Tansley review

Meiosis evolves: adaptation to external and internal environments

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Summary

Meiosis is essential for the fertility of most eukaryotes and its structures and progression are conserved across kingdoms. Yet many of its core proteins show evidence of rapid or adaptive evolution. What drives the evolution of meiosis proteins? How can constrained meiotic processes be modified in response to challenges without compromising their essential functions? In surveying the literature, we found evidence of two especially potent challenges to meiotic chromosome segregation that probably necessitate adaptive evolutionary responses: whole-genome duplication and abiotic environment, especially temperature. Evolutionary solutions to both kinds of challenge are likely to involve modification of homologous recombination and synopsis, probably via adjustments of core structural components important in meiosis I. Synthesizing these findings with broader patterns of meiosis gene evolution suggests that the structural components of meiosis coevolve as adaptive modules that may change in primary sequence and function while maintaining three-dimensional structures and protein interactions. The often sharp divergence of these genes among species probably reflects periodic modification of entire multiprotein complexes driven by genomic or environmental changes. We suggest that the pressures that cause meiosis to evolve to maintain fertility may cause pleiotropic alterations of global crossover rates. We highlight several important areas for future research.

I. Introduction

Meiosis is essential for fertility in sexually reproducing eukaryotes. This special cell division precisely halves the number of chromosomes and produces haploid gametes or spores. The progression of meiosis, as well as its core structures and processes, is conserved across kingdoms (Villeneuve & Hillers, 2001; Gerton & Hawley, 2005; Mercier & Grelon, 2008). Yet the proteins that orchestrate meiosis are often surprisingly divergent in primary sequence, and several recent studies have reported that meiosis genes can show evidence of directional selection in natural populations (Turner et al., 2008; Anderson et al., 2009; Chowdhury et al., 2009; Kong et al., 2014; Wright et al., 2015). Why this occurs is not yet clear, but environmental factors have been hypothesized as a cause (Turner et al., 2008; Anderson et al., 2009; Wright et al., 2015). While efficient meiosis is critical for fertility, the process can indeed
be perturbed, for example by environmental factors, leading to deleterious outcomes such as reduced fertility or aneuploidy (Hassold & Hunt, 2001; Inoue & Lupski, 2002).

Understanding the challenges that compromise meiosis, as well as solutions that can evolve, has important implications for our basic understanding of evolutionary processes, as well as human health and crop improvement. While many factors are known to affect meiosis, in our literature searches we identified two commonly encountered factors that stand out as being capable of causing outright failures of meiotic processes, and thus probably necessitate meiotic adaptation: whole-genome duplication (WGD) and temperature. How (and just as importantly, why) constrained processes such as meiosis can be modified by evolution without affecting essential roles remains largely unknown.

An aspect of meiosis that appears to be especially sensitive to perturbation is the suite of chromosome management processes of meiosis I that culminate in homologous recombination, chromosome pairing, and synopsis (Nebel & Hackett, 1961; Bayliss & Riley, 1972; Henderson, 1988; Loidl, 1989; Blat et al., 2002). The resulting DNA exchanges are highly relevant in population genetics and breeding. Crossover rates are well known to vary among species and even within them (Sanchez-Moran et al., 2002; López et al., 2012; Bauer et al., 2013), and extensive theory has sought to explain the causes and consequences of this variation (e.g. Otto & Barton, 1997, 2001; Marais & Charlesworth, 2003; Roze & Barton, 2006; Webster & Hurst, 2012). We suggest that at least some of the observed crossover rate variation may reflect the particular sensitivity of structural meiotic components to perturbation, and could be rooted in part in meiotic adaptation to genomic or environmental challenges. Much remains to be discovered about the adaptive evolution of meiosis, but now is an exciting time in which results from older studies that demonstrated many relevant trends can be revisited with newer approaches to answer longstanding questions. To contextualize our discussion, we define key terms in Box 1, and illustrate relevant meiotic stages and the progression of crossover formation in Box 2.

II. Whole-genome duplication and the evolutionary adjustment of meiosis

WGD is a dramatic mutation that abruptly doubles the chromosome complement of a genome, resulting in polyploidy. WGD has occurred in most eukaryotic lineages, and is implicated in adaptation, as well as phenotypic and genetic novelty (Gilles & Randolph, 1951; Hazarika & Rees, 1967; Jauhar, 1970; Gibson & Spring, 1998; Kellis et al., 2004; Dehal & Boore, 2005; Solits et al., 2007, 2014; te Beest et al., 2012; Jiao & Paterson, 2014). In plants, extant cytotypic variants occur in many species and the majority of our most important crops are polyploids (Solís et al., 2007; Renney-Byfield & Wendel, 2014). But WGD initially poses substantial challenges for meiotic chromosome segregation. Neopolyploids, saddled with a meiotic program inherited from diploids, often form aberrant associations among the additional homologs (called multivalents; Fig. 1) in meiosis I that can cause missegregation and losses of fertility (Myers, 1945; McCollum, 1958; Hazarika & Rees, 1967; Charpentier et al., 1986; Schwarzacher-Robinson, 1986; Hassan & Ahmad, 1999; Ramsey & Schemske, 2002; Yant et al., 2013). Many established polyploids, however, form mostly or only diploid-like bivalents during meiosis (Dawson, 1941; Solits & Rieseberg, 1986; Krebs & Hancock, 1989; Wolf et al., 1989; Yant et al., 2013), demonstrating that solutions to WGD can evolve. Are the core processes of meiosis evolutionarily adjusted to suppress multivalent formation? The answer seems to be yes, although mechanisms vary among species.

There are two major types of polyploid (although intermediates exist between these). Autopolyploids form by genome duplication within species by somatic doubling or from fusion of unreduced gametes (Ramsey & Schemske, 1998; Mason & Pires, 2015) and thus have no prior differentiation among constituent genomes. Allopolyploids, by contrast, form by hybridization between different species or divergent populations, coupled with WGD.

<table>
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<th>Box 1 Glossary</th>
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<tr>
<td><strong>Autopolyploid</strong>: polyploid resulting from genome duplication in a single species.</td>
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<tr>
<td><strong>Allopolyploid</strong>: polyploid resulting from hybridization of at least somewhat genetically distinct taxa followed by genome duplication.</td>
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<tr>
<td><strong>Neopolyploid</strong>: newly formed polyploid, for example within a few generations.</td>
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<tr>
<td><strong>Axis</strong>: linear proteinaceous structure that forms at the base of chromatid loops, links sister chromatids, and forms a context for crossover formation and maturation, as well as synaptonemal complex assembly.</td>
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<tr>
<td><strong>Synaptonemal complex (SC)</strong>: tripartite proteinaceous structure consisting of a central element that forms between the axial elements (called lateral elements in SC) of homologous chromosomes during meiotic prophase I.</td>
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<td><strong>Chiasma</strong>: cytological manifestation (visible in diakinesis-metaphase I) of DNA exchange between homologous chromosomes.</td>
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<tr>
<td><strong>Crossover (CO)</strong>: physical site of DNA exchange between homologous chromosomes.</td>
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<td><strong>Crossover interference (COI)</strong>: the observation that crossovers are more rarely formed in proximity to one another than expected by chance.</td>
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<td><strong>Homologs</strong>: equivalent copies of two chromosomes; in diploids, one is inherited from each parent.</td>
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<tr>
<td><strong>Homeologs (or homoeologs)</strong>: chromosomes that are more distantly related than homologs and derived from distinct parental genomes, but still clearly have a common origin.</td>
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<td><strong>Bivalent</strong>: paired homologous chromosomes.</td>
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<td><strong>Multivalent</strong>: chromosomes associated in groups of more than two (e.g. quadrivalents are groups of four and trivalents groups of three).</td>
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<tr>
<td><strong>Univalent</strong>: an unpaired chromosome that will segregate randomly in meiosis I and/or can form micronuclei and therefore not be represented in meiosis I products.</td>
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and therefore harbor two or more at least somewhat distinct sets of chromosomes (Ladizinsky, 1973; Sybenga, 1973; Sears, 1976; Jenkins & Rees, 1991; Jenczewski et al., 2003; Grandont et al., 2013). The evolved solutions to meiotic problems in auto- and allopolyploids appear to be at least somewhat distinct, but a prime target for selection in both types appears to be cytological

**Box 2** Key steps in meiotic prophase I relevant to crossover formation and synapsis

**Prophase I**

- **G2:** double blue and red bands illustrate replicated sister chromatids (DNA synthesis of each sister occurs during premeiotic S-phase; not shown here). The zoomed-in portion (i) shows the two homologs (red and blue), each consisting of identical dual sisters, with components of the cohesion complex (SYN1, SMC1/3 and SCC3) loaded as foci, thus creating a scaffold for the meiosis-specific axis components ASY1/ASY3 to bind in localized foci (blue and green circles). DNA double-strand break (DSB) complexes containing SPO11 and its accessory proteins (dark circles) localize to the chromatin loops, and then migrate to protoaxis complexes to create DSBs (gray arrow). (ii) A single strand of each of the homologs, with a resected DSB on one of them.

- **Leptotene:** homologous chromosomes pair and align with recombination nodules between them (dark circles). (iii) The axes (consisting of ASY1 and ASY3; blue and green circles) form linear structures with chromatin loops extending from them. The recombination nodules (dark circles) consist of protein complexes including the recombinases RAD51 and DMC1 which perform a DNA base homology search by invading the nonsister homolog duplex. This ‘strand invasion’ stage is illustrated below (iv).

- **Zygotene:** chromosomes remain aligned, but fewer recombination nodules are present. (v) The synaptonemal complex (SC), a proteinaceous structure consisting primarily of the central element protein ZYP1 in plants, nucleates at recombination nodules and begins to form linear structures that bring the homologs closer together. (vi) Strand invasion interactions are stabilized by extension of the invading sequence.

- **Pachytene:** synapsis is complete; the SC extends the full length of each bivalent and few recombination nodules remain. (vii) The SC has matured into a linear structure spanning the two axes (now called lateral elements). Recombination nodules maturing as crossover sites are marked as a future crossover (CO) site by MLH1/3 and HEI10. (viii) A double Holliday junction recombination intermediate has formed between the strands.

- **Diplotene/diakinesis:** the SC and the axes break down and the homologous chromosomes remain attached at chiasmata (cytological sites of COs) (ix). (x) At this stage, the double Holliday junction has been resolved into a CO and the homologs have physically separated.

- **Metaphase I:** chromosomes attach to the spindle via their centromeres and tension builds to pull homologs apart which remain tethered to one another by chiasmata (xi). At least a single ‘obligate’ CO is essential for correct chromosome orientation at metaphase I (xii) so that homologs segregate reliably at anaphase I (xii). Sister chromatids subsequently segregate during meiosis II.

**G2:** double blue and red bands illustrate replicated sister chromatids (DNA synthesis of each sister occurs during premeiotic S-phase; not shown here). The zoomed-in portion (i) shows the two homologs (red and blue), each consisting of identical dual sisters, with components of the cohesion complex (SYN1, SMC1/3 and SCC3) loaded as foci, thus creating a scaffold for the meiosis-specific axis components ASY1/ASY3 to bind in localized foci (blue and green circles). DNA double-strand break (DSB) complexes containing SPO11 and its accessory proteins (dark circles) localize to the chromatin loops, and then migrate to protoaxis complexes to create DSBs (gray arrow). (ii) A single strand of each of the homologs, with a resected DSB on one of them.

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‘diploidization’ of meiosis via suppression of multivalent associations. Interestingly, in several species at least some degree of cytological stabilization can be achieved in neopolyploids after just a few generations of selection for fertility (Gilles & Randolph, 1951; Srivastava & Lavania, 1990; Santos et al., 2003). The molecular mechanism underlying the observed rapid changes in multivalent frequencies remains unknown, but it seems likely that epigenetic modifications play a role (Henderson, 2012).

Fig. 1 Examples of chromosome associations in tetraploid meiosis. (a) Top panels (i–iii) show four homologous chromosomes (each a different color) aligned with early recombination nodules (black ovals) with stretches of synaptonemal complex (SC) beginning to initiate (bars between chromosomes). (ai) Set with four chiasmata situated such that, as the SC extends in zygotene, the homologs have a pairing partner switch (PPS) in the middle; these structures often show nondisjunction at anaphase I. (aii) Set of chromosomes with two chiasmata, with the brown homolog experiencing two crossovers and the red none, leaving it as an unpaired univalent which will segregate randomly or be lost from the chromosome set. (iiii) Set of four homologs consolidated by two chiasmata such that pairing is as two bivalents; these segregate stably in meiosis just as in diploids. (b) The process of SC dissolution and reassembly thought to give rise to bivalents in polyploids that are able to resolve PPS sites. (bi) A multivalent with a single PPS, with blue arrows indicating sites of SC instability near the PPS where dissolution may initiate. (bii) SC reassembles along pairs of homologs (gray arrows); centromere locations are indicated with orange octagons. (biii) This process generates bivalents that show regular disjunction in metaphase I (biv). (c) The likely trigger of the process described in (b) has some similarities to the interlock resolution that occurs in diploids, where trapped nonhomologous chromosomes prevent full SC extension and initiate a resolution process dependent on MLH1 and Topoisomerase II; it is noteworthy that, in many polyploids, SC failures are often also associated with failures in interlock resolution. (d, e) Pachytene/diakinesis structures of unresolved multivalents with incomplete SC extension caused by PPS sites (d, e, left panels) and how these configure in metaphase I (d, e, right panels). (d) An unresolved multivalent with a single PPS can resolve in two distinct ways (d versus e), both of which result in complex multivalents in metaphase I that may cause chromosome missegregation. The configuration in (e) is called a ‘ring’ multivalent. (f) Multivalents with a single PPS and three crossovers have incomplete synopsis and form ‘chain’ multivalents in metaphase I. (g) A trivalent plus univalent configuration that causes random segregation or loss of the unpaired red chromosome and aneuploidy with one meiosis I product probably receiving only a single copy (brown). These configurations have been shown in most polyploids to be more damaging to fertility than quadrivalents.
1. Adaptation to WGD in autopolypsids

In autopolypsids, all duplicated chromosome copies are homologous, and in neopolypsids, multivalents often prevail in meiosis (Fig. 1) (McCollum, 1958; Charpentier et al., 1986; Schwarzacher-Robinson, 1986; Hassan & Ahmad, 1999; Ramsey & Schemske, 2002; Yant et al., 2013). By contrast, most established autopolypsids are cytologically diploidized, meaning they primarily form bivalents at metaphase I even though chromosome associations among available homologs usually remain random (Dawson, 1941; Soltis & Rieseberg, 1986; Krebs & Hancock, 1989; Wolf et al., 1989; Hollister et al., 2012; Yant et al., 2013). This results in tetrasomic inheritance, where each locus segregates four alleles instead of two. Bivalent formation in the absence of pairing preferences among homologs can be accomplished through a reduction in crossover rates, as a minimum of two crossovers are required for a chromosome to associate with multiple partners (Fig. 1) (Shaver, 1962; Watanabe, 1983; Lavinia, 1985, 1991; Gillies et al., 1987; Wolf et al., 1989; Srivastava & Lavinia, 1990; Chatterjee & Jenkins, 1993; Stack & Roelofs, 1996; Khawaja et al., 1997). Indeed, although crossover frequency may rise immediately following WGD (Hazarika & Rees, 1967; Koul & Raina, 1996; Brubaker et al., 1999; Desai et al., 2006; Leffon et al., 2010; Pecinka et al., 2011), established (evolved) autopolypsids generally exhibit reduced crossover rates compared with diploid relatives (Shaver, 1962; Watanabe, 1983; Gillies et al., 1987; Yant et al., 2013). In at least some species, crossover rates in diploids are predictive of polyploid meiotic stability such that diploid variants with higher crossover rates give rise to polyploids with higher multivalent frequencies, and thus some genotypes are more likely to spawn stable polyploid lineages than others (Morrison & Rajhathy, 1960; Hazarika & Rees, 1967).

Although there is much to be discovered surrounding the molecular basis of autopolyploid stabilization, some hints recently emerged from analysis of the established autotetraploid Arabidopsis arenosa, an outcrossing relative of Arabidopsis thaliana (Koch & Matschinger, 2007). Like many other autotetraploids, A. arenosa has stable meiosis and is highly fertile; all four homologs align early in prophase I, but subsequently sort into orderly diploid-like bivalents by metaphase I (Carvalho et al., 2010; Yant et al., 2013; Higgins et al., 2014). There is no evidence of pairing preferences among homologs (Hollister et al., 2012) and meiotic stabilization and bivalent formation are coupled with a reduction in chiasma frequency to around one per chromosome (Comai et al., 2003; Yant et al., 2013). By contrast, A. arenosa neopolypsids suffer strongly aberrant meiosis with rampant multivalent formation, suggesting that bivalent formation of the established autotetraploids is an evolved trait (Yant et al., 2013). A recent genome scan comparing diploid and evolved autotetraploid A. arenosa populations showed that a suite of eight unlinked genes encoding interacting proteins important for meiotic chromosome pairing, synapsis and crossover formation displayed unambiguous selective sweep signatures and sharp allelic differentiation between ploïdies (Yant et al., 2013). The proteins encoded by these genes comprise chromosome axis and cohesin subunits ASY1, ASY3, PDS5, SMC3 and SYN1; the synaptonemal complex transverse filament proteins ZYP1a and ZYP1b; and PRD3, a protein that associates with double-strand break sites and the chromosome axes (Bai et al., 1999; Armstrong, 2002; Higgins et al., 2005; Lam et al., 2005; De Muyt et al., 2009; Ferdous et al., 2012; Yant et al., 2013).

Mutant studies in A. thaliana show that the meiosis proteins with the strongest evidence of selection in tetraploid A. arenosa can affect crossover rates (Bai et al., 1999; Armstrong, 2002; Higgins et al., 2005; De Muyt et al., 2009; Ferdous et al., 2012; Yant et al., 2013), and thus it is plausible that the derived alleles enriched in tetraploids coordinate the observed global reduction in crossing over. However, a purely numeric decline in crossover frequency would leave some chromosomes lacking crossovers altogether (e.g. Fig. 1aii,g). Such univalents segregate randomly or disappear, and in many species create greater problems than quadrivalents (Myers, 1945; McCollum, 1958; Hazarika & Rees, 1967; Simonsen, 1975). As in most established autotetraploids, univalents are very rare in A. arenosa (Carvalho et al., 2010; Higgins et al., 2014), showing that the single ‘obligate’ crossover per chromosome that is essential in most species for chromosome segregation (Jones & Franklin, 2006) is selectively maintained in meiotically stable autotetraploids. In other words, the distribution of those few crossovers that remain is decidedly nonrandom.

One way in which genome-wide crossover reduction could be achieved without forming univalents is by an increase in the strength of crossover interference. Crossover interference refers to the observation that crossovers form in close proximity more rarely than expected by chance, which suggests that crossover events ‘signal’ along chromosomes to prevent additional crossovers from forming nearby (Copenhaver et al., 2002; Bishop & Zickler, 2004; Hillers, 2004). Increasing interference could reduce crossover numbers without affecting the formation of at least the single ‘obligate’ crossover (Jones & Franklin, 2006). Interference has been previously discussed in the polyploidy literature as a possible mechanism for multivalent prevention, although these models lacked a modern understanding of interference (Shaver, 1962; Muramatsu, 1990; Lavinia, 1991; Srivastava et al., 1992). A current model for interference with good empirical support is the ‘beam–film model’, which posits that a mechanical force generated by tension between expanding chromosome loops and the rigid chromosome axes drives crossover formation and, by releasing stress, prevents nearby prerecombination interactions from maturing as crossovers (Kleckner et al., 2004; Wang et al., 2014; Zhang et al., 2014a,b). Under the beam–film model, a decline in crossover number could be achieved by an increase in the distance the interference signal travels along a chromosome, by a decrease in overall chromosome tension, or by a decrease in chromosome axis/synaptonemal complex (SC) length.

Several of the genes under selection in A. arenosa are of interest in the context of interference (Yant et al., 2013). For example, in budding yeast, SUMOylation of the axis protein Red1 (whose homolog is ASY3 in A. thaliana and which shows evidence of selection in autotetraploid A. arenosa) is required for interference (Eichinger & Jentsch, 2010; Zhang et al., 2014b). Therefore, the strong signature of selection on protein-coding changes in ASY3 and its interactor ASY1 in A. arenosa may reflect an increase in crossover interference strength in the tetraploid. Other
mechanisms, such as effects on crossover versus noncrossover designation, are also plausible, although, under the beam-film model, crossover designation may be inextricably related to the same physical process that generates interference (Zhang et al., 2014b). Some of the proteins under selection in A. arenosa could also affect the length of the axes and size of the chromatin loops that emerge from them, which can also alter effective crossover rates. The cohesin SMC1, whose partner SMC3 is under strong selection in A. arenosa tetraploids, is known from studies in mammals to affect chromosome axis length and the size of chromatin loops (Revenkova et al., 2004; Novak et al., 2008). In this scenario, even if the strength of interference is unaltered, it could effectively propagate proportionally further along the chromosome (Zickler & Kleckner, 1999). Consistent with this idea, evolved A. arenosa tetraploids have shorter chromosome axis lengths than closely related diploids (Higgins et al., 2014); a similar trend has been reported in autotetraploid Medicago sativa (Gillies, 1969). In addition, ASY3, ASY1 and REC8 are important for homologous recombination and promote homolog rather than sister chromatid use (Zickler & Kleckner, 1999; Sanchez-Moran et al., 2007; Kim et al., 2010; De Massey, 2013), suggesting a role in crossover designation that could also be important in tetraploid crossover number reductions, for example if a higher proportion of intermediates are ushered to sister exchange after the obligate crossover is designated. The mechanistic details underlying the selection signatures in A. arenosa remain to be fully uncovered, but understanding the causes of these clear signatures promises interesting insights into the mechanisms of crossover rate modulation.

2. Adaptation to WGD in allopolyploids

Allopolyploids commonly stabilize meiosis and prevent multivalents by enforcing preferential associations of more similar homologs over less similar homeologs, a feature commonly called ‘preferential pairing’ (Ladizinsky, 1973; Sybenga, 1973; Sears, 1976; Jones et al., 1989; Jenczewski et al., 2003; Grandont et al., 2014). Most allopolyploids are therefore not only cytologically, but also genetically diploidized, with each locus having an independently segregating duplicate. For many allopolyploids structural divergence is not sufficient to explain meiotic diploidization and genetic loci are known to control preferential pairing (Ladizinsky, 1973; Sybenga, 1973; Sears, 1976; Jones et al., 1989; Jenczewski et al., 2003; Grandont et al., 2014). The most extensively studied of these loci is Pairing homeologous 1 (Ph1) from allohexaploid bread wheat, Triticum aestivum (Sears, 1976). Similarly acting loci exist in other allopolyploids, for example Brassica napus (Jenczewski et al., 2003; Grandont et al., 2014), Arabidopsis suecica (Henry et al., 2014), and Avena strigosa (Ladizinsky, 1973; Jones et al., 1989). Although in B. napus and A. suecica the loci have been mapped (Jenczewski et al., 2003; Henry et al., 2014), causal genes have yet to be identified.

Genes like Ph1 prevent crossover formation among homeologs and promote assembly of SC only between proper homologs. Thus, in metaphase I, chromosomes are associated purely as bivalents (Fig. 1b) even if they align, or even synapse also with homeologs to form ‘multivalents’ in earlier stages (Levan, 1940; Rasmussen & Holm, 1979; Hobolth, 1981; Loidl, 1986; Gillies et al., 1987; Jenkins et al., 1988; Davies et al., 1990; Jenkins & Rees, 1991; Chatterjee & Jenkins, 1993; Carvalho et al., 2010). Failure to correct early multivalents leads to incomplete synopsis, homoeologous recombination, multivalent persistence to metaphase, and defects in the resolution of entanglements (interlocks) among unrelated chromosomes (Hobolth, 1981; Yacobi et al., 1982; Holm & Wang, 1988; Zickler & Kleckner, 1999).

Of several loci mapped in bread wheat that prevent homoeologous pairing, Ph1 has the largest effect and is the best understood (Sears, 1976; Prieto et al., 2004; Griffiths et al., 2006; Colas et al., 2008; Moore & Shaw, 2009; Bhullar et al., 2014; Rey & Prieto, 2014). The Ph1 allele that confers preferential pairing appears to have arisen concomitantly with polyploidization (Moore & Shaw, 2009). This allele imposes a dominant effect on processes relevant to chromosome pairing and segregation, including the rate of premeiotic DNA replication, chromatin remodeling, prevention of homologous centromere association at metaphase I, and interlock resolution (Yacobi et al., 1982; Martínez-Pérez et al., 1999; Prieto et al., 2004; Colas et al., 2008; Bhullar et al., 2014; Rey & Prieto, 2014). It was recently shown that Ph1 prevents MLH1-marked nascent recombination sites from maturing into crossovers on associated homeologs during meiosis (Martin et al., 2014). As MLH1 is also implicated in interlock resolution (Storlazzi et al., 2010), a role of Ph1 in regulating MLH1 activity could help explain the association between homoeologous crossing over and the persistence of unresolved interlocks. Ph1 also reduces expression of the gene encoding the axis protein ASY1 (Boden et al., 2009), which may establish a link between Ph1 and another wheat diploidization locus, Ph2, which affects progression of synopsis (Martínez et al., 2001; Prieto et al., 2005). It also hints at parallels with autotetraploid A. arenosa, where ASY1 was under selection in the tetraploid lineage (Yant et al., 2013).

Currently, there are two nonexclusive hypotheses about the genetic identity of Ph1. The first proposes that a cluster of cell division cycle (cdc; also known as cyclin-dependent kinase (CDK))-related genes is responsible for the Ph1 effect (Griffiths et al., 2006). In the allele that prevents homoeologous pairing, Ph1 contains a heterochromatic insertion in a cluster of CDK2 pseudogenes that appears to suppress expression of corresponding CDK2 genes encoded in...
III. Environment as a driver of meiotic evolution

Another probably important driving factor for meiotic evolution is the environment, particularly temperature. In plants, reduced fertility as a consequence of temperature extremes is common, and at least sometimes this is directly attributable to meiotic failures (see De Storme & Geelen, 2014 for a thorough review). Variation exists among species in the temperatures at which meiosis fails (e.g. Fig. 2; Table 1), showing that meiotic systems can be tuned. But which meiotic processes are sensitive to environment? Does evolutionary change in the temperature tolerance of meiosis alter structural proteins or the regulation of meiosis? Are there trade-offs with increasing temperature tolerance? Might the signatures of selection that have been reported in meiosis genes in diverging populations in fact be footprints of environmental adaptation (Turner et al., 2008; Anderson et al., 2009; Wright et al., 2015)?

1. Meiosis at temperature extremes

Meiosis fails altogether at temperature extremes in a wide range of species (examples in Table 1 and Fig. 2), but the thresholds are distinct, demonstrating that tolerance limits are evolutionarily labile. For example, members of the genus *Solanum* show meiotic failure in either summer or winter fields depending on the species (Karihhaloo, 1991), wheat meiosis is more temperature sensitive than that of a related grass, *Dasypyrum villosum*, known for its wide environmental tolerance (Stefani & Colonna, 1996), in grasshoppers there is variation among species in meiotic sensitivity to heat shocks (Buss & Henderson, 1971a; Shaw, 1971), and *Drosophila melanogaster* populations from tropical locations have greater meiotic heat tolerance and faster recovery of fertility after heat exposure than those from cooler regions (Rohmer et al., 2004;

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<tr>
<td>Ecdyssononscriptus</td>
<td><em>Cynops pyrhogaster</em></td>
<td>Low</td>
<td>Yaza et al. (2003)</td>
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<tr>
<td>Hordeum vulgare</td>
<td>High</td>
<td>Pao &amp; Li (1948); Higgins et al. (2012)</td>
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<td>Hyacinthus orientalis</td>
<td>Low</td>
<td>Elliott (1955)</td>
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<tr>
<td>Locusta migratoria</td>
<td>High</td>
<td>Buss &amp; Henderson (1988)</td>
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<tr>
<td>Mus musculus</td>
<td>High</td>
<td>Nebel &amp; Hackett (1961)</td>
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<td>Rhoeo spathacea</td>
<td>High</td>
<td>Lin (1982)</td>
<td></td>
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<tr>
<td>Schistocerca gregaria</td>
<td>High</td>
<td>Henderson (1962)</td>
<td></td>
</tr>
<tr>
<td>Solanum torvum</td>
<td>High</td>
<td>Karihhaloo (1991)</td>
<td></td>
</tr>
<tr>
<td>Solanum melongena</td>
<td>Low</td>
<td>Karihhaloo (1991)</td>
<td></td>
</tr>
<tr>
<td>Solanum violaceum</td>
<td>Low</td>
<td>Karihhaloo (1991)</td>
<td></td>
</tr>
<tr>
<td>Triticum aestivum</td>
<td>High</td>
<td>Bayliss &amp; Riley (1972)</td>
<td></td>
</tr>
<tr>
<td>T. aestivum 5B+</td>
<td>High</td>
<td>Avivi (1976)</td>
<td></td>
</tr>
<tr>
<td>Triticum monococcum</td>
<td>High</td>
<td>Rana (1964)</td>
<td></td>
</tr>
<tr>
<td>Vicia cracca</td>
<td>High</td>
<td>Pao &amp; Li (1948)</td>
<td></td>
</tr>
<tr>
<td>Vicia fava</td>
<td>High</td>
<td>Pao &amp; Li (1948)</td>
<td></td>
</tr>
<tr>
<td>Arabidopsis thaliana (cdkg1 mutant)</td>
<td>Elevated</td>
<td>Zheng et al. (2014)</td>
<td></td>
</tr>
<tr>
<td>Caenorhabditis elegans (Pgi-1 mutant)</td>
<td>Elevated</td>
<td>Bilgir et al. (2013)</td>
<td></td>
</tr>
<tr>
<td>Unresolved interlocks/‘stickiness’</td>
<td><em>Cynops pyrhogaster</em></td>
<td>Low</td>
<td>Luomajoji (1977)</td>
</tr>
<tr>
<td>Larix gmelinii</td>
<td>Low</td>
<td>Buss &amp; Henderson (1971a,b)</td>
<td></td>
</tr>
<tr>
<td>Locusta migratoria</td>
<td>High</td>
<td>Elliott (1955)</td>
<td></td>
</tr>
<tr>
<td>Triticum aestivum</td>
<td>High</td>
<td>Fu &amp; Sears (1973)</td>
<td></td>
</tr>
<tr>
<td>T. aestivum 5B+</td>
<td>High</td>
<td>Avivi (1976)</td>
<td></td>
</tr>
<tr>
<td>Triticum monococcum</td>
<td>High</td>
<td>Rana (1964)</td>
<td></td>
</tr>
<tr>
<td>Triturus vulgaris</td>
<td>High</td>
<td>Callan &amp; Pearce (1979)</td>
<td></td>
</tr>
<tr>
<td>Defective spindles/cell plate failures/unreduced gametes</td>
<td><em>Arabidopsis thaliana</em></td>
<td>Low</td>
<td>De Storme et al. (2012)</td>
</tr>
<tr>
<td>Hordeum vulgare</td>
<td>High</td>
<td>Pao &amp; Li (1948)</td>
<td></td>
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<tr>
<td>Rosa hybrida</td>
<td>High</td>
<td>Pécris et al. (2011)</td>
<td></td>
</tr>
<tr>
<td>Triticum aestivum</td>
<td>High</td>
<td>Pao &amp; Li (1948)</td>
<td></td>
</tr>
<tr>
<td>Uvularia perfoliata</td>
<td>High</td>
<td>Barber (1941)</td>
<td></td>
</tr>
</tbody>
</table>

CDK1, CYCLIN-DEPENDENT KINASE G1; SC, synaptonemal complex.
of ZYP1 foci (Higgins becomes disordered. These problems coincide with the appearance decreases, and loading of the SC central element protein, ZYP1, glimmers of failure are evident: fertility declines, chiasma frequency decreases, and loading of the SC central element protein, ZYP1, becomes disordered. These problems coincide with the appearance of ZYP1 foci (Higgins et al., 2012) that probably mirror the SC aggregations reported in Allium (Loidl, 1989). These results suggest that near a critical threshold, beyond which synapsis fails altogether, SC instabilities are already evident. Similar trends are seen in animals, from grasshoppers to mice (Nebel & Hackett, 1961; Henderson, 1962). Most reported SC failures involve high temperature, but low-temperature failure has been reported in Hyacinthus orientalis, two species of Solanum, and the new Cynops pyrrhogaster (Elliott, 1955; Karihaloo, 1991; Yazawa et al., 2003).

The importance of mitigating temperature effects on SC stability is highlighted by the identification of genes in both plants and animals that are required to stabilize meiosis only at elevated temperatures. In A. thaliana, mutation of a protein kinase (CDKG1) causes SC failures at elevated, but normally well-tolerated temperatures, but has no effect at lower temperatures (Zheng et al., 2014). The failures in the mutant are similar to those seen in wild-type plants at higher growth temperatures (Loidl, 1989; Higgins et al., 2012; Zheng et al., 2014), suggesting that mutation of CDKG1 does not qualitatively alter the nature of meiotic failure, but rather shifts the tolerance threshold. In Caenorhabditis elegans, mutation of an unrelated protein (a P-granule component called PGL1) similarly lowers the threshold of temperature tolerance for SC assembly and extension (Bilgir et al., 2013). Also important for meiotic temperature stability in C. elegans is eIF4E, which promotes increased translation of crossover proteins at elevated temperatures (Song et al., 2010), perhaps to compensate for a decline in their efficiency.

SC failure is not the only temperature-associated meiotic problem. Temperature extremes can also cause chromosomes to behave in a ‘sticky’ fashion, which is thought to represent a chromatin condensation defect (Fu & Sears, 1973; Luomajoki, 1977). Excess chromosome contraction and chiasma terminalization have been observed in wheat and rye (Secale cereale) at high temperatures (Pao & Li, 1948). Interlock resolution can fail at high temperatures in animals and in wheat (Buss & Henderson, 1971a,b; Avivi, 1976; Callan & Pearce, 1979; Yazawa et al., 2003). Interlocks arise when synapsis proceeds from two chromosome regions and traps another chromosome between the synapsing homologs (Fig. 1c) (Zickler & Kleckner, 1999; Wang et al., 2009) and their resolution requires coordinated, multistep disentangling mediated by MLH1 and TOPO II (Holm & Rasmussen, 1980; Rasmussen, 1986; Storlazzi et al., 2010). Whether it is disruption of these proteins that causes failure is unknown. Defects in spindle or cell plate formation, both of which can lead to unreduced gamete production, have also been reported at temperature extremes (Barber, 1941; Pao & Li, 1948; Pécrix et al., 2011; De Storme et al., 2012). In lilies and mice, elevated (in mice, also lower) temperature directly and strongly reduces activity of meiotic recombines (Hotta et al., 1985, 1988; Stern, 1986).

While it is clear that different species or populations have distinct meiotic temperature tolerances, it is currently unknown how meiotic temperature tolerance evolves in nature. This will certainly become clearer as mechanistic examples of tolerance variants are characterized from natural populations. We also do not know if high- and low-temperature tolerances are connected. Might the low and high thresholds be linked, for example, by the physical properties of the proteins that form the SC or other structures important for meiosis? Or can low and high thresholds be adjusted independently, perhaps through regulation of genes like CDKG1, PGL-1 or eIF4E? Might meiotic temperature adjustment cause signatures of selection in meiosis genes as seen in Drosophila or A. arenosa populations from different habitats (Turner et al., 2008; Anderson et al., 2009; Wright et al., 2015)?

2. Environmental effects on crossover number

Between the temperature extremes at which meiosis fails altogether, environmental variation also causes variation in crossover frequency, which has important implications for models of the evolution of recombination as well as for population genetics and breeding (Otto & Michalakis, 1998; Otto & Barton, 2001; Marais & Charlesworth, 2003; Roze & Barton, 2006). The range of biotic and abiotic environmental factors known to affect recombination rates is remarkably broad and includes temperature, nutrient availability, fungicide application, pathogen attack, drought — and, in grasshoppers, even swarming (Grant, 1952; Law, 1963; Nolte, 1968; Bennett & Rees, 1970; Fedak, 1973; Sharma et al., 1983; Choudhary & Sajid, 1986; De Storme & Geelen, 2014). This begs the question why so many diverse environmental inputs affect meiosis. Do they all independently affect recombination frequencies, or is there an integrative signal? There is some evidence for the latter: in plants, abscisic acid, a broadly responsive stress hormone, influences recombination rates (De Storme & Geelen, 2014), and in animals hormones are also known or suspected to affect chiasma frequency (Nolte, 1968; Cobror et al., 1986). In precisely what ways a connection between stress, hormones, and meiotic recombination might be useful remains to be explored, but its occurrence across kingdoms hints that there is probably a good reason for this provocative trend; it will be very interesting to learn what that
reason might be. One factor could be stress-mediated chromatin remodeling, which can affect crossover rates and distribution (Henderson, 2012).

Among environmental influences on crossover frequency, temperature has especially strong, or at least especially well-documented effects, and the literature presents a dizzying array of trends: elevated temperature reduces chiasma frequency in some species (Barber, 1941; Dowrick, 1957; Lin, 1982) and increases it in others (Elliott, 1955; Lamb, 1969a,b; Rose & Baillie, 1979; Francis et al., 2007), and more complicated trends surface in yet more (Smith, 1936; Wilson, 1959b; Abel, 1964; Lamb, 1969b; Parsons, 2008); examples are given in Table 2. As pointed out decades ago (Wilson, 1959b), at least some of this variation arises from differences in experimental design (e.g. heat shocks versus constant growth), differences among mapped regions in genetic studies, or variation among strains in the degree to which chiasma frequency is sensitive to temperature (e.g. Bayliss & Riley, 1972; Hossain, 1978; Ahmad et al., 1984; Saggoo et al., 2010). The mechanisms of temperature-mediated crossover alteration remain largely unknown, but it is known that transient heat treatments can accelerate meiosis (Bennett et al., 1972; De la Peña et al., 1980; Stefani & Colonna, 1996). In barley, this acceleration has a phenotypic consequence for crossover regulation: elevated temperature causes earlier replication of heterochromatic regions that form the bulk of the chromosomes, allowing more chiasmata to form within them, probably because of greater accessibility of the chromatin and synchrony with the euchromatic regions during critical stages of crossover formation (Higgins et al., 2012).

Five major trends of crossover frequency in relation to increasing temperature were already evident over 50 yr ago (Wilson, 1959b) and still effectively summarize the evidence today: (1) steady increases; (2) steady decreases; (3) U-shaped curves; (4) inverted U-shaped curves; and (5) no effect (summarized in Fig. 3a; empirical examples are given in Table 2). The inverted U-shaped curve is uncommon in the literature, but the other trends are all supported by multiple studies (see Table 2). Distinguishing among models can be challenging: for example, if one were sampling a temperature range that covers only part of a U-shaped curve, the data obtained might be interpreted as a steady increase or decrease of chiasma rate with temperature. Furthermore, as chiasma rates are often low near or past a failure point, but high just below it (Parsons, 2008), unknowingly sampling into the failure range would also cause misinterpretation if temperatures in between were not sampled.

Table 2 Temperature-associated chiasma formation trends as shown in Fig. 2 or discussed in the main text

<table>
<thead>
<tr>
<th>Trend</th>
<th>Species</th>
<th>Comments</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>U-shaped m</td>
<td>Drosophila melanogaster</td>
<td>Minimum at 22–25°C, strongest effect at centromeres, drops just below lethal</td>
<td>Smith (1936); Parsons (2008)</td>
</tr>
<tr>
<td>m</td>
<td>Neurospora crassa</td>
<td>Minimum at 25°C (15–30°C); variation among map regions</td>
<td>Ahmad et al. (1984)</td>
</tr>
<tr>
<td>c</td>
<td>Allium cepa</td>
<td>Maxima at 9 and 44°C (tested heat shocks 0–53°C); chiasma increase associated with terminalization</td>
<td>Pollakova (1940), as cited in Wilson (1959b)</td>
</tr>
<tr>
<td>m</td>
<td>Sordaria brevicolus</td>
<td>Minimum 20–25°C</td>
<td>Lamb (1969a)</td>
</tr>
<tr>
<td>m</td>
<td>Sphaerocarpus sp.</td>
<td>Minimum at 22°C (6–33°C); some regional variation</td>
<td>Abel (1964)</td>
</tr>
<tr>
<td>c</td>
<td>Coprinus lagopus</td>
<td>Tested: 5°C, 25°C, 35°C; Max increase if heat applied during SC formation</td>
<td>Lu (1969, 1974)</td>
</tr>
<tr>
<td>c</td>
<td>Endymion nonscriptus</td>
<td>Tested: 1°C, 5°C, 15°C, 20°C (asynaptic at 20°C)</td>
<td>Elliott (1955)</td>
</tr>
<tr>
<td>Increase with temperature m</td>
<td>Sordaria fimicola</td>
<td>General increase with temperature</td>
<td>Lamb (1969b)</td>
</tr>
<tr>
<td>c</td>
<td>Hyacinthus orientalis</td>
<td>Tested: 5°C, 10°C, 15°C, 20°C; asynaptic at 5°C</td>
<td>Elliott (1955)</td>
</tr>
<tr>
<td>m</td>
<td>Arabidopsis thaliana</td>
<td>Tested: 19–28°C</td>
<td>Francis et al. (2007)</td>
</tr>
<tr>
<td>m</td>
<td>Caenorhabditis elegans</td>
<td>Tested 13.5–26°C</td>
<td>Rose &amp; Baillie (1979)</td>
</tr>
<tr>
<td>Decrease with temperature c</td>
<td>Endymion nonscriptus</td>
<td>Temporary shifts (0–30°C)</td>
<td>Wilson (1959a)</td>
</tr>
<tr>
<td>c</td>
<td>Antirrhinum majus</td>
<td>Tested shifts to 10–30°C</td>
<td>Ernst (1938, 1939)</td>
</tr>
<tr>
<td>Annual cycles c</td>
<td>Eclipta alba</td>
<td>Low chiasmata in warm times</td>
<td>Saggoo et al. (2010)</td>
</tr>
<tr>
<td>c</td>
<td>Phyllodactylus marmoratus</td>
<td>Low chiasmata in warm times</td>
<td>King &amp; Hayman (1978)</td>
</tr>
<tr>
<td>c</td>
<td>Podarcis sicula</td>
<td>Unclear link with temperature</td>
<td>Cobor et al. (1986)</td>
</tr>
</tbody>
</table>

'm' in leftmost column indicates trends concluded from mapping data, while 'c' indicates cytological data. 1Result depends on which mapping region is considered. 2Ernst (1999) found that temperature shifts caused a sudden drop in chiasma frequency followed by a gradual return to preshift levels.
Many studies sample only two temperatures, often ‘normal’ and ‘heat shock,’ and from these, global trends cannot be inferred. Table 2 therefore presents only cases for which a range of temperatures was sampled. Studies that use mapping (instead of cytology) may also come to different conclusions, as most reported mapping studies sample just one or a few regions in the genome. It is now known that chiasma position (e.g. centromere proximal versus distal) can also change with temperature, and several mapping studies indeed report contrasting trends for different intervals (Abel, 1964; McNelly-Ingle et al., 2009).

Interesting results also arise from differences in experimental design. For example, when *Endymion nonscriptus* plants are grown for extended periods at different temperatures, elevated temperatures correlate with slight increases in chiasma frequency.
15°C, with a dramatic plunge at 20°C where synopsis fails (Elliott, 1955). Another study reported a steady decline in chiasma frequency from 0 to 30°C when heat treatments were applied only in bursts long enough for meiosis to complete (Wilson, 1959a). Differences arising from timing have also been highlighted, for example in *Antirrhinum majus* chiasma frequency increased rapidly for a few hours after a temperature shift, followed by a period over several days in which frequencies returned gradually to about where they were before the temperature shift (Ernst, 1938, 1939). In the grasshopper *Schistocerca gregaria*, the precise timing of heat shock in meiosis also matters: shocks in leptotene/zygotene decrease chiasma number, while shocks in late zygotene/early pachytene increase chiasma number (Henderson, 1988). Furthermore, in the grasshoppers *S. gregaria* and *Locusta migratoria*, individuals with lower chiasma frequencies overall are more sensitive to temperature shock (Rees & Thompson, 1958; Shaw, 1971), presumably because a quantitative crossover decline would cause univalents earliest in genotypes that have low crossover numbers to begin with. Finally, in some studies, shifts in temperature have more dramatic effects than constant growth at the same temperatures (Landner, 1970). This variability is interesting, but also underscores the need for consistency within and across experiments, and care in interpretation of observed patterns.

Although most reported trends are from laboratory studies, temperature-associated crossover rate variation is also observed in nature. For example, the gecko *Phylloctaylus marmoratus* and the plant *Eclipta alba* both show annual cycles in crossover number in nature, with the lowest rates observed when temperatures are highest (King & Hayman, 1978; Saggoo et al., 2010). Another lizard, *Podarcis sicula*, shows an annual cycle in chiasma frequency, but a link to temperature is less clear (Cobrorn et al., 1986). It has not yet been established whether annual cycles are adaptive, or unavoidable consequences of environmental variation. In some species, variation in chiasma number when measured in common conditions is associated with habitat of origin. For example, in *Sordaria fimicola*, strains found on a highly variable, harsh, south-facing canyon wall in Israel show higher recombination rates than those from nearby lush north-facing walls when both strains are grown at 18°C in the laboratory (Saleem et al., 2001). It is not known whether this difference is also observed in nature, nor do we know whether the observed crossover rates (or a change to some other aspect of meiosis that secondarily triggers crossover variation) directly benefit the fungi in harsh environments. Alternatively, crossover increases can also arise as a byproduct of strong or variable selection on traits unrelated to meiosis such as geotaxis, DDT resistance, or body size (Flexon & Rodell, 1982; Gorlov et al., 1992; Korol & Iliadi, 1994), which would predict that organisms that regularly experience strong selection, as might occur in harsh or fluctuating environments, would generally have higher crossover rates. The *Sordaria* result would be consistent with this. Interestingly, the observation that crossover rates are lower in more stable environments implies that there is something that drives them back down. Indeed, there may be a trade-off with fertility: in mice, while selection on a variety of traits increases crossover rates, when selection was applied instead for high fertility, recombination rates declined (Gorlov et al., 1992). This suggests that in at least some species there can be a cost to fertility of increasing crossover rates, implying that increases in recombination in response to selection might be relatively short-lived.

Just as for the tolerance of extremes, there are also currently very little data on whether or how the temperature response curves of chiasma number might evolve. For example, as a population invades a new habitat, if temperature tolerance is shifted upwards, does the entire curve shift (Fig. 2bv)? There is also evidence that temperature responsiveness can be muted (Buss & Henderson, 1971b; Shaw, 1971); does this broaden temperature tolerance without moving the minimum point (Fig. 2bvi)? More explicit comparisons of temperature tolerance and crossover number relationships for populations adapted to distinct temperature regimes are needed. In combination with molecular work, this will greatly aid our understanding of the mechanisms of adaptive evolution of meiosis in response to environment.

The possibility that response curves can move or change shape (as illustrated in Fig. 3b) has important repercussions for how we interpret the finding of crossover variation among populations. If two populations are adapted to different prevailing temperature regimes their responses may be shifted accordingly (Fig. 3b). When tested in a single common condition in the laboratory, the isolates may exhibit different crossover rates, but, while this could reflect a global difference, it could also arise because the same temperature falls in a different part of the curve for each population. It may be that in the wild, where individuals would be reproducing at their respective temperature optima, crossover rates may not differ. If what we measure as crossover variation in the laboratory is not fully representative of what occurs in nature, this has very important implications for how we translate results from the laboratory into models of the causes and consequences of crossover rate evolution. Thus, exploring crossover variation in wild populations in their native settings, or investigating ranges of temperatures in the laboratory, merits more detailed study.

### 3. Temperature and polyploidy

The relationship between temperature and chiasma number is of special interest for the study of autopolyploids. Consider the relationships between temperature tolerance and chiasma frequency (Fig. 3a). As discussed earlier, autopolyploids with higher crossover rates have higher rates of meiotic aberrations associated with multivalent formation. Thus, we can infer that there is a limit on crossover number above which polyploids become less fertile because of excess multivalents. Adding such a limit to the environmental effects on crossing over, we see that this could also affect the temperature tolerance of meiosis in newly formed polyploids (see Fig. 3c). With the U-shaped curve, for example, new polyploids would be predicted to have a narrower temperature tolerance than diploids because they could reach an untenable level of crossing over before meiosis collapses from other causes, making them less tolerant of both higher and lower temperatures than diploids (Fig. 3cvii). The effect of a crossover limit on the other response curve types is also summarized in Fig. 3(c), and the message is the same: a lower tolerance of high crossover numbers should decrease the temperature tolerance of meiosis in newly formed autopolyploids.
The predictions summarized in Fig. 3(c) provide a set of hypotheses that have not, to our knowledge, been explicitly tested. One of the very few direct comparisons of diploid and tetraploid meiotic responses to environment was performed in the grass *Festuca pratensis*, but not with temperature; phosphate treatment increased chiasma number in both diploids and tetraploids, and in tetraploids this did correlate with an increase in multivalent frequency (Deniz & Tufan, 1998). We speculate that similar trends would be seen with temperature, and the predictions summarized in Fig. 3(c) thus raise pertinent questions regarding the nature of selection on meiosis after WGD. As discussed earlier, initial selection events could drive a reduction in crossover number to eliminate multivalent formation. Globally suppressed crossover rates might then pleiotropically result in reduced sensitivity to temperature as WGD lineages evolve because the ‘high chiasma number cutoff’ is not as quickly reached. However, a reduction in chiasma number has been shown in grasshoppers to make them more susceptible to crossover declines that occur near the SC-failure point, making them more temperature sensitive (Shaw, 1971). Thus, we might accordingly expect that selection for lower crossover number might make evolved polyploids less susceptible to a high chiasma number threshold, but more susceptible to SC failures at temperature extremes, perhaps limiting ranges or necessitating additional evolutionary restabilization of meiosis. WGD-associated selection for reduced crossover rates might thus drive additional compensatory evolution to restabilize meiosis to environmental extremes, providing fertile ground for studying the evolutionary dynamics of meiosis.

IV. Broader evolutionary dynamics

1. Conservation of meiotic structures

Meiotic chromosome pairing, crossing over, and segregation are broadly conserved across eukaryotic kingdoms (Villeneuve & Hillers, 2001; Harrison et al., 2010). It is therefore surprising that meiosis genes often exhibit high nucleotide sequence divergence between closely related populations and/or classic signatures of selective sweeps (Turner et al., 2008; Anderson et al., 2009; Chowdhury et al., 2009; Fledel-Alon et al., 2011; Yant et al., 2013; Kong et al., 2014; Wright et al., 2015). Investigation of the tripartite SC shows that, despite such widespread protein sequence divergence, its ultrastructure remains conserved across kingdoms (Page & Hawley, 2004), allowing for broad conservation of meiotic processes in the face of evident primary sequence plasticity (Bogdanov, 2003; Bogdanov et al., 2007; Kumar et al., 2010). For example, SYCP1, the meetoan SC transverse filament, shows only short blocks of conserved domains in a background of otherwise very low amino acid identity between rat and hydra (Fraune et al., 2012), but ultrastructural characteristics are nevertheless strikingly similar. Recognition of the importance of structure enables identification of meiotic components even when sequence divergence renders them essentially unrecognizable through primary sequence homology searches. For example, tertiary structure profiling enabled identification of the *A. thaliana* Zip1 functional homolog (Higgins et al., 2005) and basal meatoan SC components (Fraune et al., 2013).

2. Coevolution of meiosis genes

Although sequence mutability with structural conservation explains how meiosis proteins can vary while maintaining conserved functions, it does not explain why they diverge in primary sequence. We suspect that this probably reflects a long history of periodic reoptimizing of multicomponent complexes in response to environmental or genome changes. In *A. arenosa*, a suite of functionally related, unlinked genes encoding proteins that interact dynamically to mediate sister chromatid cohesion, axis formation, crossover designation, and synapsis show strong evidence of having undergone selective sweeps after WGD (Yant et al., 2013). As discussed above, the co-occurrence of selective sweeps in functionally related, but unlinked loci suggests orchestrated coevolution of these proteins following WGD, evoking the idea that they function together to modify meiotic events post-WGD. Coevolution is a process by which mutations in one protein that rise in frequency (as a result, for example, of selection) place evolutionary pressure on interacting partners, leading to further selection for compensatory mutations that reoptimize complexes. Indeed, this process has been shown to be capable of driving rapid divergence in genes encoding components of multiprotein complexes (Castillo-Davis et al., 2004; Takahasi, 2009).

Coevolution of proteins that function in chromosome management is also evidenced by the coordinated evolutionary rates of interacting meiotic and mismatch repair proteins in 40 yeast and mammal species, suggesting not only that protein interactions are conserved, but also that, when change occurs in one protein, it can drive change in interacting partners (Clark et al., 2013). Indeed, meiotic double-strand break repair protein heterocomplex conservation is evident across kingdoms, from yeast to mice (Kumar et al., 2010). Long-term coevolution is also indicated by evolutionary patterns of strict co-presence and co-absence of particular DNA mismatch repair (MMR) proteins across bacteria and archaea (Lin et al., 2007).

The idea that coevolution has measurable, functionally relevant consequences in meiosis is supported by the observation that divergence in loci mediating MMR can result in maladaptive allelic combinations with dominant negative phenotypes arising in interspecies hybrids (Milne & Weaver, 1993). Even within species (*Saccharomyces cerevisiae*), physically interacting proteins MLH1 and PMS1 display evidence of coevolution: naturally occurring variants in these proteins can produce a ‘hypermutator’ phenotype as a result of MMR failures when alleles from different strains are combined in hybrids, although each is perfectly functional with its native partner (Heck et al., 2006; Demogines et al., 2008). Hypermutator allele combinations are absent from natural populations in extensive surveys, suggesting that selection or geographic isolation normally maintain compatible allele combinations. Additional modifiers were detected in synthetic crosses of yeast, suggesting that combinatorial allelic tuning involves more than just these two interactors (Demogines et al., 2008). A similar trend is evident in mammals, where divergence of
meiosis genes in subspecies of house mice can lead to reproductive isolation as a result of failures in hybrids of double-strand break formation and synopsis (Hunter et al., 1996; Bhattacharyya et al., 2013). This suggests that within populations there may be selection to maintain protein sequence homozygosity for members of complexes more generally. Thus, we expect that, if an environmental or genomic shift selected for a change in one protein, this could snowball over an entire network. If individual changes are subtle and interactions maintained, this would allow complex molecular machines to undergo refined shifts in function without catastrophically altering essential roles.

Could the structural roles and extensive interactions of meiotic proteins be the primary reason for the remarkable and apparently coordinated evolutionary trajectories we see in these loci in A. arenosa following WGD? Across eukaryotes, heteromeric protein complexes comprise the axes and SC, which in turn participate in extensive physical interactions with chromosomes during prophase I (Zickler & Kleckner, 1999; Kleckner, 2006). Although interactions can suffice to explain rapid and coordinated divergence of multiple proteins, the set under selection in A. arenosa orchestrates a structural process in which the precise mediation of mechanical stresses may be critical, as suggested by the beam-film model. Thus, changes in any protein may set in motion a domino retuning of the entire system of interacting structural proteins, driving what appears to be particularly exquisitely coordinated coevolution. As noted earlier, A. arenosa exhibits signs indicative of increased crossover interference strength after WGD, and the interference signal probably involves mechanical forces arising from chromosome expansion against the SC axes in the best current model (Kleckner et al., 2004; Kleckner, 2006; Zhang et al., 2014b), emphasizing the potential importance of tight, force-modulating interactions between heteromeric physical structures that would mediate interference.

3. Rapid loss of duplicate copies of meiosis genes following WGD

The availability of dozens of plant reference genomes has allowed comparison of global gene complements before and following gene (or genome) duplication events. Numerous studies have investigated global patterns of duplicate gene loss and retention and the general patterns and interpretations have been reviewed elsewhere (Paterson et al., 2006; Birchler & Veitia, 2007; Hahn, 2009; De Smet et al., 2013). Here, we focus only on meiosis genes, for which it has been well established that duplicate copies of homologous recombination and repair genes are among the most rapidly lost after both WGD and local duplications in plants, animals and fungi (Paterson et al., 2006; De Smet et al., 2013; Lloyd et al., 2014). How do we interpret these pan-eukaryotic patterns?

Some models treat gene loss as a neutral process, and for many genes this trend is indeed probably the rule (Birchler & Veitia, 2007), but the strong enrichment for restoration to a single copy among DNA repair and recombination genes is statistically robust, even in a large study of 20 angiosperm genomes, supporting the idea that for these genes duplicate loss is neither neutral nor random (Paterson et al., 2006; De Smet et al., 2013). Under-retention relative to neutral expectation could suggest that maintenance of dual, diverging copies is not well tolerated for these proteins. A recent study showed that new polyploids often do retain active copies of these genes, suggesting that duplication per se is not always problematic in the short term (Lloyd et al., 2014). This raises the possibility that selection may act against duplicates over the longer term which manifests only as mutations begin to accumulate in duplicate copies. This would be consistent with selection for homozygosity and the observation that these genes commonly encode subunits of protein complexes that are particularly prone to dominant negative effects (Koonin et al., 2004; Casneuf et al., 2006; Paterson et al., 2006; Waterhouse et al., 2011; De Smet et al., 2013). Thus, the loss of duplicate DNA repair and recombination genes may be selectively favored as mildly deleterious heterocomplexes begin to form following sequence divergence (Hahn, 2009). This harmonizes with the general tendency toward coevolution of interacting proteins, highlighting again that the evolutionary trends characteristic of meiosis genes may be shaped by their extensive participation in dynamic structural complexes whose overall form and function are constrained. As a result, longer term meiosis protein evolution is probably characterized by (1) functional and topological constraints on proteins that otherwise differ widely in primary sequence, (2) coevolution of unlinked, functionally and physically interacting proteins, and (3) intolerance of long-term duplicate persistence.

V. Summary and conclusions

WGD and temperature are two major challenges to regular chromosome segregation in meiosis and there is abundant evidence that core meiotic processes evolve in response. In particular, shifts in either genome structure or ambient temperature can pose problems for chromosome interactions, crossover formation, and synopsis. Both internal (genomic) and external (environmental) challenges may thus drive selection directly on core protein constituents important for chromosome interaction and recombination in meiosis I to prevent aberrant associations or chromosome missegregation. Selection for functional change in core meiotic structural processes may also have pleiotropic consequences for genome-wide crossover rates. At least some of the previously noted variation in crossover rates among populations may in fact be attributable to adaptation of meiosis to the environment, as opposed to direct selection for particular levels of crossing over, though this remains to be explicitly tested.

Meiosis is a dynamic structural process, broadly conserved across eukaryotes. The need to maintain tertiary structures may mean that coevolutionary divergence will be the rule for meiosis proteins. The genes controlling meiotic recombination and crossover interference processes therefore exhibit distinctive evolutionary dynamics characterized by compensatory evolution among members of interacting complexes that maintains overall heteroprotein complex robustness and may lead to the divergence of entire functional modules rather than just single genes. Many exciting research avenues remain to explore how and why meiosis can be altered in response to challenges, and how these alterations may secondarily affect traits such as crossover frequency.
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References


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