Meiotic Recombination Gets Stressed Out: CO Frequency is Plastic Under Pressure

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Abstract

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.

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 other species, such as *Fritillaria meleagris*, *Allium ursinum*, and *Hyacinthus* [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 decrease 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 reinhardtii* [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.

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 species has both higher CO frequencies 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 heterochiasmic 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 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 homologous

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 mismatched 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 MLH1 works to both promote somatic homologous recombination and prevent recombination between divergent sequences [96]. In meiosis, MLH1 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 without the use of genetic modifications.

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of significance because it provides evidence that stress-induced changes in CO frequency can affect fitness and may thus have adaptive consequences.

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Figure 1. A proposed Arabidopsis model for stress-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.

Crossover Frequency

Temperature