes, dependent on and at sites of Red1p, but in addition requires Hop1p for the accumulation [175]. The order of accumulation (Red1p–Hop1p–Mek1p) correlates with SC formation dependence on these proteins, in that AEs fail to form in *red1Δ* [97,98], form but fail to synapse in *hop1Δ* [2,168,169] and synapse to form short segments of SCs in *mek1Δ* [177]. Each of these proteins also is required for normal levels of DSB accumulation [118,149,162,178], and one model places *RED1* and *HOP1* in an interchromosomal, but not intrachromosomal, recombination pathway [178]. It has been suggested that Red1p may function specifically at hot spots for recombination [118] along with Mek1p, perhaps to stabilize the cut product at a reversible step in DSB formation/processing [162]. Immunolocalization indicates that these proteins typically accumulate in patches along the chromosomes, rather than in continuous lines as might be expected for a structural component of AEs (although Red1p does appear more continuous in a *zip1Δ* background [98]). Chromosome condensation defects are reported

for *red1Δ* and *hop1Δ* [33] and premature sister chromatid separation is visualized during meiotic prophase in *red1Δ* and *mek1Δ*, and to a lesser extent in *hop1Δ* [175]. The latter observations are consistent with growing evidence for the roles of sister chromatid cohesion in SC morphogenesis and recombination as well as in chiasma function [179,180].

4.9. Proteins implicated in strand invasion and DSB processing are localized to spots presumed to represent recombination nodules

In the electron microscope, recombination nodules (RNs) are large, discrete, spherical to rod-shaped structures distributed along the SCs in a number of organisms, including *Sac. cerevisiae* [22]. Their involvement in recombination has been inferred from the timing of their appearance and from changes in number and structure in recombination mutants [181,182]. RNs change in number, morphology and distribution over the course of meiotic prophase, presumably reflecting progressive stages in recombination [28]. Rad51p in mammals [183] and Dmc1p in lily (*Lilium longiflorum* [184]) have been localized to electron-dense RNs, and immunocytological localizations of a number of additional proteins have demonstrated their accumulation in discrete spots along the chromosome axes and SCs (see below).

Sac. cerevisiae contains four proteins, Dmc1p, Rad51p, Rad55p and Rad57p, related to the bacterial strand-exchange enzyme recAp, and there is evidence for related biochemical activities for some of these proteins from *Sac. cerevisiae* and human [185–188]. These proteins are required for normal meiotic recombination [123,124,162,189–192]. These and the functionally related proteins Rad52p and Rpa1p colocalize (to varying degrees) in spots along the chromosome axes or SCs early in meiotic prophase in *Sac. cerevisiae* [190–193]. In mouse, Dmc1p and Rad51p also colocalize along axes or SCs [183,194,195] including the non-synapsing segment of the X chromosome (but not of the Y chromosome), as observed also for the colocalizing Bloom syndrome-associated *BLM* protein [196]. Whether Dmc1p and Rad51p form mixed vs. adjacent filaments in vivo is currently under debate (see [195]). In *Sac. cerevisiae*, Rad52p is required for accumulation of Rad51p and Dmc1p [192] and for the DSB-to-joint molecule transition (see [118]). Deletion of *DMC1*, the only meiosis-specific member of this group, prevents turnover of the DSBs and causes a block in meiotic prophase in some *Sac. cerevisiae* strains [123,190], but results only in abnormal recombination and segregation outcomes in another strain [197], for reasons that are not yet clear. In mouse, *dmc1* mutants cause a block in meiosis [198,199] similar to that observed in (some strains of) *Sac. cerevisiae*, although in mouse there is an associated induction of apoptosis (as seen also for other deficiencies, for example, of *ATM* and of *MSH5*).

In mouse, a number of other proteins implicated in DNA repair and regulation of repair have been localized in meiotic prophase nuclei to spots whose timing of appearance and associations suggest roles in meiotic recombination — *BRCA1* and *BRCA2* [200,201], *Atm* (and perhaps *Atr*) [202–205], *Chk1* [203], *RPA* [205], DNA polymerase β [206], and *BLM* protein [196,207]. The related proteins, Atrp and Rad1p, are distributed more evenly along the chromosomes [208,209]. Disruption of *ATM* results in defects in early prophase [52,160,210,211], in perturbations in localizations of Atrp, Dmc1p, and Rad51p [211] and in apoptotic degeneration in meiotic prophase which is partially rescued by deficiencies in p53 or p21 [160]. Conservation of these proteins and their functions in meiosis largely is untested. An interesting counter-example in this regard is the *HSP70-2* gene, whose product localizes to SCs in spermatocytes but not in oocytes [212] and is required for spermatogenesis but not for oogenesis [213].

The *SEP1* gene product of *Sac. cerevisiae* has been implicated in a number of processes, including DNA strand exchange [214,215], regulation of telomere repeat length [216] and G4-DNA-dependent nuclease activity [217]. Deletion of *SEP1* causes a block in pachytene with apparently normal SCs and levels of gene conversion but with decreased levels of crossing over [218]. Sep1p is abundant in vegetative and meiotic cells and is localized mainly to the cytoplasm although some fraction is found in association with vegetative nuclei.

4.10. Synapsis may influence the regulation of crossing over

Given that SC formation per se is not required for the initiation of recombination in *Sac. cerevisiae*, and certainly not in *Sch. pombe*, the question remains whether it may influence the course of recombination, perhaps to mediate positive crossover interference. This inference was first made based on observations that positive interference and synapsis both are absent from *Sch. pombe* [219,220] (and from *Aspergillus* [221]). Positive interference is completely absent in a *zip1* null mutant in *Sac. cerevisiae* [10]. Remarkably, insertions and deletions in Zip1p result in commensurate changes in the spacing between the LEs and in the respective levels of synapsis, crossing over and interference [72,73]. Taken together, these observations suggest the simple conclusion that synapsis is a critical event in interference. However, *ZIP1* also functions earlier in recombination [74], leaving the door open for models for crossover control based on other factors, e.g., on mechanical properties inherent in the axial chromosome structures themselves [1,74].

Any model that addresses crossover control in its various manifestations may need to incorporate observations that even the shortest of chromosome pairs form at least one crossover per meiosis and that chromosome or SC length alone seems to influence levels of crossing over and of interference. Decreasing length correlates both with increasing crossing over per kb of DNA [222] and with decreasing levels of interference [6]. A scaling of interference distances, based on a correlation between SC length and the distance between 2 foci of Mlh1p on a single SC, has been proposed for mouse [223], and it is noteworthy that the positions of single Mlh1p foci also depend on the length of the SC. These observations are more easily accommodated by models that depend on physical features of the chromosomes (and axes) themselves [3]. However, because the pattern and kinetics of synapsis also are likely to be influenced by chromosome size or regional differences in chromatin which may respond differentially to various mutations [57], the question of how interference is mediated remains open. It should be noted that competition for formation of DNA DSBs between neighboring sites has been observed but seems too local a phenomenon to contribute to interference on the chromosome level [224,225].

4.11. Mismatch repair proteins implicated in later stages of recombination also localize to spots, presumably marking late recombination nodules, along the SCs

Immunocytology in spread preparations demonstrates that Msh4p in *Sac. cerevisiae* [226] and Mlh1p in mouse [223,227] and human [228] localize in spots along the SCs. Deletion of *MLH1*, *MSH4* or *MSH5* in *Sac. cerevisiae* [170,229] reduces crossing over. Deletion of *Mlh1* in mouse [227,230] similarly appears to reduce or to eliminate crossing over, indicating a key role for these proteins in determining the outcome of recombination. However, deletion of *Pms2* [231] and of *Msh5* [232,233] in mouse cause failures of pairing and/or synapsis. The specific functions served by the different members of this class of proteins and when they become critical to meiosis in different organisms remain to be worked out.

4.12. Mature crossover products normally do not appear until SC dissolution, in desynapsis

One physical assay for crossover products in *Sac. cerevisiae* monitors the production of fragments of new lengths following crossing over in segments flanked by restriction enzyme heterozygosities [234,235]. Experiments addressing the kinetics of recombination have found not only that mature products of crossing over form late, around the time of SC disassembly [117], but that the bulk of heteroduplex DNA formed in association with the completion of meiotic recombination also does not appear until relatively late in prophase, just before the appearance of crossover products [236–238]. These final steps in recombination, however, do not require desynapsis, as *ndt80* and *cdc28*^{ts} mutants arrest with SCs but still form crossovers (although at $\sim 1/2$ the *wild-type* levels) ([239 and 162], respectively).

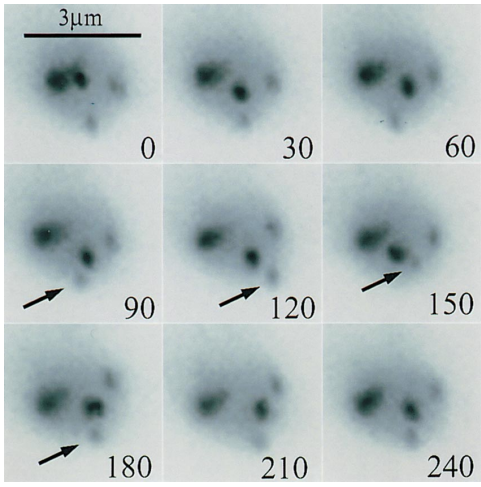

Fig. 3. Maximum intensity projections of image stacks taken every 30 s of a living meiotic prophase nucleus (brighter signals are shown as darker spots). Each chromosome IV has two GFP-marked spots, a small one near the centromere and a larger one near one telomere. The spindle pole body is labeled with *TUB4*-GFP and is visible at the left as a large, slightly irregular spot which remains relatively still during this part of the time course. The telomere spots are paired (one signal) and remain near the middle of the image. The black arrows point to one of the centromere markers which between 90 and 180 s moves away from then toward the spindle pole body. Starting plasmid constructs provided by A. Murray laboratory.

4.13. High-fidelity haploidization requires meiosis-specific regulation of sister centromere association as well as chiasma formation and function

Unique to the first meiotic division, sister centromeres must remain associated in order to allow ordered disjunction, that is, to prevent premature sister separation and non-disjunction [179,240,241]. It remains poorly understood how sister chromatid cohesion can be regulated differently along the chromosome arms and at centromeres during the first and second meiotic divisions although there is evidence in *Sac. cerevisiae* that suggests that *SPO13* functions to delay the loss of Rec8p and Smc3p at centromeres in the first division [105], and an immunocytological observation in mouse that suggests the involvement of *SCP3 / COR1* protein [92]. Premature separation of centromeres has not been seen in *SCP3* $-/-$ mice but cells fail to progress to the first division [96].

Whether formation of the SC per se is required for crossing over to lead to functional chiasmata in *Sac. cerevisiae* [242] is not clear, in part because crossover position along the bivalent seems related to its efficiency in guiding disjunction (e.g., in model chromosomes [243]). Similarly, centromere-proximal conversion events are associated with missegregations in the first meiotic division [244], consistent with recombination events causing, or perhaps being associated with, a local relaxation of sister chromatid cohesion [179]. Thus, perturbations in the SC may disregulate the position and/or frequency of crossovers and thus influence segregation indirectly.

5. Future directions

Current experimental capabilities are far from being exhausted, and ''more of the same'' directed at new genes, alleles and combinations of perturbations will continue to contribute insights into the molecular mechanisms driving meiotic chromosome behavior. Nevertheless, several directions warrant mention. High resolution electron microscopy, in particular immunocytology or related approaches, will be required to address questions of structure. Already

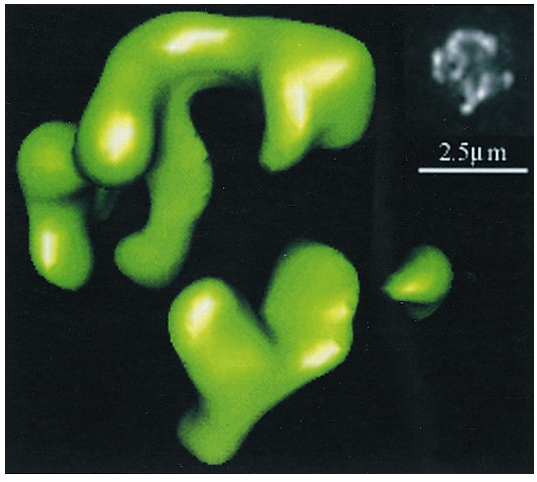

Fig. 4. Isosurface representation of fluorescent signal from GFP-tagged meiosis-specific cohesin *SPO69 / REC8*, which lies along the chromosome axes in *Sac. cerevisiae* [105]. Inset: Maximum intensity projection of the original image stack, before deconvolution, smoothing, and isosurface extraction. Image data provided by A. Kateneva. The magnification bar refers to the inset.

there are cautionary tales of disparate localizations of proteins examined in spread preparations vs. sections [19,20] and the simple scale of the structures involved will require analyses that take advantage of newer methods of structural preservation and of image processing and display [245]. Time-lapse microscopy in three dimensions, or ''4D'' microscopy, of fluorescent protein-tagged gene products and structures, will allow demonstration of the kinetics of chromosome movements (for examples, see Fig. 3 and [3,54]) and of the assembly of structures along them (see Fig. 4), or of the disassembly of the structures and of the segregation of the chromosomes during the divisions [246]. Advances in the preparation and biochemical analysis of large complexes (e.g., spindle pole bodies [247]) have allowed and will continue to provide progress in dealing with structures as large as recombination nodules or SCs, or with sizeable portions of chromosomes ([107]), and fluorescence resonance energy transfer (FRET) may soon allow real-time analysis of the molecular associations of defined proteins in these structures. Best of all is that each approach is applicable to mammals as well as to *Sac. cerevisiae*, and as much information lies in the differences of detail as in the similarities.

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References

[1] N. Kleckner, Meiosis: how could it work?, Proc. Natl. Acad. Sci. U. S. A. 93 (16) (1996) 8167–8174.
[2] G.S. Roeder, Meiotic chromosomes: it takes two to tango, Genes Dev. 11 (20) (1997) 2600–2621.
[3] D. Zickler, N. Kleckner, The leptotene–zygotene transition of meiosis, Annu. Rev. Genet. 32 (1998) 619–697.
[4] R.E. Malone, R.E. Esposito, Recombinationless meiosis in *Saccharomyces cerevisiae*, Mol. Cell Biol. 1 (10) (1981) 891–901.
[5] M. Cool, R.E. Malone, Molecular and genetic analysis of the yeast early meiotic recombination genes REC102 and REC107/MER2, Mol. Cell Biol. 12 (3) (1992) 1248–1256.
[6] D.B. Kaback, D. Barber, J. Mahon, J. Lamb, J. You, Chromosome size-dependent control of meiotic reciprocal recombination in *Saccharomyces cerevisiae*. The role of crossover interference, Genetics 152 (4) (1999) 1475–1486, [in process citation].
[7] M.E. Dresser, D.J. Ewing, S.N. Harwell, D. Coody, M.N. Conrad, Nonhomologous synapsis and reduced crossing over in a heterozygous paracentric inversion in *Saccharomyces cerevisiae*, Genetics 138 (3) (1994) 633–647.
[8] J. Loidl, Q.W. Jin, M. Jantsch, Meiotic pairing and segregation of translocation quadrivalents in yeast, Chromosoma 107 (4) (1998) 247–254.
[9] S. Klapholz, C.S. Waddell, R.E. Esposito, The role of the *SPO11* gene in meiotic recombination in yeast, Genetics 110 (2) (1985) 187–216.
[10] M. Sym, G.S. Roeder, Crossover interference is abolished in the absence of a synaptonemal complex protein, Cell 79 (2) (1994) 283–292.
[11] D.B. Kaback, H.Y. Steensma, P. de Jonge, Enhanced meiotic recombination on the smallest chromosome of *Saccharomyces cerevisiae*, Proc. Natl. Acad. Sci. U. S. A. 86 (10) (1989) 3694–3698.
[12] D.B. Kaback, Chromosome-size dependent control of meiotic recombination in humans, Nat. Genet. 13 (1) (1996) 20–21, [letter].
[13] E.J. Lambie, G.S. Roeder, A yeast centromere acts in cis to inhibit meiotic gene conversion of adjacent sequences, Cell 52 (6) (1988) 863–873.
[14] S. Klein, D. Zenvirth, V. Dror, A.B. Barton, D.B. Kaback, G. Simchen, Patterns of meiotic double-strand breakage on native and artificial yeast chromosomes, Chromosoma 105 (5) (1996) 276–284.
[15] M.E. Dresser, M.J. Moses, Silver staining of synaptonemal complexes in surface spreads for light and electron microscopy, Exp. Cell Res. 121 (2) (1979) 416–419.
[16] M.E. Dresser, C.N. Giroux, Meiotic chromosome behavior in spread preparations of yeast, J. Cell Biol. 106 (3) (1988) 567–573.
[17] F. Klein, T. Laroche, M.E. Cardenas, J.F. Hofmann, D. Schweizer, S.M. Gasser, Localization of RAP1 and topoisomerase II in nuclei and meiotic chromosomes of yeast, J. Cell Biol. 117 (5) (1992) 935–948.
[18] P.B. Moens, W.C. Earnshaw, Anti-topoisomerase II recognizes meiotic chromosome cores, Chromosoma 98 (5) (1989) 317–322.
[19] K. Schmekel, R.L. Meuwissen, A.J. Dietrich, A.C. Vink, J. van Marle, H. van Veen, C. Heyting, Organization of SCP1 protein molecules within synaptonemal complexes of the rat, Exp.Cell Res. 226 (1) (1996) 20–30.
[20] J.A. Schalk, A.J. Dietrich, A.C. Vink, H.H. Offenberg, M. van Aalderen, C. Heyting, Localization of SCP2 and SCP3 protein molecules within synaptonemal complexes of the rat, Chromosoma 107 (8) (1998) 540–548.
[21] P.B. Moens, E. Rapport, Synaptic structures in the nuclei of sporulating yeast, *Saccharomyces cerevisiae* (Hansen), J. Cell Sci. 9 (3) (1971) 665–677.
[22] B. Byers, L. Goetsch, Electron microscopic observations on the meiotic karyotype of diploid and tetraploid *Saccha-*

romyces cerevisiae, Proc. Natl. Acad. Sci. U. S. A. 72 (12) (1975) 5056–5060.
[23] D. Zickler, L.W. Olson, The synaptonemal complex and the spindle plaque during meiosis in yeast, Chromosoma 50 (1) (1975) 1–23.
[24] O. Horesh, G. Simchen, A. Friedmann, Morphogenesis of the synapton during yeast meiosis, Chromosoma 75 (1) (1979) 101–115.
[25] P.B. Moens, M.L. Ashton, Synaptonemal complexes of normal and mutant yeast chromosomes (*Saccharomyces cerevisiae*), Chromosoma 91 (2) (1985) 113–120.
[26] H. Scherthan, J. Bahler, J. Kohli, Dynamics of chromosome organization and pairing during meiotic prophase in fission yeast, J. Cell Biol. 127 (2) (1994) 273–285.
[27] M.J. Moses, Structure and function of the synaptonemal complex, Genetics 61 (1) (1969) Suppl. 51.
[28] D. von Wettstein, S.W. Rasmussen, P.B. Holm, The synaptonemal complex in genetic segregation, Annu. Rev. Genet. 18 (1984) 331–413.
[29] H. Dong, G.S. Roeder, Organization of the yeast zip 1 protein within the central region of the synaptonemal complex, J. Cell Biol. 148 (3) (2000) 417–426, (Feb. 7).
[30] H. Scherthan, J. Loidl, T. Schuster, D. Schweizer, Meiotic chromosome condensation and pairing in *Saccharomyces cerevisiae* studied by chromosome painting, Chromosoma 101 (10) (1992) 590–595.
[31] B.M. Weiner, N. Kleckner, Chromosome pairing via multiple interstitial interactions before and during meiosis in yeast, Cell 77 (7) (1994) 971–977.
[32] J. Loidl, F. Klein, H. Scherthan, Homologous pairing is reduced but not abolished in asynaptic mutants of yeast, J. Cell Biol. 125 (6) (1994) 1191–1200.
[33] D.K. Nag, H. Scherthan, B. Rockmill, J. Bhargava, G.S. Roeder, Heteroduplex DNA formation and homolog pairing in yeast meiotic mutants, Genetics 141 (1) (1995) 75–86.
[34] B. Rockmill, J.A. Engebrecht, H. Scherthan, J. Loidl, G.S. Roeder, The yeast *MER2* gene is required for chromosome synapsis and the initiation of meiotic recombination, Genetics 141 (1) (1995) 49–59.
[35] S. Prinz, A. Amon, F. Klein, Isolation of COM1, a new gene required to complete meiotic double-strand break-induced recombination in *Saccharomyces cerevisiae*, Genetics 146 (3) (1997) 781–795.
[36] J. Bahler, G. Hagens, G. Holzinger, H. Scherthan, W.D. Heyer, *Saccharomyces cerevisiae* cells lacking the homologous pairing protein p175SEP1 arrest at pachytene during meiotic prophase, Chromosoma 103 (2) (1994) 129–141.
[37] H. Scherthan, R. Eils, E. Trelles-Sticken, S. Dietzel, T. Cremer, H. Walt, A. Jauch, Aspects of three-dimensional chromosome reorganization during the onset of human male meiotic prophase, J. Cell Sci. 111 (1998) 2337–2351, (Pt 16).
[38] S.M. Burgess, N. Kleckner, B.M. Weiner, Somatic pairing of homologs in budding yeast: existence and modulation, Genes Dev. 13 (12) (1999) 1627–1641.
[39] R.S. Cha, B.M. Weiner, S. Keeney, J. Dekker, N. Kleckner, Progression of meiotic DNA replication is modulated by interchromosomal interaction proteins, negatively by Spo11p and positively by Rec8p, Genes Dev. 14 (4) (2000) 493–503, (Feb. 15).
[40] J. Loidl, H. Scherthan, D.B. Kaback, Physical association between nonhomologous chromosomes precedes distributive disjunction in yeast, Proc. Natl. Acad. Sci. U. S. A. 91 (1) (1994) 331–334.
[41] D.S. Dawson, A.W. Murray, J.W. Szostak, An alternative pathway for meiotic chromosome segregation in yeast, Science 234 (4777) (1986) 713–717.
[42] C. Mann, R.W. Davis, Meiotic disjunction of circular minichromosomes in yeast does not require DNA homology, Proc. Natl. Acad. Sci. U. S. A. 83 (16) (1986) 6017–6019.
[43] V. Guacci, D.B. Kaback, Distributive disjunction of authentic chromosomes in *Saccharomyces cerevisiae*, Genetics 127 (3) (1991) 475–488.
[44] P.R. Cook, The transcriptional basis of chromosome pairing, J. Cell Sci. 110 (1997) 1033–1040, (Pt 9).
[45] J.Y. Leu, P.R. Chua, G.S. Roeder, The meiosis-specific Hop2 protein of *S. cerevisiae* ensures synapsis between homologous chromosomes, Cell 94 (3) (1998) 375–386.
[46] M.J. Moses, P.A. Poorman, Synaptosomal complex analysis of mouse chromosomal rearrangements: II. Synaptic adjustment in a tandem duplication, Chromosoma 81 (4) (1981) 519–535.
[47] M. Gotta, T. Laroche, A. Formenton, L. Maillet, H. Scherthan, S.M. Gasser, The clustering of telomeres and colocalization with Rap 1, Sir3, and Sir4 proteins in wild-type *Saccharomyces cerevisiae*, J. Cell Biol. 134 (6) (1996) 1349–1363.
[48] Q. Jin, E. Trelles-Sticken, H. Scherthan, J. Loidl, Yeast nuclei display prominent centromere clustering that is reduced in nondividing cells and in meiotic prophase, J. Cell Biol. 141 (1) (1998) 21–29.
[49] E. Trelles-Sticken, J. Loidl, H. Scherthan, Bouquet formation in budding yeast: initiation of recombination is not required for meiotic telomere clustering, J. Cell Sci. 112 (1999) 651–658, (Pt 5).
[50] A.F. Dernburg, J.W. Sedat, W.Z. Cande et al., in: Telomeres, E.H. Blackburn, C.W. Greider (Eds.), Cytology of Telomeres Cold Spring Harbor Lab, Cold Spring Harbor, NY, 1995, pp. 295–338.
[51] H. Scherthan, S. Weich, H. Schwegler, C. Heyting, M. Harle, T. Cremer, Centromere and telomere movements during early meiotic prophase of mouse and man are associated with the onset of chromosome pairing, J. Cell Biol. 134 (5) (1996) 1109–1125.
[52] T.K. Pandita, C.H. Westphal, M. Anger, S.G. Sawant, C.R. Geard, R.K. Pandita, H. Scherthan, Atm inactivation results in aberrant telomere clustering during meiotic prophase, Mol. Cell Biol. 19 (7) (1999) 5096–5105.
[53] M.J. Moses, Synaptonemal complex, Annu. Rev. Genet. 2 (1968) 363–412.
[54] W.F. Marshall, A. Straight, J.F. Marko, J. Swedlow, A. Dernburg, A. Belmont, A.W. Murray, D.A. Agard, J.W. Sedat, Interphase chromosomes undergo constrained diffu-

sional motion in living cells, Curr. Biol. 7 (12) (1997) 930–939.
[55] B. Rockmill, G.S. Roeder, Telomere-mediated chromosome pairing during meiosis in budding yeast, Genes Dev. 12 (16) (1998) 2574–2586.
[56] M.N. Conrad, A.M. Dominguez, M.E. Dresser, Ndj1p, a meiotic telomere protein required for normal chromosome synapsis and segregation in yeast, Science 276 (5316) (1997) 1252–1255, [see comments].
[57] P.R. Chua, G.S. Roeder, Tam1, a telomere-associated meiotic protein, functions in chromosome synapsis and crossover interference, Genes Dev. 11 (14) (1997) 1786–1800.
[58] A.S. Goldman, M. Lichten, The efficiency of meiotic recombination between dispersed sequences in *Saccharomyces cerevisiae* depends upon their chromosomal location, Genetics 144 (1) (1996) 43–55.
[59] A. Hayashi, H. Ogawa, K. Kohno, S.M. Gasser, Y. Hiraoka, Meiotic behaviours of chromosomes and microtubules in budding yeast: relocalization of centromeres and telomeres during meiotic prophase, Genes Cells 3 (9) (1998) 587–601.
[60] Y. Chikashige, D.Q. Ding, H. Funabiki, T. Haraguchi, S. Mashiko, M. Yanagida, Y. Hiraoka, Telomere-led premeiotic chromosome movement in fission yeast, Science 264 (5156) (1994) 270–273.
[61] J. Kohli, Meiosis. Telomeres lead chromosome movement, Curr. Biol. 4 (8) (1994) 724–727.
[62] D.Q. Ding, Y. Chikashige, T. Haraguchi, Y. Hiraoka, Oscillatory nuclear movement in fission yeast meiotic prophase is driven by astral microtubules, as revealed by continuous observation of chromosomes and microtubules in living cells, J. Cell Sci. 111 (1998) 701–712, (Pt 6).
[63] M. Shimanuki, F. Miki, D.Q. Ding, Y. Chikashige, Y. Hiraoka, T. Horio, O. Niwa, A novel fission yeast gene, *kms1+*, is required for the formation of meiotic prophase-specific nuclear architecture, Mol. Gen. Genet. 254 (3) (1997) 238–249.
[64] J.P. Cooper, Y. Watanabe, P. Nurse, Fission yeast Taz1 protein is required for meiotic telomere clustering and recombination, Nature 392 (6678) (1998) 828–831, [see comments].
[65] E.R. Nimmo, A.L. Pidoux, P.E. Perry, R.C. Allshire, Defective meiosis in telomere-silencing mutants of *Schizosaccharomyces pombe*, Nature 392 (6678) (1998) 825–828, [see comments].
[66] A. Yamamoto, R.R. West, J.R. McIntosh, Y. Hiraoka, A cytoplasmic dynein heavy chain is required for oscillatory nuclear movement of meiotic prophase and efficient meiotic recombination in fission yeast, J. Cell Biol. 145 (6) (1999) 1233–1250.
[67] A. Svoboda, J. Bahler, J. Kohli, Microtubule-driven nuclear movements and linear elements as meiosis-specific characteristics of the fission yeasts *Schizosaccharomyces versatilis* and *Schizosaccharomyces pombe*, Chromosoma 104 (3) (1995) 203–214.
[68] C.A. Bascom-Slack, D.S. Dawson, The yeast motor protein, Kar3p, is essential for meiosis I, J. Cell Biol. 139 (2) (1997) 459–467.
[69] M.J. Moses, M.E. Dresser, P.A. Poorman, Composition and role of the synaptonemal complex, Symp. Soc. Exp. Biol. 38 (1984) 245–270.
[70] T. Ashley, A. Plug, Caught in the act: deducing meiotic function from protein immunolocalization, Curr. Top. Dev. Biol. 37 (1998) 201–239.
[71] C. Heyting, A.J. Dietrich, P.B. Moens, R.J. Dettmers, H.H. Offenberg, E.J. Redeker, A.C. Vink, Synaptonemal complex proteins, Genome 31 (1) (1989) 81–87.
[72] M. Sym, G.S. Roeder, Zip 1-induced changes in synaptonemal complex structure and polycomplex assembly, J. Cell Biol. 128 (4) (1995) 455–466.
[73] K.S. Tung, G.S. Roeder, Meiotic chromosome morphology and behavior in zip 1 mutants of *Saccharomyces cerevisiae*, Genetics 149 (2) (1998) 817–832.
[74] A. Storlazzi, L. Xu, A. Schwacha, N. Kleckner, Synaptonemal complex (SC) component Zip 1 plays a role in meiotic recombination independent of SC polymerization along the chromosomes, Proc. Natl. Acad. Sci. U. S. A. 93 (17) (1996) 9043–9048.
[75] M. Sym, J.A. Engebrecht, G.S. Roeder, ZIP 1 is a synaptonemal complex protein required for meiotic chromosome synapsis, Cell 72 (3) (1993) 365–378.
[76] J. Loidl, K. Nairz, F. Klein, Meiotic chromosome synapsis in a haploid yeast, Chromosoma 100 (4) (1991) 221–228.
[77] J. Loidl, Meiotic chromosome pairing in triploid and tetraploid *Saccharomyces cerevisiae*, Genetics 139 (4) (1995) 1511–1520.
[78] E. Alami, R. Padmore, N. Kleckner, Analysis of wild-type and rad50 mutants of yeast suggests an intimate relationship between meiotic chromosome synapsis and recombination, Cell 61 (3) (1990) 419–436.
[79] T.M. Menees, P.B. Ross-Macdonald, G.S. Roeder, *MEI4*, a meiosis-specific yeast gene required for chromosome synapsis, Mol. Cell Biol. 12 (3) (1992) 1340–1351.
[80] J. Bhargava, J. Engebrecht, G.S. Roeder, The rec102 mutant of yeast is defective in meiotic recombination and chromosome synapsis, Genetics 130 (1) (1992) 59–69.
[81] K.S. Schin, Core-strukturen in den meiotischen und postmeiotischen kernen der spermatogenese von *Gryllus domesticus*, Chromosoma 16 (1965) 436–452.
[82] H.H. Heng, J.W. Chamberlain, X.M. Shi, B. Spyropoulos, L.C. Tsui, P.B. Moens, Regulation of meiotic chromatin loop size by chromosomal position, Proc. Natl. Acad. Sci. U. S. A. 93 (7) (1996) 2795–2800.
[83] A.J. Solari, Synaptosomal complexes and associated structures in microspread human spermatocytes, Chromosoma 81 (3) (1980) 315–337.
[84] J. Loidl, H. Scherthan, J.T. Den Dunnen, F. Klein, Morphology of a human-derived YAC in yeast meiosis, Chromosoma 104 (3) (1995) 183–188.
[85] S. Klein, D. Zenvirth, A. Sherman, K. Ried, G. Rappold, G. Simchen, Double-strand breaks on YACs during yeast meiosis may reflect meiotic recombination in the human genome, Nat. Genet. 13 (4) (1996) 481–484.

[86] P.B. Moens, R.E. Pearlman, Chromatin organization at meiosis, Bioessays 9 (5) (1988) 151–153.
[87] L.O. Ross, D. Treco, A. Nicolas, J.W. Szostak, D. Dawson, Meiotic recombination on artificial chromosomes in yeast, Genetics 131 (3) (1992) 541–550.
[88] H.H. Heng, L.C. Tsui, P.B. Moens, Organization of heterologous DNA inserts on the mouse meiotic chromosome core, Chromosoma 103 (6) (1994) 401–407.
[89] H.H. Offenberg, J.A. Schalk, R.L. Meuwissen, M. van Aalderen, H.A. Kester, A.J. Dietrich, C. Heyting, SCP2: a major protein component of the axial elements of synaptonemal complexes of the rat, Nucleic Acids Res. 26 (11) (1998) 2572–2579.
[90] J.H. Lammers, H.H. Offenberg, M. vanAalderen, A.C. Vink, A.J. Dietrich, C. Heyting, The gene encoding a major component of the lateral elements of synaptonemal complexes of the rat is related to X-linked lymphocyte-regulated genes, Mod. Cell Biol. 14 (2) (1994) 1137–1146.
[91] M.J. Dobson, R.E. Pearlman, A. Karaiskakis, B. Spyropoulos, P.B. Moens, Synaptonemal complex proteins: occurrence, epitope mapping and chromosome disjunction, J. Cell Sci. 107 (1994) 2749–2760, (Pt 10).
[92] P.B. Moens, B. Spyropoulos, Immunocytology of chiasmata and chromosomal disjunction at mouse meiosis, Chromosoma 104 (3) (1995) 175–182.
[93] C. Heyting, Synaptonemal complexes: structure and function, Curr. Opin. Cell Biol. 8 (3) (1996) 389–396.
[94] M. Tarsounas, R.E. Pearlman, P.J. Gasser, M.S. Park, P.B. Moens, Protein–protein interactions in the synaptonemal complex, Mol. Biol. Cell 8 (8) (1997) 1405–1414.
[95] O.V. Kovalenko, A.W. Plug, T. Haaf, D.K. Gonda, T. Ashley, D.C. Ward, C.M. Radding, E.I. Golub, Mammalian ubiquitin-conjugating enzyme Ubc9 interacts with Rad51 recombination protein and localizes in synaptonemal complexes, Proc. Natl. Acad. Sci. U. S. A. 93 (7) (1996) 2958–2963.
[96] L. Yuan, J.G. Liu, J. Zhao, E. Brundell, B. Daneholt, C. Hoog, The murine SCP3 gene is required for synaptonemal complex assembly, chromosome synapsis, and male fertility, Mol. Cell Jan. 5 (1) (2000) 73–83.
[97] B. Rockmill, G.S. Roeder, Meiosis in asynaptic yeast, Genetics 126 (3) (1990) 563–574.
[98] A.V. Smith, G.S. Roeder, The yeast Red1 protein localizes to the cores of meiotic chromosomes, J. Cell Biol. 136 (5) (1997) 957–967.
[99] T. Orr-Weaver, The ties that bind: localization of the sister-chromatid cohesin complex on yeast chromosomes, Cell 99 (1999) 1–4.
[100] P.J. Moreau, D. Zickler, G. Leblon, One class of mutants with disturbed centromere cleavage and chromosome pairing in *Sordaria macrospora*, Mol. Gen. Genet. 198 (1985) 189–197.
[101] D. van Heemst, F. James, S. Poggeler, V. Berteaux-Lecellier, D. Zickler, Spo76p is a conserved chromosome morphogenesis protein that links the mitotic and meiotic programs, Cell 98 (2) (1999) 261–271.
[102] M. Molnar, J. Bahler, M. Sipiczki, J. Kohli, The *rec8* gene of *Schizosaccharomyces pombe* is involved in linear element formation, chromosome pairing and sister-chromatid cohesion during meiosis, Genetics 141 (1) (1995) 61–73.
[103] S. Parisi, M.J. McKay, M. Molnar, M.A. Thompson, P.J. van der Spek, E. van Drunen-Schoenmaker, R. Kanaar, E. Lehmann, J.H. Hoeijmakers, J. Kohli, Rec8p, a meiotic recombination and sister chromatid cohesion phosphoprotein of the Rad21p family conserved from fission yeast to humans, Mol. Cell Biol. 19 (5) (1999) 3515–3528.
[104] Y. Watanabe, P. Nurse, Cohesin rec8 is required for reductional chromosome segregation at meiosis, Nature 400 (1999) 461–464.
[105] F. Klein, P. Mahr, M. Galova, S.B. Buonomo, C. Michaelis, K. Nairz, K. Nasmyth, A central role for cohesins in sister chromatid cohesion, formation of axial elements, and recombination during yeast meiosis, Cell 98 (1) (1999) 91–103.
[106] V. Guacci, D. Koshland, A. Strunnikov, A direct link between sister chromatid cohesion and chromosome condensation revealed through the analysis of MCD1 in *S. cerevisiae*, Cell 91 (1) (1997) 47–57, [see comments].
[107] Y. Blat, N. Kleckner, Cohesions bind to preferential sites along yeast chromosome III, with differential regulation along arms versus the centric region, Cell 98 (2) (1999) 249–259, [in process citation].
[108] M. Eijpe, C. Heyting, B. Gross, R. Jessberger, Association of mammalian SMC1 and SMC3 proteins with meiotic chromosomes and synaptonemal complexes, J. Cell Sci. 113 (2000) 673–682, (Pt. 4).
[109] D.D. Sears, P. Hieter, G. Simchen, An implanted recombination hot spot stimulates recombination and enhances sister chromatid cohesion of heterologous YACs during yeast meiosis, Genetics 138 (4) (1994) 1055–1065.
[110] M.J. Moses, M. Serio, L. Martini (Eds.), in: Animal Models in Human Reproduction, New Cytogenetic Studies on Mammalian Meiosis Raven Press, New York, 1980, pp. 169–190.
[111] M.J. Moses, G. Jagiello, H.J. Vogel (Eds.), in: Bioregulators of reproduction, Meiosis, Synaptonemal Complex and Cytogenetic Analysis Academic Press, New York, 1981, pp. 187–206.
[112] M.E. Dresser, M.J. Moses, Synaptonemal complex karyotyping in spermatocytes of the Chinese hamster (*Cricetulus griseus*): IV. Light and electron microscopy of synapsis and nucleolar development by silver staining, Chromosoma 76 (1) (1980) 1–22.
[113] M.J. Moses, P.A. Poorman, T.H. Roderick, M.T. Davisson, Synaptonemal complex analysis of mouse chromosomal rearrangements: IV. Synapsis and synaptic adjustment in two paracentric inversions, Chromosoma 84 (4) (1982) 457–474.
[114] P.R. Chua, G.S. Roeder, Zip2, a meiosis-specific protein required for the initiation of chromosome synapsis, Cell 93 (3) (1998) 349–359.
[115] R.L. Meuwissen, P.H. Offenberg, A.J. Dietrich, A. Riesewijk, M. van Iersel, C. Heyting, A coiled-coil related protein specific for synapsed regions of meiotic prophase chromosomes, EMBO J. 11 (13) (1992) 5091–5100.
[116] J.G. Liu, L. Yuan, E. Brundell, B. Bjorkroth, B. Daneholt,

C. Hoog, Localization of the N-terminus of SCP1 to the central element of the synaptonemal complex and evidence for direct interactions between the N-termini of SCP1 molecules organized head-to-head, Exp. Cell Res. 226 (1) (1996) 11–19.
[117] R. Padmore, L. Cao, N. Kleckner, Temporal comparison of recombination and synaptonemal complex formation during meiosis in *S. cerevisiae*, Cell 66 (6) (1991) 1239–1256.
[118] A. Schwacha, N. Kleckner, Interhomolog bias during meiotic recombination: meiotic functions promote a highly differentiated interhomolog-only pathway, Cell 90 (6) (1997) 1123–1135.
[119] J. Loidl, K. Nairz, Karyotype variability in yeast caused by nonallelic recombination in haploid meiosis, Genetics 146 (1) (1997) 79–88.
[120] S. Jinks-Robertson, T.D. Petes, High-frequency meiotic gene conversion between repeated genes on nonhomologous chromosomes in yeast, Proc. Natl. Acad. Sci. U. S. A. 82 (10) (1985) 3350–3354.
[121] M. Lichten, R.H. Borts, J.E. Haber, Meiotic gene conversion and crossing over between dispersed homologous sequences occurs frequently in *Saccharomyces cerevisiae*, Genetics 115 (2) (1987) 233–246.
[122] S. Jinks-Robertson, S. Sayeed, T. Murphy, Meiotic crossing over between nonhomologous chromosomes affects chromosome segregation in yeast, Genetics 146 (1) (1997) 69–78.
[123] D.K. Bishop, D. Park, L. Xu, N. Kleckner, DMC1: a meiosis-specific yeast homolog of *E. coli* recA required for recombination, synaptonemal complex formation, and cell cycle progression, Cell 69 (3) (1992) 439–456.
[124] B. Rockmill, M. Sym, H. Scherthan, G.S. Roeder, Roles for two RecA homologs in promoting meiotic chromosome synapsis, Genes Dev. 9 (21) (1995) 2684–2695.
[125] K.N. Smith, A. Nicolas, Recombination at work for meiosis, Curr. Opin. Genet. Dev. 8 (2) (1998) 200–211.
[126] F. Paques, J.E. Haber, Multiple pathways of recombination induced by double-strand breaks in *Saccharomyces cerevisiae*, Microbiol. Mol. Biol. Rev. 63 (2) (1999) 349–404.
[127] H. Sun, D. Treco, N.P. Schultes, J.W. Szostak, Double-strand breaks at an initiation site for meiotic gene conversion, Nature 338 (6210) (1989) 87–90.
[128] L. Cao, E. Alani, N. Kleckner, A pathway for generation and processing of double-strand breaks during meiotic recombination in *S. cerevisiae*, Cell 61 (6) (1990) 1089–1101.
[129] L.W. Thorne, B. Byers, Stage-specific effects of X-irradiation on yeast meiosis, Genetics 134 (1) (1993) 29–42.
[130] A. Malkova, L. Ross, D. Dawson, M.F. Hoekstra, J.E. Haber, Meiotic recombination initiated by a double-strand break in rad50 delta yeast cells otherwise unable to initiate meiotic recombination, Genetics 143 (2) (1996) 741–754.
[131] K. Jiao, S.A. Bullard, L. Salem, R.E. Malone, Coordination of the initiation of recombination and the reductional division in meiosis in *Saccharomyces cerevisiae*, Genetics 152 (1) (1999) 117–128, [in process citation].
[132] R.E. Esposito, M.S. Esposito, Genetic recombination and commitment to meiosis in *Saccharomyces*, Proc. Natl. Acad. Sci. U. S. A. 71 (8) (1974) 3172–3176.
[133] J.C. Game, K.C. Sitney, V.E. Cook, R.K. Mortimer, Use of a ring chromosome and pulsed-field gels to study interhomolog recombination, double-strand DNA breaks and sister-chromatid exchange in yeast, Genetics 123 (4) (1989) 695–713.
[134] H. Sun, D. Treco, J.W. Szostak, Extensive 3′-overhanging, single-stranded DNA associated with the meiosis-specific double-strand breaks at the ARG4 recombination initiation site, Cell 64 (6) (1991) 1155–1161.
[135] A.H. McKee, N. Kleckner, A general method for identifying recessive diploid-specific mutations in *Saccharomyces cerevisiae*, its application to the isolation of mutants blocked at intermediate stages of meiotic prophase and characterization of a new gene *SAE2*, Genetics 146 (3) (1997) 797–816.
[136] K. Nairz, F. Klein, mre11S — a yeast mutation that blocks double-strand-break processing and permits nonhomologous synapsis in meiosis, Genes Dev. 11 (17) (1997) 2272–2290.
[137] M. Furuse, Y. Nagase, H. Tsubouchi, K. Murakami-Murofushi, T. Shibata, K. Ohta, Distinct roles of two separable in vitro activities of yeast Mre11 in mitotic and meiotic recombination, EMBO J. 17 (21) (1998) 6412–6425.
[138] J.C. Game, Pulsed-field gel analysis of the pattern of DNA double-strand breaks in the *Saccharomyces* genome during meiosis, Dev. Genet. 13 (6) (1992) 485–497.
[139] D. Zenvirth, T. Arbel, A. Sherman, M. Goldway, S. Klein, G. Simchen, Multiple sites for double-strand breaks in whole meiotic chromosomes of *Saccharomyces cerevisiae*, EMBO J. 11 (9) (1992) 3441–3447.
[140] T.C. Wu, M. Lichten, Meiosis-induced double-strand break sites determined by yeast chromatin structure, Science 263 (5146) (1994) 515–518.
[141] F. Baudat, A. Nicolas, Clustering of meiotic double-strand breaks on yeast chromosome III, Proc. Natl. Acad. Sci. U. S. A. 94 (10) (1997) 5213–5218.
[142] B. de Massy, V. Rocco, A. Nicolas, The nucleotide mapping of DNA double-strand breaks at the CYS3 initiation site of meiotic recombination in *Saccharomyces cerevisiae*, EMBO J. 14 (18) (1995) 4589–4598.
[143] J. Liu, T.C. Wu, M. Lichten, The location and structure of double-strand DNA breaks induced during yeast meiosis: evidence for a covalently linked DNA–protein intermediate, EMBO J. 14 (18) (1995) 4599–4608.
[144] L. Xu, N. Kleckner, Sequence non-specific double-strand breaks and interhomolog interactions prior to double-strand break formation at a meiotic recombination hot spot in yeast, EMBO J. 14 (20) (1995) 5115–5128.
[145] F. Xu, T.D. Petes, Fine-structure mapping of meiosis-specific double-strand DNA breaks at a recombination hotspot associated with an insertion of telomeric sequences upstream of the *HIS4* locus in yeast, Genetics 143 (3) (1996) 1115–1125.
[146] A. Stapleton, T.D. Petes, The Tn3 beta-lactamase gene acts as a hotspot for meiotic recombination in yeast, Genetics 127 (1) (1991) 39–51.
[147] V. Borde, T.C. Wu, M. Lichten, Use of a recombination reporter insert to define meiotic recombination domains on chromosome III of *Saccharomyces cerevisiae*, Mol. Cell Biol. 19 (7) (1999) 4832–4842, [in process citation].

[148] I. Collins, C.S. Newlon, Meiosis-specific formation of joint DNA molecules containing sequences from homologous chromosomes, Cell 76 (1) (1994) 65–75.
[149] A. Schwacha, N. Kleckner, Identification of joint molecules that form frequently between homologs but rarely between sister chromatids during yeast meiosis, Cell 76 (1) (1994) 51–63.
[150] A. Schwacha, N. Kleckner, Identification of double Holliday junctions as intermediates in meiotic recombination, Cell 83 (5) (1995) 783–791.
[151] L. Bell, B. Byers, Occurrence of crossed strand-exchange forms in yeast DNA during meiosis, Proc. Natl. Acad. Sci. U. S. A. 76 (1979) 3445–3449, (GENERIC) Ref Type: Generic.
[152] J.W. Szostak, T.L. Orr-Weaver, R.J. Rothstein, F.W. Stahl, The double-strand-break repair model for recombination, Cell 33 (1) (1983) 25–35.
[153] L.C. Kadyk, L.H. Hartwell, Sister chromatids are preferred over homologs as substrates for recombinational repair in *Saccharomyces cerevisiae*, Genetics 132 (2) (1992) 387–402.
[154] S.A. Bullard, S. Kim, A.M. Galbraith, R.E. Malone, Double strand breaks at the HIS2 recombination hot spot in *Saccharomyces cerevisiae*, Proc. Natl. Acad. Sci. U. S. A. 93 (23) (1996) 13054–13059.
[155] V. Rocco, A. Nicolas, Sensing of DNA non-homology lowers the initiation of meiotic recombination in yeast, Genes Cells 1 (7) (1996) 645–661.
[156] S. Keeney, N. Kleckner, Communication between homologous chromosomes: genetic alterations at a nuclease-hypersensitive site can alter mitotic chromatin structure at that site both in cis and in trans, Genes Cells 1 (5) (1996) 475–489.
[157] B. deMassy, F. Baudat, A. Nicolas, Initiation of recombination in *Saccharomyces cerevisiae* haploid meiosis, Proc. Natl. Acad. Sci. U. S. A. 91 (25) (1994) 11929–11933.
[158] L.A. Gilbertson, F.W. Stahl, Initiation of meiotic recombination is independent of interhomologue interactions, Proc. Natl. Acad. Sci. U. S. A. 91 (25) (1994) 11934–11937.
[159] D. Lydall, Y. Nikolsky, D.K. Bishop, T. Weinert, A meiotic recombination checkpoint controlled by mitotic checkpoint genes, Nature 383 (6603) (1996) 840–843.
[160] C. Barlow, M. Liyanage, P.B. Moens, C.X. Deng, T. Ried, A. Wynshaw-Boris, Partial rescue of the prophase I defects of Atm-deficient mice by p53 and p21 null alleles, Nat. Genet. 17 (4) (1997) 462–466.
[161] P.A. San-Segundo, G.S. Roeder, Pch2 links chromatin silencing to meiotic checkpoint control, Cell 97 (3) (1999) 313–324.
[162] L. Xu, B.M. Weiner, N. Kleckner, Meiotic cells monitor the status of the interhomolog recombination complex, Genes Dev. 11 (1) (1997) 106–118.
[163] A.M. Galbraith, S.A. Bullard, K. Jiao, J.J. Nau, R.E. Malone, Recombination and the progression of meiosis in *Saccharomyces cerevisiae*, Genetics 146 (2) (1997) 481–489.
[164] A. Bergerat, B. de Massy, D. Gadelle, P.C. Varoutas, A. Nicolas, P. Forterre, An atypical topoisomerase II from Archaea with implications for meiotic recombination, Nature 386 (6623) (1997) 414–417, [see comments].
[165] S. Keeney, C.N. Giroux, N. Kleckner, Meiosis-specific DNA double-strand breaks are catalyzed by Spo11, a member of a widely conserved protein family, Cell 88 (3) (1997) 375–384.
[166] A.F. Dernburg, K. McDonald, G. Moulder, R. Barstead, M. Dresser, A.M. Villeneuve, Meiotic recombination in *C. elegans* initiates by a conserved mechanism and is dispensable for homologous chromosome synapsis, Cell 94 (3) (1998) 387–398.
[167] K.S. McKim, A. Hayashi-Hagihara, *mei-W68* in *Drosophila melanogaster* encodes a Spo11 homolog: evidence that the mechanism for initiating meiotic recombination is conserved, Genes Dev. 12 (18) (1998) 2932–2942.
[168] N.M. Hollingsworth, B. Byers, *HOP1*: a yeast meiotic pairing gene, Genetics 121 (3) (1989) 445–462, [published erratum appears in Genetics 122 (3) (Jul 1989) 719].
[169] N.M. Hollingsworth, L. Goetsch, B. Byers, The *HOP1* gene encodes a meiosis-specific component of yeast chromosomes, Cell 61 (1) (1990) 73–84.
[170] N.M. Hollingsworth, L. Ponte, C. Halsey, MSH5, a novel MutS homolog, facilitates meiotic reciprocal recombination between homologs in *Saccharomyces cerevisiae* but not mismatch repair, Genes Dev. 9 (14) (1995) 1728–1739.
[171] N.M. Hollingsworth, A.D. Johnson, A conditional allele of the *Saccharomyces cerevisiae HOP1* gene is suppressed by overexpression of two other meiosis-specific genes: *RED1* and *REC104*, Genetics 133 (4) (1993) 785–797.
[172] D.B. Friedman, N.M. Hollingsworth, B. Byers, Insertional mutations in the yeast *HOP1* gene: evidence for multimeric assembly in meiosis, Genetics 136 (2) (1994) 449–464.
[173] N.M. Hollingsworth, L. Ponte, Genetic interactions between HOP1, RED1 and MEK1 suggest that MEK1 regulates assembly of axial element components during meiosis in the yeast *Saccharomyces cerevisiae*, Genetics 147 (1) (1997) 33–42.
[174] S. de los, N.M. Hollingsworth, Red1p, a MEK1-dependent phosphoprotein that physically interacts with Hop1p during meiosis in yeast, J. Biol. Chem. 274 (3) (1999) 1783–1790.
[175] J.M. Bailis, G.S. Roeder, Synaptonemal complex morphogenesis and sister-chromatid cohesion require Mek1-dependent phosphorylation of a meiotic chromosomal protein, Genes Dev. 12 (22) (1998) 3551–3563.
[176] K.M. Kironmai, K. Muniyappa, D.B. Friedman, N.M. Hollingsworth, B. Byers, DNA-binding activities of Hop1 protein, a synaptonemal complex component from *Saccharomyces cerevisiae*, Mol. Cell Biol. 18 (3) (1998) 1424–1435.
[177] B. Rockmill, G.S. Roeder, A meiosis-specific protein kinase homolog required for chromosome synapsis and recombination, Genes Dev. 5 (12B) (1991) 2392–2404.
[178] Y. Mao-Draayer, A.M. Galbraith, D.L. Pittman, M. Cool, R.E. Malone, Analysis of meiotic recombination pathways in the yeast *Saccharomyces cerevisiae*, Genetics 144 (1) (1996) 71–86.
[179] M.P. Maguire, Sister chromatid cohesiveness: vital func-

tion, obscure mechanism, Biochem. Cell Biol. 68 (11) (1990) 1231–1242.
[180] A.T. Carpenter, Chiasma function, Cell 77 (7) (1994) 957–962, [published erratum appears in Cell 80 (6), (1995 Mar 24): following 957].
[181] A.T. Carpenter, Thoughts on recombination nodules, meiotic recombination and chiasmata, in: R. Kucherlapati, G.R. Smith (Eds.), Genetic Recombination, American Society for Microbiology, Washington, DC, 1988, pp. 529–548.
[182] K.S. McKim, B.L. Green-Marroquin, J.J. Sekelsky, G. Chin, C. Steinberg, R. Khodosh, R.S. Hawley, Meiotic synapsis in the absence of recombination, Science 279 (5352) (1998) 876–878, [see comments].
[183] P.B. Moens, D.J. Chen, Z. Shen, N. Kolas, M. Tarsounas, H.Q. Heng, B. Spyropoulos, Rad51 immunocytology in rat and mouse spermatocytes and oocytes, Chromosoma 106 (4) (1997) 207–215.
[184] L.K. Anderson, H.H. Offenberg, W.M.H.C. Verkuijlen, C. Heyting, RecA-like proteins are components of early meiotic nodules in lily, Proc. Natl. Acad. Sci. U. S. A. 94, pp. 6868–6873.
[185] T. Ogawa, X. Yu, A. Shinohara, E.H. Egelman, Similarity of the yeast RAD51 filament to the bacterial RecA filament, Science 259 (5103) (1993) 1896–1899.
[186] P. Sung, S.A. Stratton, Yeast Rad51 recombinase mediates polar DNA strand exchange in the absence of ATP hydrolysis, J. Biol. Chem. 271 (45) (1996) 27983–27986.
[187] Z. Li, E.I. Golub, R. Gupta, C.M. Radding, Recombination activities of HsDmc1 protein, the meiotic human homolog of RecA protein, Proc. Natl. Acad. Sci. U. S. A. 94 (21) (1997) 11221–11226.
[188] G. Petukhova, S. Stratton, P. Sung, Catalysis of homologous DNA pairing by yeast Rad51 and Rad54 proteins, Nature 393 (6680) (1998) 91–94.
[189] A. Shinohara, H. Ogawa, T. Ogawa, Rad51 protein involved in repair and recombination in *S. cerevisiae* is a RecA-like protein, Cell 69 (3) (1992) 457–470, [published erratum appears in Cell 1992 Oct 2;71(1):following 180].
[190] M.E. Dresser, D.J. Ewing, M.N. Conrad, A.M. Dominguez, R. Barstead, H. Jiang, T. Kodadek, DMC1 functions in a *Saccharomyces cerevisiae* meiotic pathway that is largely independent of the RAD51 pathway, Genetics 147 (2) (1997) 533–544.
[191] A. Shinohara, S. Gasior, T. Ogawa, N. Kleckner, D.K. Bishop, *Saccharomyces cerevisiae* recA homologues RAD51 and DMC1 have both distinct and overlapping roles in meiotic recombination, Genes Cells 2 (10) (1997) 615–629.
[192] S.L. Gasior, A.K. Wong, Y. Kora, A. Shinohara, D.K. Bishop, Rad52 associates with RPA and functions with rad55 and rad57 to assemble meiotic recombination complexes, Genes Dev. 12 (14) (1998) 2208–2221.
[193] D.K. Bishop, RecA homologs Dmc1 and Rad51 interact to form multiple nuclear complexes prior to meiotic chromosome synapsis, Cell 79 (6) (1994) 1081–1092.
[194] T. Ashley, A.W. Plug, J. Xu, A.J. Solari, G. Reddy, E.I. Golub, D.C. Ward, Dynamic changes in Rad51 distribution on chromatin during meiosis in male and female vertebrates, Chromosoma 104 (1) (1995) 19–28.
[195] M. Tarsounas, T. Morita, R.E. Pearlman, P.B. Moens, RAD51 and DMC1 form mixed complexes associated with mouse meiotic chromosome cores and synaptonemal complexes, J. Cell Biol. 147 (2) (1999) 207–220.
[196] P.B. Moens, R. Freire, M. Tarsounas, B. Spyropoulos, S.P. Jackson, Expression and nuclear localization of BLM, a chromosome stability protein mutated in Bloom's syndrome, suggest a role in recombination during meiotic prophase, J. Cell Sci. 113 ((Pt 4)) (2000) 663–672.
[197] B. Rockmill, G.S. Roeder, The yeast med1 mutant undergoes both meiotic homolog nondisjunction and precocious separation of sister chromatids, Genetics 136 (1) (1994) 65–74.
[198] K. Yoshida, G. Kondoh, Y. Matsuda, T. Habu, Y. Nishimune, T. Morita, The mouse RecA-like gene *Dmc1* is required for homologous chromosome synapsis during meiosis, Mol. Cell 1 (5) (1998) 707–718.
[199] D.L. Pittman, J. Cobb, K.J. Schimenti, L.A. Wilson, D.M. Cooper, E. Brignull, M.A. Handel, J.C. Schimenti, Meiotic prophase arrest with failure of chromosome synapsis in mice deficient for Dmc1, a germline-specific RecA homolog, Mol. Cell 1 (5) (1998) 697–705.
[200] R. Scully, J. Chen, A. Plug, Y. Xiao, D. Weaver, J. Feunteun, T. Ashley, D.M. Livingston, Association of BRCA1 with Rad51 in mitotic and meiotic cells, Cell 88 (2) (1997) 265–275.
[201] J. Chen, D.P. Silver, D. Walpita, S.B. Cantor, A.F. Gazdar, G. Tomlinson, F.J. Couch, B.L. Weber, T. Ashley, D.M. Livingston et al., Stable interaction between the products of the *BRCA1* and *BRCA2* tumor suppressor genes in mitotic and meiotic cells, Mol. Cell 2 (3) (1998) 317–328.
[202] K.S. Keegan, D.A. Holtzman, A.W. Plug, E.R. Christenson, E.E. Brainerd, G. Flaggs, N.J. Bentley, E.M. Taylor, M.S. Meyn, S.B. Moss et al., The Atr and Atm protein kinases associate with different sites along meiotically pairing chromosomes, Genes Dev. 10 (19) (1996) 2423–2437, [see comments].
[203] G. Flaggs, A.W. Plug, K.M. Dunks, K.E. Mundt, J.C. Ford, M.R. Quiggle, E.M. Taylor, C.H. Westphal, T. Ashley, M.F. Hoekstra et al., Atm-dependent interactions of a mammalian chk1 homolog with meiotic chromosomes, Curr. Biol. 7 (12) (1997) 977–986.
[204] A.W. Plug, A.H. Peters, Y. Xu, K.S. Keegan, M.F. Hoekstra, D. Baltimore, P. de Boer, T. Ashley, *ATM* and *RPA* in meiotic chromosome synapsis and recombination, Nat. Genet. 17 (4) (1997) 457–461.
[205] A.W. Plug, A.H. Peters, K.S. Keegan, M.F. Hoekstra, P. de Boer, T. Ashley, Changes in protein composition of meiotic nodules during mammalian meiosis, J. Cell Sci. 111 (1998) 413–423, (Pt 4).
[206] A.W. Plug, C.A. Clairmont, E. Sapi, T. Ashley, J.B. Sweasy, Evidence for a role for DNA polymerase beta in mammalian meiosis, Proc. Natl. Acad. Sci. U. S. A. 94 (4) (1997) 1327–1331.
[207] D. Walpita, A.W. Plug, N.F. Neff, J. German, T. Ashley,

Bloom's syndrome protein, BLM, colocalizes with replication protein A in meiotic prophase nuclei of mammalian spermatocytes, Proc. Natl. Acad. Sci. U. S. A. 96 (10) (1999) 5622–5627.
[208] R. Freire, J.R. Marguia, M. Tarsounas, N.F. Lowndes, P.B. Moens, S.P. Jackson, Human and mouse homologs of *Schizosaccharomyces pombe rad1(+)* and *Saccharomyces cerevisiae RAD17*: linkage to checkpoint control and mammalian meiosis, Genes Dev. 12 (16) (1998) 2560–2573.
[209] P.B. Moens, M. Tarsounas, T. Morita, T. Habu, S.T. Rottinghaus, R. Freire, S.P. Jackson, C. Barlow, A. Wynshaw-Boris, The association of ATR protein with mouse meiotic chromosome cores, Chromosoma 108 (2) (1999) 95–102.
[210] Y. Xu, T. Ashley, E.E. Brainerd, R.T. Bronson, M.S. Meyn, D. Baltimore, Targeted disruption of ATM leads to growth retardation, chromosomal fragmentation during meiosis, immune defects, and thymic lymphoma, Genes Dev. 10 (19) (1996) 2411–2422, [see comments].
[211] C. Barlow, M. Liyanage, P.B. Moens, M. Tarsounas, K. Nagashima, K. Brown, S. Rottinghaus, S.P. Jackson, D. Tagle, T. Ried et al., Atm deficiency results in severe meiotic disruption as early as leptonema of prophase I, Development 125 (20) (1998) 4007–4017.
[212] J.W. Allen, D.J. Dix, B.W. Collins, B.A. Merrick, C. He, J.K. Selkirk, P. Poorman-Allen, M.E. Dresser, E.M. Eddy, HSP70-2 is part of the synaptonemal complex in mouse and hamster spermatocytes, Chromosoma 104 (6) (1996) 414–421.
[213] D.J. Dix, J.W. Allen, B.W. Collins, C. Mori, N. Nakamura, P. Poorman-Allen, E.H. Goulding, E.M. Eddy, Targeted gene disruption of Hsp70-2 results in failed meiosis, germ cell apoptosis, and male infertility, Proc. Natl. Acad. Sci. U. S. A. 93 (8) (1996) 3264–3268.
[214] W.D. Heyer, A.W. Johnson, D.N. Norris, D. Tishkoff, R.D. Kolodner, *Saccharomyces cerevisiae* proteins involved in hybrid DNA formation in vitro, Biochimie 73 (2–3) (1991) 269–276.
[215] C.C. Dykstra, K. Kitada, A.B. Clark, R.K. Hamatake, A. Sugino, Cloning and characterization of *DST2*, the gene for DNA strand transfer protein beta from *Saccharomyces cerevisiae*, Mol. Cell Biol. 11 (5) (1991) 2583–2592.
[216] Z. Liu, A. Lee, W. Gilbert, Gene disruption of a G4-DNA-dependent nuclease in yeast leads to cellular senescence and telomere shortening, Proc. Natl. Acad. Sci. U. S. A. 92 (13) (1995) 6002–6006.
[217] Z. Liu, W. Gilbert, The yeast KEM1 gene encodes a nuclease specific for G4 tetraplex DNA: implication of in vivo functions for this novel DNA structure, Cell 77 (7) (1994) 1083–1092.
[218] D.X. Tishkoff, B. Rockmill, G.S. Roeder, R.D. Kolodner, The sep1 mutant of *Saccharomyces cerevisiae* arrests in pachytene and is deficient in meiotic recombination, Genetics 139 (2) (1995) 495–509.
[219] M.P. Maguire, Homologous chromosome pairing. Philos, Trans. R. Soc. London B. Biol. Sci. 277 (955) (1977) 245–258.
[220] R. Egel, Synaptonemal complex and crossing-over: structural support or interference, Heredity (Edinburgh) 41 (2) (1978) 233–237.
[221] M. Egel-Mitani, L.W. Olson, R. Egel, Meiosis in *Aspergillus nidulans*: another example for lacking synaptonemal complexes in the absence of crossover interference, Hereditas 97 (1982) 179–187.
[222] D.B. Kaback, V. Guacci, D. Barber, J.W. Mahon, Chromosome size-dependent control of meiotic recombination, Science 256 (5054) (1992) 228–232.
[223] L.K. Anderson, A. Reeves, L.M. Webb, T. Ashley, Distribution of crossing over on mouse synaptonemal complexes using immunofluorescent localization of MLH1 protein, Genetics 151 (4) (1999) 1569–1579.
[224] Q.Q. Fan, F. Xu, M.A. White, T.D. Petes, Competition between adjacent meiotic recombination hotspots in the yeast *Saccharomyces cerevisiae*, Genetics 145 (3) (1997) 661–670.
[225] T.C. Wu, M. Lichten, Factors that affect the location and frequency of meiosis-induced double-strand breaks in *Saccharomyces cerevisiae*, Genetics 140 (1) (1995) 55–66.
[226] P. Ross-Macdonald, G.S. Roeder, Mutation of a meiosis-specific MutS homolog decreases crossing over but not mismatch correction, Cell 79 (6) (1994) 1069–1080.
[227] S.M. Baker, A.W. Plug, T.A. Prolla, C.E. Bronner, A.C. Harris, X. Yao, D.M. Christie, C. Monell, N. Arnheim, A. Bradley et al., Involvement of mouse Mlh1 in DNA mismatch repair and meiotic crossing over, Nat. Genet. 13 (3) (1996) 336–342, [see comments].
[228] A.L. Barlow, M.A. Hulten, Crossing over analysis at pachytene in man, Eur. J. Hum. Genet. 6 (4) (1998) 350–358.
[229] N. Hunter, R.H. Borts, Mlh1 is unique among mismatch repair proteins in its ability to promote crossing-over during meiosis, Genes Dev. 11 (12) (1997) 1573–1582.
[230] W. Edelmann, P.E. Cohen, M. Kane, K. Lau, B. Morrow, S. Bennett, A. Umar, T. Kunkel, G. Cattoretti, R. Chaganti et al., Meiotic pachytene arrest in MLH1-deficient mice, Cell 85 (7) (1996) 1125–1134.
[231] S.M. Baker, C.E. Bronner, L. Zhang, A.W. Plug, M. Robatzek, G. Warren, E.A. Elliott, J. Yu, T. Ashley, N. Arnheim, Male mice defective in the DNA mismatch repair gene PMS2 exhibit abnormal chromosome synapsis in meiosis, Cell 82 (2) (1995) 309–319.
[232] W. Edelmann, P.E. Cohen, B. Kneitz, N. Winand, M. Lia, J. Heyer, R. Kolodner, J.W. Pollard, R. Kucherlapati, Mammalian MutS homologue 5 is required for chromosome pairing in meiosis, Nat. Genet. 21 (1) (1999) 123–127.
[233] S.S. de Vries, E.B. Baart, M. Dekker, A. Siezen, D.G. de Rooij, P. de Boer, R.H. Te, Mouse MutS-like protein Msh5 is required for proper chromosome synapsis in male and female meiosis, Genes Dev. 13 (5) (1999) 523–531.
[234] R.H. Borts, J.E. Haber, Length and distribution of meiotic gene conversion tracts and crossovers in *Saccharomyces cerevisiae*, Genetics 123 (1) (1989) 69–80.
[235] R.H. Borts, M. Lichten, J.E. Haber, Analysis of meiosis-defective mutations in yeast by physical monitoring of recombination, Genetics 113 (3) (1986) 551–567.

[236] C. Goyon, M. Lichten, Timing of molecular events in meiosis in *Saccharomyces cerevisiae*: stable heteroduplex DNA is formed late in meiotic prophase, Mol. Cell Biol. 13 (1) (1993) 373–382.
[237] D.K. Nag, T.D. Petes, Physical detection of heteroduplexes during meiotic recombination in the yeast *Saccharomyces cerevisiae*, Mol. Cell Biol. 13 (4) (1993) 2324–2331.
[238] A. Storlazzi, L. Xu, L. Cao, N. Kleckner, Crossover and noncrossover recombination during meiosis: timing and pathway relationships, Proc. Natl. Acad. Sci. U. S. A. 92 (18) (1995) 8512–8516.
[239] L. Xu, M. Ajimura, R. Padmore, C. Klein, N. Kleckner, NDT80, a meiosis-specific gene required for exit from pachytene in *Saccharomyces cerevisiae*, Mol. Cell Biol. 15 (12) (1995) 6572–6581.
[240] W.Y. Miyazaki, T.L. Orr-Weaver, Sister-chromatid cohesion in mitosis and meiosis, Annu. Rev. Genet. 28 (1994) 167–187.
[241] D.P. Moore, T.L. Orr-Weaver, Chromosome segregation during meiosis: building an unambivalent bivalent, Curr. Top. Dev. Biol. 37 (1998) 263–299.
[242] J. Engebrecht, J. Hirsch, G.S. Roeder, Meiotic gene conversion and crossing over: their relationship to each other and to chromosome synapsis and segregation, Cell 62 (5) (1990) 927–937.
[243] L.O. Ross, R. Maxfield, D. Dawson, Exchanges are not equally able to enhance meiotic chromosome segregation in yeast, Proc. Natl. Acad. Sci. U. S. A. 93 (10) (1996) 4979–4983.
[244] D.D. Sears, J.H. Hegemann, J.H. Shero, P. Hieter, Cis-acting determinants affecting centromere function, sister-chromatid cohesion and reciprocal recombination during meiosis in *Saccharomyces cerevisiae*, Genetics 139 (3) (1995) 1159–1173.
[245] A.J. Dietrich, J. van Marle, C. Heyting, A.C. Vink, Ultrastructural evidence for a triple structure of the lateral element of the synaptonemal complex, J. Struct. Biol. 109 (3) (1992) 196–200.
[246] A.F. Straight, W.F. Marshall, J.W. Sedat, A.W. Murray, Mitosis in living budding yeast: anaphase A but no metaphase plate, Science 277 (5325) (1997) 574–578.
[247] P.A. Wigge, O.N. Jensen, S. Holmes, S. Soues, M. Mann, J.V. Kilmartin, Analysis of the *Saccharomyces* spindle pole by matrix-assisted laser desorption/ionization (MALDI) mass spectrometry, J. Cell Biol. 141 (4) (1998) 967–977.