Meiotic recombination gets stressed out: CO frequency is plastic under pressure

Jennifer L Modliszewski[1] and Gregory P Copenhaver[1,2]

Meiotic recombination ensures the fertility of gametes and creates novel genetic combinations. Although meiotic crossover (CO) frequency is under homeostatic control, CO frequency is also plastic in nature and can respond to environmental conditions. Most investigations have focused on temperature and recombination, but other external and internal stimuli also have important roles in modulating CO frequency. Even less is understood about the molecular mechanisms that underly these phenomenon, but recent work has begun to advance our knowledge in this field. In this review, we identify and explore potential mechanisms including changes in: the synaptonemal complex, chromatin state, DNA methylation, and RNA splicing.

Addresses
[1] Department of Biology and the Integrative Program for Biological and Genome Sciences, University of North Carolina at Chapel Hill, Chapel Hill, United States
[2] Lineberger Comprehensive Cancer Center, University of North Carolina School of Medicine, Chapel Hill, United States

Corresponding author: Modliszewski, Jennifer L (jenmod@live.unc.edu)

Current Opinion in Plant Biology 2017, **36**:95–102

This review comes from a themed issue on **Genome studies and molecular genetics**

Edited by **Ian Henderson** and **Korbinian Schneeberger**

http://dx.doi.org/10.1016/j.pbi.2016.11.019

Introduction

Meiosis is a defining feature of sexually-reproducing organisms. During meiosis, homologous chromosomes pair and reciprocally exchange DNA, forming crossovers (COs). This process creates new allelic combinations in the resulting gametes, which may aid evolution by creating favorable allelic combinations and breaking up undesirable ones [1]. Meiotic recombination also generates physical connections between homologous chromosomes (chiasmata), which are crucial for proper chromosome segregation. In Arabidopsis, ~200 DNA double-strand breaks (DSBs) are formed, but only ~10 develop into COs; the remainder are repaired as non-crossovers (NCOs) [2–4]. Perturbation of DSB frequency in yeast does not correspondingly alter CO frequency, suggesting that recombination is homeostatically regulated [5]. Nevertheless, CO frequency can be modulated by external factors, such as temperature, and varies by intrinsic factors, such as age [*e.g.*, 6,7]. Understanding and manipulating the placement and frequency of COs has enormous potential to aid in plant breeding efforts, and to ensure crop productivity in the face of external stressors.

Meiotic recombination is initiated when the conserved topoisomerase VI-like SPO11 creates DSBs [8]. After DSB formation, the 5′ ends are resected, leaving 3′ tails, which can invade both sister and non-sister chromatids. RAD51 and DMC1, bacterial RecA homologs, aid invasion of non-sister chromatids in meiotic recombination [9–11]. Following strand-invasion, intermediates can be resolved by two pathways—double-strand break repair (DSBR), which results in COs, or synthesis dependent strand annealing (SDSA), which results in NCOs [12,13, for a review see 14]. In Arabidopsis and many other organisms, COs can be further divided into those that are mediated by ZMM proteins (*e.g.*, ZIP4, MSH4, MSH5, MER3, HEI10 in Arabidopsis) and are subject to interference (Type I) and those that are mediated by MUS81 and are not sensitive to interference (Type II) [15–19]. To date, it is largely unknown how CO formation in these pathways is modulated in response to extrinsic and intrinsic factors. In this review, we first provide an overview of the factors that can modulate CO frequency. We then identify and explore the molecular mechanisms that may be responsible for the plastic nature of CO frequency.

Meiotic CO frequency is plastic and modulated by stress

Factors that affect genome-wide CO frequency fall into two categories: (1) extrinsic factors, such as temperature, and (2) intrinsic factors, such as sex or age. Historically, the most-well studied of these factors is the effect of temperature (Table 1) [20, reviewed in 21,22]. The effect of temperature on CO frequency is complex (Table 1). The most common finding is that CO frequency follows a U-shaped pattern as temperature increases from low to high (Figure 1). In some species, such as *Arabidopsis thaliana*, *Hordeum vulgare* (barley), *Caenorhabditis elegans*, the grasshopper *Melanoplus femurrubrum*, and *Hyacinthus orientalis* [6,7,23,24••], an increase in CO frequency with increasing temperature is observed. In others species, such as *Fritillaria meleagris*, *Allium ursinum*, and *Hyacinthus*

Table 1

Stressors that modulate CO frequency

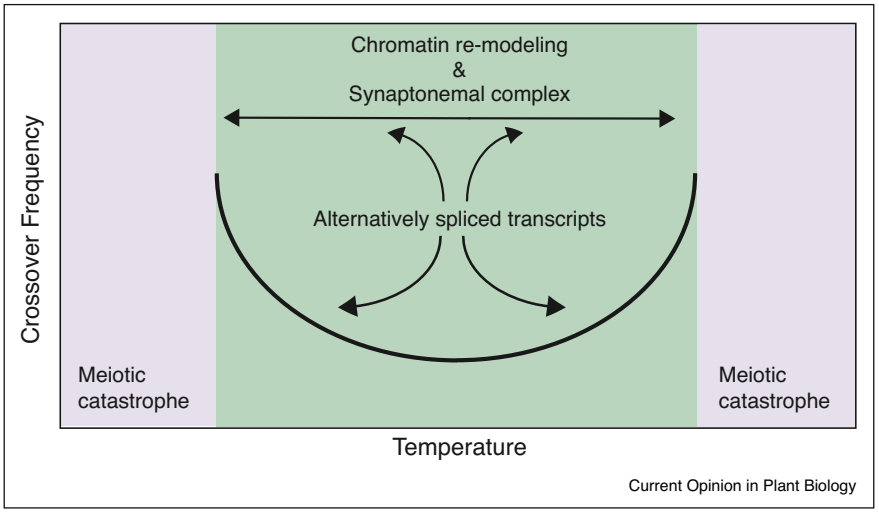
Species	Category	CO frequency	Reference
Caenorhabditis elegans	Age	Decrease	[6]
Lycopersicon pimpinellifolium × *L. esculentum*	Age	Decrease	[30]
Mus musculus	Age	Female: significant decrease Male: non-significant increase	[38]
Mus musculus	Behavioral	Increase	[100] (referenced in [101])
Lycopersicon pimpinellifolium × *L. esculentum*	Chemical	Decrease	[30]
Zea mays	Defoliation	No effect	[a]
Arabidopsis thaliana	Developmental stage	Increase	[7,76]
Zea mays	Drought	Increase	[a]
Chlamydomonas reinhardi	Nutrient	Increase	[34]
Drosophila melanogaster	Nutrient	Increase	[31]
Drosophila melanogaster	Nutrient		[33]
Lycopersicon pimpinellifolium × *L. esculentum*	Nutrient	Na decrease, all others no change	[30]
Saccharomyces cerevisiae	Nutrient	Increase	[32]
Lycopersicon pimpinellifolium × *L. esculentum*	Nutrient availability	Decrease without fertilizer	[30]
Allium ursinum	Temperature	Decrease	[27]
Arabidopsis thaliana	Temperature	Increase	[7,76]
Caenorhabditis elegans	Temperature	Increase	[6]
Chorthippus parallelus (Stenobothrus parallelus)	Temperature	Increase then decrease	[102]
Coprinus lagopus	Temperature	Increase	[103]
Drosophila melanogaster	Temperature	Increase then decrease	[20,37]
Fritillaria meleagris	Temperature	Decrease	[25]
Hordeum vulgare	Temperature	Increase	[24••,40]
Hyacinthoides non-scripta (Endymion nonscriptus)	Temperature	Decrease	[21]
Hyacinthus orientalis	Temperature	Increase	[26]
Locusta migratoria	Temperature	Increase	[102]
Melanoplus femurrubrum	Temperature	Decrease	[23]
Rhoeo spathacea var. variegata	Temperature	Decreased distal chiasma	[104]
Saccharomyces cerevisiae	Temperature	Increase/no effect	[46,105]
Schistocerca gregaria	Temperature	Increase-decrease-increase	[102]
Sordaria fimicola	Temperature	Results varied based on locus examined	[106]
Tradescantia bracteata	Temperature	Increase then decrease	[107]
Uvularia perfoliata	Temperature	Increase then decrease	[107]

[a] LA Verde, PhD Thesis, Iowa State University, 2003.

[25–27], a decrease in CO frequency is observed. At stressful temperatures, synapsis may be impaired, its timing altered, or the orientation of the spindle in meiosis II may be altered [28]. At extreme temperatures, fertility is reduced, suggesting catastrophic failure of meiosis [29]. Other external stressors have also been shown to modulate CO frequency. Lack of nutrients, treatment with the CNS depressant barbituric acid and the antibiotic streptomycin causes a decease in CO frequency in tomato [30]. In *Drosophila melanogaster* and *Saccharomyces cerevisiae*, lack of nutrients causes an increase in CO frequency [31,32], as does the chemical EDTA in Drosophila and *Chlamydomonas reinhardii* [33,34].

Intrinsically, heterochiasmy, or differences in CO frequency between the sexes, occurs in a wide variety of taxa; most often there is a tendency towards elevated recombination rates in females compared to males, although this pattern is not universal [35,36]. In plants, the tendency towards higher female recombination rates is associated with outbreeding [35,36]. In humans, mice, Drosophila and *C. elegans*, CO frequency decreases with maternal age [6,37–39]. In plants, a similar pattern may hold. In Lycopersicon, CO frequency decreases with age of fruit on the primary meristem [30], while in Arabidopsis, no effect of age on the primary meristem is observed, although an increase in CO frequency is observed when the primary versus secondary and tertiary meristems are compared [7]. The experiments performed in Arabidopsis and Lycopersicon are critically different in one aspect: in Arabidopsis, only the products of male meiosis were observed, while the Lycopersicon data is derived from F2 plants, which include both male and female meiosis. Together, this data suggests that age may play a sex-specific role in CO frequency in plants and other higher eukaryotes.

Figure 1



A proposed Arabidopsis model for stess-induced modulation of CO frequency. As temperature deviates from standard conditions, meiotic CO frequency increases until conditions become unfavorable for meiosis, and meiotic catastrophe ensues. Chromatin re-modeling, specifically, H2A.Z deposition, and the synaptonemal complex (SC) may play a role in CO frequency modulation as temperature changes. Additionally, alternatively-spliced transcripts may contribute to this response.

The synaptonemal complex may play a critical role in modulating CO frequency

The mechanism and genes responsible for changes in meiotic CO frequency in response to extrinsic and intrinsic factors are presently unknown, although several plausible candidates exist (Figure 1). A mechanistic clue may come from the observation that CO placement can also change in response to temperature. In *Fritillaria meleagris* and barley, chiasma were shown to decrease in distal regions with an accompanying shift to interstitial and proximal regions [24••,25]. In other organisms, the response of CO frequency to temperature was locus dependent (Table 1). In barley, the shift from distal to proximal was associated with an increase in synaptonemal complex (SC) length [40]; the SC is a tripartite protein structure responsible for meiotic chromosome pairing [41]. Increases in SC length are also associated with intrinsic factors that affect CO frequency, such as sex. In heterochiasmic species, such as humans and mice, the heterogametic sex has both higher CO frequency and longer SC length [42,43]. In Arabidopsis, males exhibit a higher recombination rate, which appears to also be related to SC length [44,45••]. In barley, the increase in CO frequency in response to temperature was male meiosis-specific and was accompanied with an increase in SC length [24••].

The association between SC length and CO frequency, both in response to temperature and in heterochiamsic species, suggests that the SC or the process of its elongation may act to alter CO frequency. In budding yeast, the SC transverse filament protein, ZIP1, increases spore viability in response to increased temperature in the absence of the ZMM proteins MSH4 and MSH5, although in this case, a corresponding alteration of CO frequency is not observed [46]. In *C. elegans* and *Orzya sativa*, the SC appears to limit rather than enhance CO frequency [47–49]. Meiotic CO frequency is increased in *C. elegans* in response to temperature [6]; consequently, lengthening the SC in *C. elegans* would be expected to decrease rather than increase CO frequency. Perhaps not coincidentally, pairing of homologous chromosomes is not dependent upon the SC in *C. elegans*, and a positive association between chromosome length and CO frequency is still found in *C. elegans* [47]. Thus if the SC itself plays a causal role in modulating CO frequency, its mode is unlikely to be a universal one.

Chromatin state alters the frequency of crossovers

Several lines of evidence suggest that local CO frequency may also be related to local chromatin state. CO hotspots in Arabidopsis and Mimulus appear to be associated with transcriptional start sites and chromatin [50••,51••]. Specifically, CO hotspots in Arabidopsis are associated with H2A.Z-containing nucleosomes; a decrease in CO frequency is observed in mutants defective for H2A.Z placement [50••]. H2A.Z deposition decreases with increasing temperature [52], suggesting that CO frequency should also increase as temperature decreases. Indeed, in plants grown at 12°C an increase in CO frequency is observed relative to plants grown at 21°C; this difference disappears in mutants defective for H2A.Z deposition [50••]. This data, combined with earlier findings in Arabidopsis of an increase in CO frequency as temperature increases [7], implies that the mechanism

responsible for temperature-dependent modulation of CO frequency has non-linear dynamics across moderate temperature ranges (~12°C to ~29°C), or that there are multiple mechanisms that combine to produce a complex response.

DNA methylation status transforms CO distribution and is temperature-sensitive

Epigenetic modifications are also known to affect the local frequency of COs. In Arabidopsis, mutants of the chromatin-remodeling protein DDM1 and DNA methyltransferase MET1 experience a remodeling of CO placement along chromosome arms—COs are shifted from pericentromeric regions to interstitial regions as a result of epigenetic remodeling [53–55]. It is interesting that DNA methylation is also temperature-dependent. In a survey of Arabidopsis accessions an increase in transposon-associated CHH methylation was observed at 16°C relative to 10°C [56••], demonstrating that DNA methylation is temperature-dependent. A relationship between northern accessions that inhabit cooler environments and an increase in CG methylation of genes was also observed, suggesting that CG methylation of genes may be locally adaptive [56••]. It is currently unknown how and if the distribution of COs in Arabidopsis changes in response to temperature and other biotic and abiotic stressors, although it certainly seems plausible that epigenetic modifications may act along with other factors to remodel the CO landscape in response to such stressors.

The genetics of modulating meiotic CO frequency

Regardless of the roles of the SC, chromatin, and DNA methylation in modulating CO frequency, we are still left with unanswered questions—for example, which genes are responsible for inducing stress-related changes in CO frequency? Recently, it was discovered that absence of the cyclin-dependent kinase CDKG1 in Arabidopsis results in a temperature-dependent meiotic phenotype of reduced crossing over, resulting from defects in SC formation [57••]. Although CDKG1 acts in a pivotal temperature-dependent manner to maintain the SC, it remains unclear if it can act to alter the SC causing an increase in CO frequency in plants under heat stress. However, there is some evidence that supports a role for RNA splicing genes and alternatively-spliced transcripts in the meiotic thermosensory response. Genes involved in RNA splicing function in thermosensory-induced floral initiation [58], while diurnal temperature fluctuations result in alternatively-spliced transcripts of circadian clock genes [59]. Together, this suggests that RNA splicing factors or alternatively-spliced transcripts may be important for temperature sensing in plants, as well as alteration of CO frequency in response to temperature fluctuations.

Variation in CO frequency among lines suggests that CO frequency is modulated by trans effects as well [60–62]. Similarly, heterozygous regions in Arabidopsis have more COs when they are juxtaposed with regions of adjacent homozygosity [63••], and CO frequency is increased in Arabidopsis F1 hybrids [64]. However, on a local scale, sequence diversity appears to impede recombination in yeast, humans, and mice [65–67], presumably this phenomenon is caused by sequence mismatches which impair successful strand invasion [68]. In maize, transposon polymorphism attenuates CO frequency [69,70], however it seems possible that in this case transposon polymorphism may be confounded with methylation status, as transposons may be heavily methylated and COs display a negative association with methylation [71,50••]. Within species nucleotide diversity is known to correlate with recombination rate [72], although it seems likely that recombination, along with selection, shapes patterns of nucleotide diversity by reducing Hill–Robertson effects [73–75], rather than polymorphism driving recombination.

Type I and Type II CO pathways may play unique roles in response to stress

Plants have both Type I and Type II COs, and exhibit plasticity in their meiotic CO frequency. It remains unclear if both types of COs contribute to frequency modulations, either independently or in conjunction. Furthermore, it is possible that changes in CO frequency in response to abiotic and biotic factors are not regulated by the same mechanisms or pathways across species. In Arabidopsis, temperature modulates both CO and gene conversion frequency, while differences in developmental stage are associated only with alteration of CO frequency but not gene conversion frequency, suggesting that separate processes, and potentially, pathways, regulate the temperature and development phenomenon [76]. While most, if not all, currently described hyper-recombinant mutants in Arabidopsis that have been characterized at the pathway level drive increases in Type II CO frequency alone [77,78•,79•], loss of CG methylation in *met1* mutants reveals that DNA methylation controls the placement (but not frequency) of Type I COs [80••]. Evidence from barley suggests that both pathways may play important but unique role in alterations in CO frequency in response to temperature; an overall increase in CO frequency in response to heat was accompanied by a shift in the distribution, but not number, of Type I (MLHI) foci [24••]. This suggests, although not conclusively, that in barley the placement of Type I COs is altered at elevated temperatures, perhaps via epigenetic modifications, and that at elevated temperatures, additional COs are derived from the Type II pathway. Intriguingly, polyploidization causes an increase in Type I COs in Brassica [81] and overall CO frequency in neopolyploids has been observed [82–84]. Neopolyploids often exhibit extensive changes in methylation [85,86], which

may play a role in alteration of CO frequency and distribution post-polyploidization.

Putting it all together: an inevitable link between stress and recombination?

Finally, it is possible that alterations in meiotic CO frequency are a consequence of the evolutionary heritage of meiotic machinery. Many components of the meiotic recombination pathway are either directly involved in mitotic DNA damage repair, or are homologs to proteins involved in mitotic DNA damage repair (*e.g.*, MSH4, MLH1). Alteration of recombination frequency by external factors is not restricted to meiosis; the frequency of somatic homologous recombination events is also altered by external factors. Induced DNA damage is repaired by either non-homologous end joining or somatic homologus recombination [87]. Abiotic stresses, such as viral infection, temperature shifts, osmotic and oxidative stress, and UV-radiation are followed by an increase in somatic homologous recombination [88–93]. Interestingly, in Arabidopsis, mitotic recombination follows the same temperature pattern as seen in meiosis: an increase in CO frequency is observed at temperature extremes [94].

Both Type I and Type II CO proteins either have known mitotic functions or are homologs of bacterial genes involved in mitotic recombination or DNA damage repair. Meiosis-specific Type I ZMM proteins MSH4 and MSH5 are homologs of the bacterial MutS mismatch repair (MMR) proteins which have lost their mismatch repair function [16,18]. MSH4 and MSH5 have likely retained their ability to identify mis-matched regions of heteroduplex DNA, which is an intermediate product of both the DSBR and SDSA pathways of meiotic recombination. In the MMR system, MutS homologs recognize mismatched DNA sequences and interact with MutL [95]. The MutL homolog and Type I protein MLHI works to both promote somatic homologous recombination and prevent recombination between divergent sequences [96]. In meiosis, MLHI co-localizes with MLH3 to mark sites that will become Type I COs, but its absence is not marked by severe reductions in fertility like those seen in *msh4* plants [96,97]. MUS81, the only confirmed Type II pro-recombination protein, is an endonuclease that also has a function in mitotic DNA damage repair [17,98]. Together, this data suggests that the evolution of meiosis from mitosis may affect how meiotic CO frequency is modulated in response to stress.

Conclusions

The varied response of CO frequency to temperature across organisms suggests a recurrent evolutionary innovation that may have diverse mechanistic basis across organisms. Regardless, the SC, DNA methylation, chromatin modifications, and RNA splicing all seem to be plausible candidates for the mechanism underpinning modulation of meiotic CO frequency in response to stressors. In many species, CO frequency in response to temperature follows a U shaped pattern [21,22] (Table 1). Thus, in addition to different mechanisms modulating CO frequency across species, it is also possible that different mechanisms mediate changes in CO frequency within species. Given their sessile nature, the ability of plants to both sense and respond to their environment in a plastic manner is of significant importance, as this ability may also have adaptive consequences. Consistent with this hypothesis, evidence from Drosophila suggests that alteration of meiotic CO frequency does not necessarily increase organismal fitness [99••] but does result in more genetically variant (recombinant) offspring; which provides grist for the evolutionary mill. In addition to its possible adaptive role, understanding the placement and frequency of meiotic COs could be an invaluable tool in plant breeding efforts that do not entail genetic modifications.

Acknowledgement

JLM and GPC are funded by The United States National Science Foundation (MCB-1121563).

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Barton NH, Charlesworth B: **Why sex and recombination?** *Science* 1998, **281**:1986-1990.
2. Mercier R, Jolivet S, Vezon D, Huppe E, Chelysheva L, Giovanni M, Nogué F, Doutriaux M-P, Horlow C, Grelon M *et al.*: **Two meiotic crossover classes cohabit in Arabidopsis**. *Curr Biol* 2005, **15**:692-701.
3. Chelysheva L, Gendrot G, Vezon D, Doutriaux M-P, Mercier R, Grelon M: **Zip4/Spo22 is required for Class I CO formation but not for synapsis completion in *Arabidopsis thaliana***. *PLoS Genet* 2007, **3**:e83.
4. Sánchez-Morán E, Santos JL, Jones GH, Franklin FCH: **ASY1 mediates AtDMC1-dependent interhomolog recombination during meiosis in Arabidopsis**. *Genes Dev* 2007, **21**:2220-2233.
5. Martini E, Diaz RL, Hunter N, Keeney S: **Crossover homeostasis in yeast meiosis**. *Cell* 2006, **126**:285-295.
6. Rose AM, Baillie DL: **The effect of temperature and parental age on recombination and nondisjunction in *Caenorhabditis elegans***. *Genetics* 1979, **92**:409-418.
7. Francis KE, Lam SY, Harrison BD, Bey AL, Berchowitz LE, Copenhaver GP: **Pollen tetrad-based visual assay for meiotic recombination in Arabidopsis**. *Proc Natl Acad Sci U S A* 2007, **104**:3913-3918.
8. Keeney S, Giroux CN, Kleckner N: **Meiosis-specific DNA double-strand breaks are catalyzed by Spo11, a member of a widely conserved protein family**. *Cell* 1997, **88**:375-384.
9. Kurzbauer M-T, Uanschou C, Chen D, Schlögelhofer P: **The recombinases DMC1 and RAD51 are functionally and spatially separated during meiosis in Arabidopsis**. *Plant Cell* 2012, **24**:2058-2070.
10. Da Ines O, Degroote F, Goubely C, Amiard S, Gallego ME, White CI: **Meiotic recombination in Arabidopsis is catalysed by DMC1, with RAD51 playing a supporting role**. *PLoS Genet* 2013, **9**:e1003787.

11. Neale MJ, Keeney S: **Clarifying the mechanics of DNA strand exchange in meiotic recombination**. *Nature* 2006, **442**:153-158.

12. Szostak JW, Orr-Weaver TL, Rothstein RJ, Stahl FW: **The double-strand-break repair model for recombination**. *Cell* 1983, **33**:25-35.

13. McMahill MS, Sham CW, Bishop DK: **Synthesis-dependent strand annealing in meiosis**. *PLoS Biol* 2007, **5**:e299.

14. Sung P, Klein H: **Mechanism of homologous recombination: mediators and helicases take on regulatory functions**. *Nat Rev Mol Cell Biol* 2006, **7**:739-750.

15. Copenhaver GP, Housworth EA, Stahl FW: **Crossover interference in Arabidopsis**. *Genetics* 2002, **160**:1631-1639.

16. Higgins JD, Armstrong SJ, Franklin FCH, Jones GH: **The Arabidopsis MutS homolog AtMSH4 functions at an early step in recombination: evidence for two classes of recombination in Arabidopsis**. *Genes Dev* 2004, **18**:2557-2570.

17. Berchowitz LE, Francis KE, Bey AL, Copenhaver GP: **The role of AtMUS81 in interference-insensitive crossovers in *A. thaliana***. *PLoS Genet* 2007, **3**:e132.

18. Higgins JD, Vignard J, Mercier R, Pugh AG, Franklin FCH, Jones GH: **AtMSH5 partners AtMSH4 in the class I meiotic crossover pathway in *Arabidopsis thaliana*, but is not required for synapsis**. *Plant J* 2008, **55**:28-39.

19. Mercier R, Mézard C, Jenczewski E, Macaisne N, Grelon M: **The molecular biology of meiosis in plants**. *Annu Rev Plant Biol* 2015, **66**:297-327.

20. Plough HH: **The effect of temperature on crossing over in Drosophila**. *J Exp Zool Part A Ecol Genet Physiol* 1917, **24**:147-209.

21. Wilson JY: **Chiasma frequency in relation to temperature**. *Genetica* 1959, **29**:290-303.

22. Bomblies K, Higgins JD, Yant L: **Meiosis evolves: adaptation to external and internal environments**. *New Phytol* 2015, **208**:306-323.

23. Church K, Wimber DE: **Meiosis in the grasshopper: chiasma frequency after elevated temperature and X-rays**. *Can J Genet Cytol* 1969, **11**:209-216.

24. •• Phillips D, Jenkins G, Macaulay M, Nibau C, Wnetrzak J, Fallding D, Colas I, Oakey H, Waugh R, Ramsay L: **The effect of temperature on the male and female recombination landscape of barley**. *New Phytol* 2015, **208**:421-429.
The authors use MLH3 foci staining and BC1 genetic maps to demonstrate that CO frequency increases with temperature in males but not females; Type I CO distribution but not frequency is altered. The first study to examine the temperature effect with regard to CO pathway.

25. Barber HN: **The experimental control of chromosome pairing in *Fritillaria***. *J Genet* 1942, **43**:359-374.

26. Elliott CG: **The effect of temperature on chiasma frequency**. *Heredity (Edinb)* 1955, **9**:385-398.

27. Loidl J: **Effects of elevated temperature on meiotic chromosome synapsis in *Allium ursinum***. *Chromosoma* 1989, **97**:449-458.

28. De Storme N, Geelen D: **The impact of environmental stress on male reproductive development in plants: biological processes and molecular mechanisms**. *Plant Cell Environ* 2014, **37**:1-18.

29. Zinn KE, Tunc-Ozdemir M, Harper JF: **Temperature stress and plant sexual reproduction: uncovering the weakest links**. *J Exp Bot* 2010, **61**:erq053-1968.

30. Griffing B, Langridge J: **Factors affecting crossing over in the tomato**. *Aust J Biol Sci* 1963, **16**:826-837.

31. Neel JV: **A relation between larval nutrition and the frequency of crossing over in the third chromosome of *Drosophila melanogaster***. *Genetics* 1941, **26**:506.

32. Abdullah MFF, Borts RH: **Meiotic recombination frequencies are affected by nutritional states in *Saccharomyces cerevisiae***. *Proc Natl Acad Sci U S A* 2001, **98**:14524-14529.

33. Levine RP: **Chromosome structure and the mechanism of crossing over**. *Proc Natl Acad Sci U S A* 1955, **41**:727-730.

34. Eversole RA, Tatum EL: **Chemical alteration of crossing-over frequency in Chlamydomonas**. *Proc Natl Acad Sci U S A* 1956, **42**:68-73.

35. Lenormand T, Dutheil J: **Recombination difference between sexes: a role for haploid selection**. *PLoS Biol* 2005, **3**:e63.

36. Brandvain Y, Coop G: **Scrambling eggs: meiotic drive and the evolution of female recombination rates**. *Genetics* 2012, **190**:709-723.

37. Stern C: **An effect of temperature and age on crossing-over in the first chromosome of *Drosophila melanogaster***. *Proc Natl Acad Sci U S A* 1926, **12**:530-532.

38. Speed RM: **The effects of ageing on the meiotic chromosomes of male and female mice**. *Chromosoma* 1977, **64**:241-254.

39. Hussin J, Roy-Gagnon M-H, Gendron R, Andelfinger G, Awadalla P: **Age-dependent recombination rates in human pedigrees**. *PLOS Genet* 2011, **7**:e1002251.

40. Higgins JD, Perry RM, Barakate A, Ramsay L, Waugh R, Halpin C, Armstrong SJ, Franklin FCH: **Spatiotemporal asymmetry of the meiotic program underlies the predominantly distal distribution of meiotic crossovers in barley**. *Plant Cell* 2012, **24**:4096-4109.

41. Page SL, Hawley RS: **The genetics and molecular biology of the synaptonemal complex**. *Annu Rev Cell Dev Biol* 2004, **20**:525-558.

42. Lynn A, Koehler KE, Judis L, Chan ER, Cherry JP, Schwartz S, Seftel A, Hunt PA, Hassold TJ: **Covariation of synaptonemal complex length and mammalian meiotic exchange rates**. *Science* 2002, **296**:2222-2225.

43. Kleckner N, Storlazzi A, Zickler D: **Coordinate variation in meiotic pachytene SC length and total crossover/chiasma frequency under conditions of constant DNA length**. *Trends Genet* 2003, **19**:623-628.

44. Drouaud J, Mercier R, Chelysheva L, Bérard A, Falque M, Martin O, Zanni V, Brunel D, Mézard C: **Sex-specific crossover distributions and variations in interference level along *Arabidopsis thaliana* chromosome 4**. *PLoS Genet* 2007, **3**:e106.

45. •• Giraut L, Falque M, Drouaud J, Pereira L, Martin OC, Mézard C: **Genome-wide crossover distribution in *Arabidopsis thaliana* meiosis reveals sex-specific patterns along chromosomes**. *PLoS Genet* 2011, **7**:e1002354.
Using BC1 genetic maps, the authors demonstrate that male and female recombination landscapes differ drastically; male CO frequency is high at ends of chromosome arms. Previously discovered relationships between GC content, TE content, gene density, and CpG ratio are best explained by the distribution of the elements along the chromosome arms rather than the features themselves.

46. Chan AC-H, Borts RH, Hoffmann E: **Temperature-dependent modulation of chromosome segregation in *msh4* mutants of budding yeast**. *PLoS One* 2009, **4**:e7284.

47. Libuda DE, Uzawa S, Meyer BJ, Villeneuve AM: **Meiotic chromosome structures constrain and respond to designation of crossover sites**. *Nature* 2013, **502**:703-706.

48. Wang K, Wang C, Liu Q, Liu W, Fu Y: **Increasing the genetic recombination frequency by partial loss of function of the synaptonemal complex in rice**. *Mol Plant* 2015, **8**:1295-1298.

49. Wang M, Wang K, Tang D, Wei C, Li M, Shen Y, Chi Z, Gu M, Cheng Z: **The central element protein ZEP1 of the synaptonemal complex regulates the number of crossovers during meiosis in rice**. *Plant Cell* 2010, **22**:417-430.

50. •• Choi K, Zhao X, Kelly KA, Venn O, Higgins JD, Yelina NE, Hardcastle TJ, Ziolkowski PA, Copenhaver GP, Franklin FCH *et al.*: **Arabidopsis meiotic crossover hot spots overlap with H2A.Z nucleosomes at gene promoters**. *Nat Genet* 2013, **45**:1327-1336.

Along with Ref. [51••], examines hotspot designation in plants; found that CO frequency is elevated at promoters and CO hotspots are associated with chromatin-associated factors, such as H2A.Z nucleosomes and H3K4me3. Mutants defective for H2A.Z nucleosome deposition show a decrease in CO frequency, as well as a reduction in the number of RAD51, DMC1, and MLH1 foci.

51. •• Hellsten U, Wright KM, Jenkins J, Shu S, Yuan Y, Wessler SR, Schmutz J, Willis JH, Rokhsar DS: **Fine-scale variation in meiotic recombination in Mimulus inferred from population shotgun sequencing**. *Proc Natl Acad Sci U S A* 2013, **110**:19478-19482.
See also Ref. [50••]. Innovative use of population-level whole genome shotgun sequencing leads to creation of fine-scale recombination map, which reveals that CO hotspots are concentrated in promoters.

52. Kumar SV, Wigge PA: **H2A.Z-containing nucleosomes mediate the thermosensory response in Arabidopsis**. *Cell* 2010, **140**:136-147.

53. Melamed-Bessudo C, Levy AA: **Deficiency in DNA methylation increases meiotic crossover rates in euchromatic but not in heterochromatic regions in Arabidopsis**. *Proc Natl Acad Sci U S A* 2012, **109**:E981-8.

54. Mirouze M, Lieberman-Lazarovich M, Aversano R, Bucher E, Nicolet J, Reinders J, Paszkowski J: **Loss of DNA methylation affects the recombination landscape in Arabidopsis**. *Proc Natl Acad Sci U S A* 2012, **109**:5880-5885.

55. Yelina NE, Choi K, Chelysheva L, Macaulay M, de Snoo B, Wijnker E, Miller N, Drouaud J, Grelon M, Copenhaver GP *et al.*: **Epigenetic remodeling of meiotic crossover frequency in *Arabidopsis thaliana* DNA methyltransferase mutants**. *PLoS Genet* 2012, **8**:e1002844.

56. •• Dubin MJ, Zhang P, Meng D, Remigereau M-S, Osborne EJ, Casale FP, Drewe P, Kahles A, Jean G, Vilhjálmsson B *et al.*: **DNA methylation in Arabidopsis has a genetic basis and shows evidence of local adaptation**. *Elife* 2015, **4**:e05255.
Transposon-associated CHH methylation is responsive to temperature and has a genetic basis; gene body methylation is associated with latitude in 19 Arabidopsis accessions. In conjunction with the finding of a genetic basis to these differences, this paper provides novel evidence that methylation may play a role in adaptation to environment.

57. •• Zheng T, Nibau C, Phillips DW, Jenkins G, Armstrong SJ, Doonan JH: **CDKG1 protein kinase is essential for synapsis and male meiosis at high ambient temperature in *Arabidopsis thaliana***. *Proc Natl Acad Sci U S A* 2014, **111**:2182-2187.
Mutants of the Arabidopsis cyclin-dependent kinase G (CDKG1) exhibits a series of temperature-dependent meiotic defects; at 23°C but not 12°C, the SC complex is not properly formed, a reduced number of bivalents are observed, and CO frequency is reduced. Provides crucial evidence that genes involved in RNA splicing may play a role in temperature sensitivity.

58. Balasubramanian S, Sureshkumar S, Lempe J, Weigel D: **Potent induction of *Arabidopsis thaliana* flowering by elevated growth temperature**. *PLoS Genet* 2006, **2**:e106.

59. James AB, Syed NH, Bordage S, Marshall J, Nimmo GA, Jenkins GI, Herzyk P, Brown JWS, Nimmo HG: **Alternative splicing mediates responses of the Arabidopsis circadian clock to temperature changes**. *Plant Cell* 2012, **24**:961-981.

60. Sanchez-Moran E, Armstrong SJ, Santos JL, Franklin FCH, Jones GH: **Variation in chiasma frequency among eight accessions of *Arabidopsis thaliana***. *Genetics* 2002, **162**:1415-1422.

61. Smukowski CS, Noor MAF: **Recombination rate variation in closely related species**. *Heredity (Edinb)* 2011, **107**:496-508.

62. Bauer E, Falque M, Walter H, Bauland C, Camisan C, Campo L, Meyer N, Ranc N, Rincent R, Schipprack W: **Intraspecific variation of recombination rate in maize**. *Genome Biol* 2013, **14**:R103.

63. •• Ziolkowski PA, Berchowitz LE, Lambing C, Yelina NE, Zhao X, Kelly KA, Choi K, Ziolkowska L, June V, Sánchez-Morán E *et al.*: **Juxtaposition of heterozygous and homozygous regions causes reciprocal crossover remodelling via interference during Arabidopsis meiosis**. *Elife* 2015, **4**:607.
Used 32 Arabidopsis accessions crossed to a reporter line to show that CO frequency is elevated both in hybrids and in regions of heterozygosity that are adjacent to homozygous regions. Furthermore, these regions of heterozygosity preclude the placement of COs in nearby regions of homozygosity, thus displaying stronger interference.

64. Barth S, Melchinger AE, Devezi-Savula B, Lübberstedt T: **Influence of genetic background and heterozygosity on meiotic recombination in *Arabidopsis thaliana***. *Genome* 2001, **44**:971-978.

65. Borts RH, Haber JE: **Meiotic recombination in yeast: alteration by multiple heterozygosities**. *Science* 1987, **237**:1459-1465.

66. Jeffreys AJ, Neumann R: **Factors influencing recombination frequency and distribution in a human meiotic crossover hotspot**. *Hum Mol Genet* 2005, **14**:2277-2287.

67. Baudat F, de Massy B: **Cis- and trans-acting elements regulate the mouse Psmb9 meiotic recombination hotspot**. *PLoS Genet* 2007, **3**:e100.

68. Chakraborty U, Alani E: **Understanding how mismatch repair proteins participate in the repair/anti-recombination decision**. *FEMS Yeast Res* 2016, **16**:fow071.

69. Yao H, Schnable PS: **Cis-effects on meiotic recombination across distinct a1-sh2 intervals in a common Zea genetic background**. *Genetics* 2005, **170**:1929-1944.

70. Dooner HK, He L: **Maize genome structure variation: interplay between retrotransposon polymorphisms and genic recombination**. *Plant Cell* 2008, **20**:249-258.

71. Slotkin RK, Martienssen R: **Transposable elements and the epigenetic regulation of the genome**. *Nat Rev Genet* 2007, **8**:272-285.

72. Begun DJ, Aquadro CF: **Levels of naturally occurring DNA polymorphism correlate with recombination rates in *D. melanogaster***. *Nature* 1992, **356**:519-520.

73. Hill WG, Robertson A: **The effect of linkage on limits to artificial selection**. *Genet Res* 1966, **8**:269-294.

74. McGaugh SE, Heil CSS, Manzano-Winkler B, Loewe L, Goldstein S, Himmel TL, Noor MAF: **Recombination modulates how selection affects linked sites in Drosophila**. *PLoS Biol* 2012, **10**:e1001422.

75. Campos JL, Halligan DL, Haddrill PR, Charlesworth B: **The relation between recombination rate and patterns of molecular evolution and variation in *Drosophila melanogaster***. *Mol Biol Evol* 2014, **31**:1010-1028.

76. Sun Y, Ambrose JH, Haughey BS, Webster TD, Pierrie SN, Muñoz DF, Wellman EC, Cherian S, Lewis SM, Berchowitz LE: **Deep genome-wide measurement of meiotic gene conversion using tetrad analysis in *Arabidopsis thaliana***. *PLoS Genet* 2012, **8**:e1002968.

77. Crismani W, Girard C, Froger N, Pradillo M, Santos JL, Chelysheva L, Copenhaver GP, Horlow C, Mercier R: **FANCM limits meiotic crossovers**. *Science* 2012, **336**:1588-1590.

78. • Girard C, Chelysheva L, Choinard S, Froger N, Macaisne N, Lehmemdi A, Mazel J, Crismani W, Mercier R: **AAA-ATPase FIDGETIN-LIKE 1 and helicase FANCM antagonize meiotic crossovers by distinct mechanisms**. *PLoS Genet* 2015, **11**:e1005369.
In a screen for rescued fertility in *zmm* mutants (see also Ref. [79•]), it was discovered that AAA-ATPase FIDGETIN-LIKE 1 (FIGL1) works to limit Type II COs. In *figl fancm* mutants, an additive effect is observed, suggesting that the the two anti-CO genes work independently. Immunolocalization of DMC1 and RAD51 foci in WT and *figl* mutants suggests that FIGL1 alters the dynamics of DMC1/RAD51 localization on CO intermediates, impeding CO formation.

79. • Séguéla-Arnaud M, Crismani W, Larchevêque C, Mazel J, Froger N, Choinard S, Lemhemdi A, Macaisne N, Van Leene J, Gevaert K *et al.*: **Multiple mechanisms limit meiotic crossovers: TOP3α and two BLM homologs antagonize crossovers in parallel to FANCM**. *Proc Natl Acad Sci U S A* 2015, **112**:4713-4718.
See also Ref. [78•]. Identified additional anti-CO proteins, TOP3α, and RECQ4A/RECQ4B, Bloom Syndrome (BLM) homologs, that work independently of FANCM to limit Type II CO formation. TOP3α and RECQ4A/RECQ4B may work jointly or independently. In *recq4a recq4b fancm* mutants, a ninefold increase in CO frequency is observed without

reductions in fertility, suggesting that CO frequency may be limited by factors other than the potentially mutagenic nature of recombination.

80. •• Yelina NE, Lambing C, Hardcastle TJ, Zhao X, Santos B, Henderson IR: **DNA methylation epigenetically silences crossover hot spots and controls chromosomal domains of meiotic recombination in Arabidopsis**. *Genes Dev* 2015, **29**:2183-2202.
Loss of CG DNA methylation in *met1* mutants leads to a remodeling of chromatin on chromosome arms, causing a decrease in pericentromeric Type I COs and an increase in Type I COs in euchromatin; thus altering the distribution but not frequency of Type I COs.

81. Leflon M, Grandont L, Eber F, Huteau V, Coriton O, Chelysheva L, Jenczewski E, Chèvre A-M: **Crossovers get a boost in Brassica allotriploid and allotetraploid hybrids**. *Plant Cell* 2010, **22**:2253-2264.

82. Brubaker CL, Paterson AH, Wendel JF: **Comparative genetic mapping of allotetraploid cotton and its diploid progenitors**. *Genome* 2011, **42**:184-203.

83. Desai A, Chee PW, Rong J, May OL, Paterson AH: **Chromosome structural changes in diploid and tetraploid A genomes of Gossypium**. *Genome* 2011, **49**:336-345.

84. Pecinka A, Fang W, Rehmsmeier M, Levy AA, Scheid OM: **Polyploidization increases meiotic recombination frequency in Arabidopsis**. *BMC Biol* 2011, **9**:1.

85. Comai L: **The advantages and disadvantages of being polyploid**. *Nat Rev Genet* 2005, **6**:836-846.

86. Song Q, Chen ZJ: **Epigenetic and developmental regulation in plant polyploids**. *Curr Opin Plant Biol* 2015, **24**:101-109.

87. Mehta A, Haber JE: **Sources of DNA double-strand breaks and models of recombinational DNA repair**. *Cold Spring Harb Perspect Biol* 2014, **6** a016428.

88. Puchta H, Swoboda P, Hohn B: **Induction of intrachromosomal homologous recombination in whole plants**. *Plant J* 1995, **7**:203-210.

89. Kovalchuk I, Kovalchuk O, Kalck V, Boyko V, Filkowski J, Heinlein M, Hohn B: **Pathogen-induced systemic plant signal triggers DNA rearrangements**. *Nature* 2003, **423**:760-762.

90. Molinier J, Ries G, Zipfel C, Hohn B: **Transgeneration memory of stress in plants**. *Nature* 2006, **442**:1046-1049.

91. Pecinka A, Rosa M, Schikora A, Berlinger M, Hirt H, Luschnig C, Scheid OM: **Transgenerational stress memory is not a general response in Arabidopsis**. *PLoS One* 2009, **4**:e5202.

92. Kathiria P, Sidler C, Golubov A, Kalischuk M, Kawchuk LM, Kovalchuk I: **Tobacco mosaic virus infection results in an increase in recombination frequency and resistance to viral, bacterial, and fungal pathogens in the progeny of infected tobacco plants**. *Plant Physiol* 2010, **153**:1859-1870.

93. Yao Y, Kathiria P, Kovalchuk I: **A systemic increase in the recombination frequency upon local infection of *Arabidopsis thaliana* plants with oilseed rape mosaic virus depends on plant age, the initial inoculum concentration and the time for virus replication**. *Front Plant Sci* 2013, **4**.

94. Boyko A, Filkowski J, Kovalchuk I: **Homologous recombination in plants is temperature and day-length dependent**. *Mutat Res* 2005, **572**:73-83.

95. Modrich P, Lahue R: **Mismatch repair in replication fidelity, genetic recombination, and cancer biology**. *Annu Rev Biochem* 2003, **65**:101-133.

96. Dion É, Li L, Jean M, Belzile F: **An Arabidopsis MLH1 mutant exhibits reproductive defects and reveals a dual role for this gene in mitotic recombination**. *Plant J* 2007, **51**:431-440.

97. Franklin FCH, Higgins JD, Sanchez-Moran E, Armstrong SJ, Osman KE, Jackson N, Jones GH: **Control of meiotic recombination in Arabidopsis: role of the MutL and MutS homologues**. *Biochem Soc Trans* 2006, **34**:542-544.

98. Hartung F, Suer S, Bergmann T, Puchta H: **The role of AtMUS81 in DNA repair and its genetic interaction with the helicase AtRecQ4A**. *Nucleic Acids Res* 2006, **34**:4438-4448.

99. •• Jackson S, Nielsen DM, Singh ND: **Increased exposure to acute thermal stress is associated with a non-linear increase in recombination frequency and an independent linear decrease in fitness in Drosophila**. *BMC Evol Biol* 2015, **15**:175.
The authors test the fitness-associated recombination (FAR) model as an explanation for the maintenance of plasticity in recombination in populations; find that increases in CO frequency in response to stress are associated with non-linear decreases in fitness, supporting the FAR model, which means that stressed individuals produce fewer offspring with a high recombinant fraction, creating a negative relationship between fitness and recombination frequency. These results are of significance because it provides evidence that stress-induced changes in CO frequency can affect fitness and may thus have adaptive consequences.

100. Belyaev DK, Borodin PM: **The influence of stress on variation and its role in evolution**. *Biol Zentralblatt* 1982, **100**:705-714.

101. Parsons PA: **Evolutionary rates: effects of stress upon recombination**. *Biol J Linnean Soc* 2008, **35**:49-68.

102. White M: **The influence of temperature on chiasma frequency**. *J Genet* 1934, **29**:203-211.

103. Lu BC: **Genetic recombination in *Coprinus*. I. Its precise timing as revealed by temperature treatment experiments**. *Can J Genet Cytol* 2011, **11**:834-847.

104. Lin YJ: **Temperature and chiasma formation in *Rhoeo spathacea* var. *variegata***. *Genetica* 1982, **60**:25-30.

105. Johnston JR, Mortimer R: **Influence of temperature on recombination in yeast**. *Heredity (Edinb)* 1967, **22**:297-303.

106. Lamb BC: **Related and unrelated changes in conversion and recombination frequencies with temperature in *Sordaria fimicola*, and their relevance to hybrid-DNA models of recombination**. *Genetics* 1969, **62**:67-78.

107. Dowrick GJ: **The influence of temperature on meiosis**. *Heredity (Edinb)* 1957, **11**:37-49.