Published in final edited form as:

Curr Opin Cell Biol. 2010 December ; 22(6): 744–751. doi:10.1016/j.ceb.2010.08.016.

Meiosis: Making a Break for It

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Summary

The perpetuation of most eukaryotic species requires differentiation of pluripotent progenitors into egg and sperm and subsequent fusion of these gametes to form a new zygote. Meiosis is a distinguishing feature of gamete formation as it leads to the two-fold reduction in chromosome number thereby maintaining ploidy across generations. This process increases offspring diversity through the random segregation of chromosomes and the exchange of genetic material between homologous parental chromosomes, known as meiotic crossover recombination. These exchanges require the establishment of unique and dynamic chromatin configurations that facilitate cohesion, homologue pairing, synapsis, double strand break formation and repair. The precise orchestration of these events is critical for gamete survival as evidenced by the majority of human aneuploidies that can be traced to defects in the first meiotic division[1] This review will focus on recent advances in our understanding of key meiotic events and how coordination of these events is occurring.

Introduction

The preservation of ploidy and maintenance of genomic integrity depend on the accurate segregation of chromosomes into gametes during the process of meiosis. The landmarks events of homologue synapsis and crossover formation occur during the first meiotic division and are subject to intense oversight and control to ensure the proper timing and execution of these events.

Over the past ten years, substantial progress has been made in model systems characterizing key proteins that facilitate chromosome pairing, synapsis and DSB formation and repair and have revealed remarkable functional, if not sequence, conservation. The advent of advanced imaging techniques is greatly expanding our understanding of these processes as they occur *in vivo* and is revealing new complexities. In addition, lessons from mitotic cell cycle checkpoints, DNA damage repair, and epigenetics brought to bear on meiosis have yielded insights into the mechanisms of crossover (CO) control and coordination of meiotic events. The emerging picture is of known players: cohesin, condensin, histone modifications, specific DNA binding sites, and repair proteins mixing in new ways with meiosis specific subunits to execute the orderly segregation of homologous chromosomes into developing gametes.

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Meiotic Entry

The decision to exit the proliferative state and begin meiosis marks the differentiation of progenitor cells into gametes. Like other developmental decisions, gamete production requires the execution of a unique transcriptional program. In yeast, the transcription factor Ime1 controls early gene expression and failure to express Ime1 accounts for the inability of aged yeast to execute the meiotic cell cycle[2]. Meiotic success also hinges on the ability to synchronize the meiotic transcriptional program with cell cycle progression and cell growth. This is achieved in yeast by coupling double strand break formation with progression of the replication fork[3]; but additional strategies have also been uncovered. In *C. elegans*, where meiotic entry is guided by a translational regulatory cascade downstream of Notch signaling, Puf domain RNA-binding proteins control expression of SC components and cell cycle genes[4]. In Arabidopsis, nuclear import of key meiotic proteins by PHS1[5] and MPA[6] proteins coordinates these processes. Furthermore, studies in male mice suggest that the inner nuclear envelop protein, Sun1, which functions in meiotic chromosome pairing also affects transcription of reproduction genes[7]. A dissonance between these events, as exemplified by the *Drosophila mitoshell* mutant[8], can lead to germ cell arrest, apoptosis, or aneuploidy.

Pairing at the periphery

The early events of meiotic prophase occur in association with the nuclear envelope (NE). Recent studies indicate that the NE actively facilitates and coordinates meiotic chromosome behaviors, mediating the initial recruitment of chromosomes to the NE; non-homologous centromere coupling, telomere bouquet formation, homologue alignment, pairing, as well as the initiation of synapsis and double strand breaks. Dissociation from the NE correlates with pachytene progress, full synapsis and CO formation.

Detailed mechanistic studies in yeast have revealed a requirement for non-homologous centromere coupling at the NE prior to full homolog alignment[5,9–11]. Since release from coupling is dependent on Spo11, the enzyme that makes meiotic double strand breaks (DSBs), this process may prevent centromere-proximal COs which lead to nondisjunction[12–14]. The possibility that active mechanisms are required to sequester repetitive DNA, like the centromere, during the homology search may be generalizable, for example, the mouse *maelstrom* mutant upregulates transposons and incurs meiotic errors[15].

3D time-lapse microscopy has revealed that chromosome movements at the NE are a conserved feature of early prophase (Figure 1). Anchoring to the nuclear periphery by associations with SUN/KASH domain proteins bridges dynein to the chromosomes[16–18], allowing cytoplasmic forces to move chromosomes within the nucleoplasm[19–21]. Although previous hypotheses had predicted that these movements were required to mediate homolog pairing, the emerging view is that these movements are required to prevent inappropriate attachments and entanglements between non-homologous chromosomes (reviewed in[22]). Homologous associations may counteract the pull of dynein to create mechanical stress[23] that leads to synapsis (Figure 1). The extent, combinations, and duration of Sun-1 phosphorylation serves as a readout of successful pairing and synapsis, regulating further progression into pachytene[24]. Identifying the factor(s) that modify Sun-1 and how these modifications alter protein-protein interactions at the NE will significantly improve our understanding of how meiotic events are temporally and spatially coordinated.

The chromosome axis

The successful segregation of meiotic chromosomes requires substantial reorganization of chromosome architecture after meiotic S phase. First it is needed to establish the chromosome axes or axial elements (AEs) between conjoined sisters and then to build the SC, the meiotic specific glue between homologs. AEs are essential for the formation of COs which in turn dictate the stepwise removal of cohesion between homologs and sisters for the equational and reductional divisions of the first and second meiotic divisions, respectively[25].

The cohesin complex is the major complex required for sister chromatid cohesion in both mitosis and meiosis. Mitotic and meiotic cohesins differ in subunit composition, with the kleisin subunit SCC1 replaced by Rec8 in meiosis. Nevertheless, in multiple systems, mitotic cohesins are associated with meiotic chromosomes axes[26–28]. Additional kleisins in worms and plants suggest increased meiotic cohesin diversity and complexity[29,30]. For example, the worm kleisins, Rec-8, Coh-3 and Coh-4 are redundantly required for assembly of the AE but only Rec-8 functions in sister chromatid cohesion[30]. Despite the involvement of cohesin complexes, the direct role of cohesion, per se, in AE assembly and other meiotic processes remains an open question.

The synaptonemal complex

The SC is a tripartite structure connecting AEs by perpendicular transverse filament proteins (TFs) and overlapping central elements (CE)[31]. Although the structural elements of the SC have been defined in most model organisms, the dynamics of SC polymerization are less well understood (Figure 2).

Mutational analysis has recently revealed a role for CE proteins, mammalian SYCE2[32,33] and TEX12[34], the *Drosophila* corona[35], and budding yeast Zip2, Zip3, and Zip4[36] in TF polymerization. A mechanistic understanding of how these proteins directly control TF formation awaits identification of additional partners and mapping of functional interactions.

The propensity of the SC-associated coiled-coil proteins to self-assemble *in vitro* and the premature synapsis of non-homologous chromosomes in several genetic backgrounds implicate mechanisms to prevent premature synapsis until homology has been ascertained. A number of studies define the AE as pivotal regulator of synapsis: both cohesins and axis-associated HORMA domain proteins are required to prevent non-homologous synapsis and to coordinate meiotic events[37].

Developments in light microscopy, specifically 3D structured illumination[38], have also allowed for the detailed examination of the chromosome axis and SC[39,40] revealing the coiling of the AE after SC formation into left-handed helices[39]. Similar techniques have been applied to the analysis of the nuclear envelope, lamina, and chromatin during mitotic prophase[41]. Combining these studies in meiotic mutants, perhaps using the nematode *C. elegans*, where the germline is organized in a temporal and spatial gradient, offers great promise to expand our understanding of the molecular organization of meiotic chromatin, the SC, and recombination foci. Future advances in ultra-resolution microscopy and time-lapse imaging promise to even further these analyses to provide mechanistic understanding of meiotic chromosome morphogenesis.

The recombination landscape

Meiotic recombination is initiated by the formation of double strand breaks (DSBs) by the conserved endonuclease Spo11[42]; yet, the mere association of Spo11 with DNA is

insufficient for cleavage[43–45]. Targeting and activity of Spo11 requires accessory factors, nine of which have been characterized in *S. cerevisiae*[46]. The growing list of genes required for DSB formation in other model systems suggests that functional rather than structural homology has been preserved. This lack of conservation is perhaps no longer surprising given our growing understanding of the flexibility in the chromosomal features that promote DSB formation.

Crossovers do not occur arbitrarily across the genome; but rather at preferred chromosomal locations known as hotspots[47]. As with other chromosomal phenomena, e.g. transcription and replication, both DNA sequence and higher order chromosome structures influence protein accessibility and activity to DSB sites. Specific DNA binding motifs, often the docking sites of transcription factors, have been identified in yeasts, mice and humans[47,48]. No single site, however, can explain the regulation of all hotspots. Indeed in *S. pombe*, it is now clear that multiple classes of hotspot-associated DNA sites exist[49], leading to the hypothesis that, like transcriptional enhancer sequences, recombination hotspots may require the concerted activity of multiple, potentially disparate binding sites[50]. These studies, together with the discovery of degenerate sequences enriched at many human hotspots[51], illuminate how hotspots can vary within and between individuals.

The association of hotspots with open chromatin and the ability to modulate hotspots through manipulation of nucleosome accessibility were among the first indicators that higher order DNA structures would have a critical role in CO formation[52–54]. As with other aspects of chromosomal dynamics, histone post-translational modifications (HPTMs) have differential effects on CO formation depending on the chromosomal context[55–58]. Yet some determinants of higher order DNA structure appear to have more universal roles in CO formation. Of particular interest is trimethylated histone H3 (H3K4me3) because it is found at a majority of hotspot-associated DSB initiation sites in yeast and mammals[59,60] and because PRDM9, a H3K4 histone methyltransferase, was identified as a mammalian hotspot-associated protein[61–63]. How HPTMs and associated enzymes directly modulate Spo11 activity is not known, but these studies lay the groundwork for substantive progress in this area.

Condensins are also required for meiotic chromosome compaction and segregation[64]. Recent studies identified three condensin complexes in *C. elegans* which serve unique mitotic and meiotic roles[65,66]. Importantly, the condensin I complex influences CO formation by manipulating chromosome axis length, thereby altering sites of DSB formation[66]. Together the studies of condensin and PRDM9 bring to light that single amino acid changes in key proteins can dramatically alter the CO landscape, thus providing a mechanism for the rapid evolution of recombination hotspots and variations between individuals[66–68]. These studies also provide plausible mechanisms how environmental factors might directly impinge on CO formation[69].

Genome-wide mapping of DSBs, COs and NCOs in individual wild type and mutant meiotic cells has revealed new insights into the natural variability of the crossover landscape and the molecular forces that are shaping it[70,71]. This work will be further advanced by the advent of deep sequencing technologies. By comparing the overall CO landscape with the emerging profile of chromatin associated proteins profiles from large scale ChIP-seq projects[72], causal links between specific chromatin binding proteins and COs can be established.

Crossover resolution

Cleavage of DNA by Spo11 creates DSBs that are resected to expose 3' single strand overhangs. These load DMC1 and/or Rad51 to form nucleoprotein filaments that catalyze strand invasion. The extended invading strands are then processed to either form CO or NCO products. In most organisms, the number of DSBs exceeds the number of resulting COs, indicating that excess DSBs are shunted into non-crossover outcomes (NCO). Whereas COs require double Holliday junction (dHJ) intermediates, NCOs can occur either by dHJs or by synthesis-dependent strand annealing. Two recent studies from the Boulton lab expand our mechanistic understanding of post-strand invasion events and the steps at which the CO/NCO decision can be made. One study, built upon their observations that human RTEL can displace D loops *in vitro*[73], shows that RTEL functions in *C. elegans* meiosis as an antirecombinase, disassembling strand invasion intermediates and thereby promoting NCO formation[74]. The other study helps to elucidate how Rad51 is a prerequisite for further processing[75] by revealing a redundant pathway for Rad51 removal from double stranded DNA filaments generated after strand exchange intermediates[76].

Regulation in the formation of CO/NCO product can also occur at the final step in CO formation: the cleavage of dHJs. The discovery of multiple resolvase complexes(reviewed in[77]) raises new questions about how alternative complexes are recruited and assembled, whether they act redundantly or are required to promote specific outcomes. The further biochemical and genetic characterization of resolvase complexes is likely to provide insight into CO control, as well as more general mechanisms that promote genome integrity.

Crossover control

CO control can be exerted either at the stage of DSB formation or at the commitment to CO or non-crossover (NCO) outcomes. The ultimate goal of CO control is two-fold: ensuring that each chromosome receives a CO; and promoting favorable placement of COs. CO assurance (COA) mechanisms are necessitated by the requirement for CO on each chromosome. One simple aspect of COA is the formation of a vast excess of DSBs versus COs, the "many are called, but few are chosen" model. Crossover homeostasis (CH) is another aspect of COA and functions to influence repair outcomes, promoting CO outcomes at the expense of NCO when DSB substrates are limiting[78]. For example, when hotspot usage was restricted, CH was manifest by the activation of COs in otherwise cold regions of the genome. Meiotic checkpoints (discussed below) are part and parcel of COA as they cull (or delay) nuclei that have failed during the process of CO formation.

COs are distributed non-randomly along a chromosome indicating that CO placement is regulated. CO placement reflects the cumulative action of DSB interference[45] and crossover interference (COI)[79]. The former describes the competition between and mutual exclusion of nearby hotspots; the latter explains the decreased probability of CO in adjacent genetic regions. Although COI has been known for many years and is clearly under genetic control, a precise mechanistic understanding of COI is lacking. Recent work has revealed that both CO and NCO can be subject to COI. Are different aspects of CO control manifestations of the same underlying process? Recent evidence for CH and COI is conflicting. One on hand, mutational analysis in yeast and worms found a concomitant decrease in crossover homeostasis when COI was affected[70,80,81]. On the other hand, analysis of a novel ZMM mutant in *spo16* revealed reduced CO numbers, (indicative of decreased CH) but maintenance of COI, suggesting that these processes can be independently regulated[82].

Meiotic checkpoints

The faithful execution of meiotic events is essential to prevent chromosome nondisjunction and concomitant aneuploidy. The substantial investment of resources into the formation of healthy, euploid egg and sperm is underscored by numerous quality assurance mechanisms. The DNA damage checkpoint, synapsis checkpoint and recombination checkpoint can induce cell cycle delay, arrest, or apoptosis depending on the germline context (reviewed in [83]). An additional checkpoint that monitors whether each chromosome has received a crossover is thought to exist, although molecular insight into this checkpoint is lacking [84]. Although prodigious progress has been made in deciphering checkpoint mechanisms, which intermediates that are being sensed, how they trigger the checkpoint, and why the outcomes differ in different organisms are pressing questions.

One interesting aspect of germline quality control is MSUC or meiotic silencing of unpaired chromatin and its specialization, MSCI or meiotic sex chromosome inactivation. MSCI of XY chromosomes in mammals and similar process on ZW chromosomes in birds [85] imply that silencing of sex chromosomes is important for gamete viability in the heterogametic sex. The unsynapsed chromosome axes of the pseudo-paired X and Y are recognized by the repair proteins BRCA1 and ATR, leading to phosphorylation of H2AX followed by heterochromatinization, silencing and compartmentalization in the XY body. Similar modifications promote MSUC on subsets of unsynapsed autosomes in both spermatogenesis and oogenesis leading to germ cell attrition due to downstream defects in germline transcription [86–88]. In *C. elegans*, acquisition of heterochromatic silencing of a lone X chromosome, as in sex transformed XO females, does not lead to apoptosis, but rather allows the X to escape checkpoint detection [89]. Thus, silencing of unpaired sex chromosomes appears to be a conserved feature of germline development that allows them to escape detection by otherwise robust meiotic checkpoint mechanisms. From an evolutionary standpoint, the co-opting of MSUC for MSCI may be a driving force behind XY evolution.

Conclusions

The successful segregation of chromosomes in meiosis exemplifies how cells have devised mechanisms to coordinate, execute and monitor complex cellular processes. From the decision to enter the meiotic cell cycle, to the interdependence of synapsis and DSB formation and subsequent chromosome remodeling, cell cycle progression is intimately connected to the molecular events of CO recombination. While many of the players involved in pairing, synapsis and DSB repair are known, the next challenge is to determine how these players functionally interact and provide the mechanistic insight into their control. The last several years have also been instrumental in defining a role for higher order DNA structures on the assembly of the chromosome axis and regulation of CO distribution and frequency. Future studies will focus on how chromatin associated proteins guide meiotic chromosome morphogenesis and shape CO dynamics. The application of advanced genomic technologies, proteomics, and advanced microscopy with traditional genetic approaches is sure to yield profound insights in meiotic processes.

Acknowledgments

The author thanks Olivia McGovern and Cynthia Wagner for critically reading of the manuscript. JLY is funded by start-up funds from Magee-Womens Research Institute and NIH grant # K01AG031296.

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Figure 1.

Attachment to the nuclear envelope promotes chromosomes movements and homologous attachments. (A) A SUN/KASH domain complex bridges the nuclear envelope connecting with dynein on the cytoplasmic face. Chromosomes attach via telomeres or specialized pairing center sequences to the NE complex. In *C. elegans*, Sun-1 phosphorylation (black circle on SUN protein with attached chromosome) early in zygotene is required for subsequent events. (B) The SUN/KASH/chromosomal foci cluster together and mature into large patches, as additional phosphorylation of Sun-1 is observed. In patches, dynein-mediated forces stress chromosomes, leading to detachment of nonhomologous attachments and synapsis and homologous ones. (C) As homologues fully synapse and execute DSB repair, SUN-1 phosphorylation status again changes, leading to dispersal of chromosomes into pachytene morphology.

Figure 2.

Chromosome axis morphogenesis and coordination of meiotic events. (A) The chromosome axis is established by interdependent loading of cohesins and HORMA domain proteins. Condensin determines axis length and chromosomal loop organization. Double strand breaks are made in the loop regions, and strand invasion promotes synapsis which (B) proceeds polymerizes bi-directionally and is facilitated by central element proteins. Due to the action of crossover interference, additional strand invasion events may be shunted into formation of non-crossovers. Recent studies reveal of the rotation of mature synapsed axes to form a left-handed helix.