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Evolution and Plasticity of Genome-Wide Meiotic Recombination Rates

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Abstract

Sex, as well as meiotic recombination between homologous chromosomes, is nearly ubiquitous among eukaryotes. In those species that use it, recombination is important for chromosome segregation during gamete production, and thus for fertility. Strikingly, although in most species only one crossover event per chromosome is required to ensure proper segregation, recombination rates vary considerably above this minimum and show variation within and among species. However, whether this variation in recombination is adaptive or neutral and what might shape it remain unclear. Empirical studies and theory support the idea that recombination is generally beneficial but can also have costs. Here, we review variation in genome-wide recombination rates, explore what might cause this, and discuss what is known about its mechanistic basis. We end by discussing the environmental sensitivity of meiosis and recombination rates, how these features may relate to adaptation, and their implications for a broader understanding of recombination rate evolution.

INTRODUCTION

In sexual eukaryotes, two important processes collaborate during gamete formation via meiosis to ensure genome maintenance and generate heritable diversity: chromosome segregation and homologous recombination. Meiotic chromosome segregation shuffles homologous chromosomes into new combinations in every gamete, while homologous recombination both is necessary for chromosome segregation in most species and creates chromosomes with novel allele combinations through crossover and gene conversion events (69, 73, 147). Together with mutation, meiotic segregation and recombination are important forces in adaptation and evolutionary change. These intertwined processes ensure both genome stability and change, and they have important effects on patterns of genetic variation and the efficiency of responses to selection (for reviews, see, e.g., 48, 102). Thus, selection could potentially act on recombination rates to alter the speed or efficiency of adaptation in certain situations. In principle, selection could target recombination at several stages.

Meiosis predates the divergence of modern eukaryotic lineages, and the mechanisms of meiosis and recombination are broadly conserved across species (53, 92, 135). Recombination initiates with the programmed formation of usually hundreds of double-strand breaks, which are resected to generate single-stranded DNA overhangs that can invade the homologous chromosome. This single-strand invasion is important for the recognition and pairing of homologs in many species (69, 146, 147). Early in prophase I, a decision point is reached where a subset of invasion events progress to form a reciprocal crossover between the homologs (18), whereas most events are dissolved as noncrossover events, which are often associated with gene conversion, or have other fates (**Figure 1**). The steps of recombination play out in the context of three-dimensional chromatin loop structures that are connected to a meiosis-specific proteinaceous axis that extends the length of chromosomes in prophase I (77). Recombination events continue to mature until metaphase I, at which point they are cytologically visible as chiasmata. Chiasmata are important for holding chromosomes together and maintaining tension on the spindle, allowing balanced segregation of homologs in anaphase I. Cytologically, these processes appear to be almost invariant across eukaryotes, although individual steps are modified in specific lineages (for reviews, see 69, 146, 147).

Though only one crossover per chromosome is required during meiosis I for balanced segregation, the number of homologous recombination events per chromosome in a given meiosis shows substantial quantitative variation above the minimum both within and between species (38, 129). Moreover, while many of the proteins essential for meiotic processes are structurally and functionally conserved, primary sequence divergence can be substantial (13, 82). Signatures of positive selection have also been observed in meiosis genes in a range of taxa (4, 128, 132, 140). If meiosis itself is so constrained that it remains physically nearly indistinguishable over eons, what drives the observed variation in genome-wide recombination rates? Is recombination rate variation stochastic, is it adaptive, or does it evolve as a pleiotropic consequence of something else that is targeted by selection?

Because genome-wide recombination rates have significant implications for evolution and population genetics, there has been considerable effort to understand how and why they vary (for reviews, see, e.g., 48, 102). Modeling has shown that under some circumstances higher or lower recombination rates between individual loci can indeed evolve under selection, and in most cases this has to do with the rate and efficiency of adaptive evolution (see the section titled Is Recombination Rate Variation Driven by Adaptive Evolution?). However, the results of modeling studies are sensitive to input assumptions, leaving somewhat ambiguous the question of whether recombination rate is commonly an adaptive trait per se. As we describe in more detail in the section
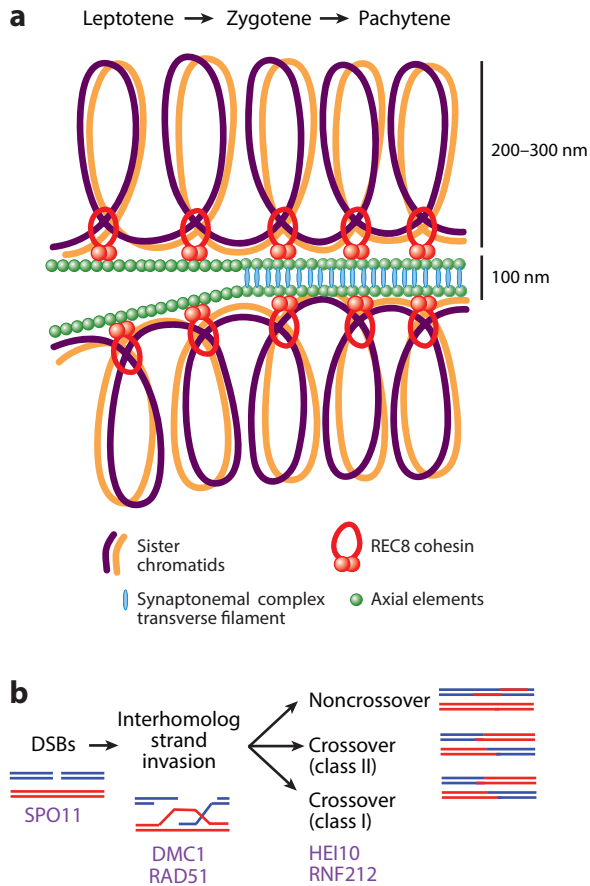
Figure 1

Mechanisms of interhomolog recombination during meiosis. (*a*) During prophase I of meiosis, the chromosomes are replicated (*purple* and *yellow lines*). These are tethered in large chromatin loops by cohesin complexes, which contain the meiosis-specific kleisin REC8. REC8 cohesin promotes the formation of a linear proteinaceous axis, which includes ASY1, ASY3, and ASY4 in plants; Hop1 and Red1 in yeast; and HORMAD1 and SYCP3 in mammals. Later, the synaptonemal complex forms between the homologs to hold them in close apposition during the maturation of recombination events. (*b*) In the lower part of the figure, the broad progression of recombination is illustrated at the DNA level, and major proteins mentioned in the text are shown at their stages of action. Coincident with axis formation, SPO11 complexes generate a large number of DNA double-strand breaks (DSBs) along the chromosomes on the chromatin loops. Resection of the DSBs generates single-stranded DNA (ssDNA), which is bound by DMC1 and RAD51 that promote interhomolog strand invasion. As prophase I progresses, the synaptonemal complex is installed and interhomolog strand invasion events may proceed to form a crossover via the class I (majority) or class II (minority) pathways. The class I pathway relies on HEI10 and RNF212, which are meiosis-specific E3 ligases that have been implicated in recombination rate variation. The processes of DNA repair and recombination are tightly coupled with, and reliant on, cohesin-mediated chromatin compaction and formation of the axis and synaptonemal complex. Figure adapted from Reference 131 (CC BY 4.0).

titled The Genetic Basis of Meiotic Recombination Rate Variation, there is evidence that in some cases recombination rate can indeed be under selection, for example, to accelerate adaptation or reduce mutational load or due to immediate and direct effects on fitness or fertility. Empirical laboratory evolution studies also support the idea that recombination is advantageous for increasing the efficiency of selection as populations adapt to a novel environment (54, 90, 114).

In this review, we draw on both theoretical and empirical studies to explore what might be driving variation in genome-wide meiotic recombination rates, leaving open the possibility that some of the variation may be neutral and stochastic. We also highlight that the environmental responsiveness of meiosis is an underappreciated and potentially key feature for better understanding recombination rate evolution. We first provide an overview of what is known to mechanistically underlie recombination rate variation within and among species. We then discuss why meiotic recombination rate might be under selection in specific cases and end by discussing the phenomenon of recombination rate plasticity and the related concept of fitness-associated recombination. We argue that better accounting for recombination plasticity in empirical and theoretical studies, and its link to the overall environmental sensitivity of meiosis, can help us gain a more complete understanding of recombination rate evolution.

There are a number of topics relevant to recombination rate variation and evolution that, in the interest of space and focus, we do not discuss here. We discuss specifically genome-wide recombination rate variation, meaning variation in the number of crossover events that form per chromosome or genome. We do not discuss other important topics, for example, local variation that arises from hotspot usage and turnover (see, e.g., 19, 133), recombination rate evolution on sex chromosomes (see 32), or relationships between transposons and recombination rates (see 76).

CORRELATES OF GENOME-WIDE MEIOTIC RECOMBINATION RATE VARIATION

Though interhomolog recombination is an almost universal feature of meiosis in sexually reproducing species, quantitative variation in meiotic recombination rates has been observed at multiple levels: among species, among populations within species, between individuals, between sexes, and even within individuals (60, 129). Several correlates have been observed that hint at mechanisms underlying recombination rate variation, which show that selection can target recombination rate at several levels and may ultimately provide insights into the question of why recombination rates evolve.

Broadly, variation in recombination rates both within and among individuals correlates especially strongly with variation in the length of proteinaceous structures that form along meiotic chromosomes, called the axis and synaptonemal complex (SC) (**Figure 1**), rather than with the number of genomic DNA base pairs (45, 89, 120, 137). The axis and SC are multiprotein structures that form specifically during meiosis, are substrates for chromosome pairing, and provide the context for recombination throughout prophase I of meiosis (77, 146, 147). Axes are recruited initially by cohesin, and axis length anticorrelates with the length of cohesin-associated chromatin loops and thus chromatin compaction (77). There is a positive correlation between recombination rate per chromosome and axis/SC length in many taxa. For example, in bovids, the length of chromatin loops negatively correlates with axis/SC length, which in turn correlates positively with crossover number per chromosome (120). Similar correlations have been observed in mice and humans (45, 89). That both SC length and recombination rate variation among mouse strains have a common genetic basis is supported by quantitative trait locus (QTL) mapping, which showed that loci controlling variation in both traits map to the same genomic intervals (136). Interestingly, though there can be substantial variation in recombination rates among cells within individuals, within single meiotic nuclei, recombination rates across chromosomes are coordinated, which also covaries with axis length (138) (see **Figure 1**).

In addition, and perhaps related to an effect on axis length, there is good evidence that chromatin structure connects directly and indirectly to both the number of crossovers and the

number of their precursors, meiotic double-strand breaks (DSBs) (20, 87, 110, 130, 141). Altered chromatin structure alters meiotic DSB patterns, which occur primarily in open chromatin (87, 110, 141). Heterochromatic marks are found in compacted chromosome regions that are generally associated with lower recombination rates, whereas euchromatic marks tend to associate with open chromatin and elevated recombination (1, 17, 20, 24, 35, 117, 134, 144, 145). In mice, ubiquitination of histone H2B can lead to more open chromatin and increased recombination (142), and in yeast, transcription factor binding decreases chromatin compaction and increases recombination at hotspots (97), while tethering of the chromatin-remodeling COMPASS complex to recombination-suppressed regions is sufficient to induce DSB formation and crossovers (1).

Broadly, genomes are organized in chromatin loop structures and large-scale domains [e.g., topologically associated domains (TADs)] that are structured by cohesins and condensins (43). In rice, TAD-like domains are associated with higher levels of polymorphism, open chromatin structure, and higher rates of meiotic crossovers (55). In mice, TAD structures disappear during meiosis, but compartmentalization is nevertheless maintained, and the gene-dense A compartment preferentially sustains the majority of DSBs and crossover events (103). While the above-noted effects are more related to crossover patterning within genomes, they suggest that modulating chromatin could be a way that genome-wide recombination rates might also evolve.

It is also possible that recombination rates can evolve via modification of the tolerance of the meiotic machinery to interhomolog polymorphism. Given that recombination occurs among non-identical homologs, meiotic recombination must tolerate, and may even prefer, some degree of sequence mismatching. Indeed, the meiosis-specific RecA recombinase DMC1 has greater affinity for mismatched than for identical substrates, in contrast to non-meiosis-specific family members, such as RAD51 (85). Supporting the idea that some degree of polymorphism promotes rather than hinders recombination, some chromosome regions in *Arabidopsis thaliana* show higher crossover frequency in interstrain hybrids than in homozygous inbreds (6, 148). Moreover, when juxtaposed with homozygous regions, heterozygous regions have increased crossover frequency at the expense of neighboring homozygous regions (148). This effect requires MSH2, a mismatch sensor protein (6, 148). Modeling of single nucleotide polymorphism density and crossover frequency in *A. thaliana* revealed a parabolic relationship that suggests crossovers are favored in regions of intermediate polymorphism and occur at lower levels in both low- and high-diversity regions (12).

The preference of recombination for intermediate levels of polymorphism is also supported by work in polyploids. In these species, more than two copies of each homolog are present, which allows testing of the recombination machinery's sensitivity to the degree of similarity among multiple differently related homologs. In polyploid rye, for example, heterozygous chromosome associations (associations among similar but non-identical homologs) show higher crossover frequencies than homozygous associations (associations among essentially identical homologs) (10). Work in polyploids also suggests that the extent to which polymorphism affects whether a particular recombination precursor progresses to a crossover event can evolve. Evidence for this comes from allohexaploid wheat, where the derived form of the *Ph1* locus, unlike the ancestral version, conditions strict preferential recombination among more similar (homologous) versus less similar (homeologous) chromosome copies (115). Functionally similar loci exist in other allopolyploids, including *Brassica napus* and *Arabidopsis suecica* (64, 70).

The above observations show that there are links between three-dimensional chromatin structure, cohesin, the structure of the meiotic chromosome axes, and recombination rate, and that it may be possible to tune the sensitivity of the meiotic machinery to respond differently to polymorphism. These correlations hint at mechanisms by which genome-wide recombination rates could evolve.

HOW LOW, OR HIGH, CAN RECOMBINATION RATES GO?

To predict how recombination rates can respond to selection, it is important to know the range of values one can reasonably expect. Recombination rates are likely to fall within particular ranges due to the interplay of costs and benefits (116). The lower bound is usually one per chromosome, as an obligate crossover is essential in most species for balanced homolog segregation at the first meiotic division (69, 73). However, many models explore the benefits of recombination comparing zero to free recombination, which is, on a chromosome scale, not realistic. However, the majority of models assess recombination between a small number of loci, where a zero recombination rate can occur, but this should not be scaled up to assume that the entire genome could have no recombination. In other words, the mechanistic requirement for the obligate crossover means that it is biologically unrealistic to assume that a population can toggle between zero and full recombination at the chromosome level with a single segregating allele. Thus, specific conclusions from models with small numbers of loci cannot necessarily be extrapolated to the genome scale but are nevertheless useful for understanding under which conditions recombination among genes is, or is not, beneficial. More biologically realistic models consider quantitative rather than qualitative (on/off) recombination rate modifiers, larger numbers of loci, and epistasis (see the section titled Is Recombination Rate Variation Driven by Adaptive Evolution?).

There is clearly a lower limit to recombination rate, but is there an upper limit? In experiments with strong directional selection, rapid adaptation is associated with increased genome-wide crossover frequency (see, e.g., 2, 81, 114, 123), supporting the idea that elevated recombination increases the efficiency of selection and thus can be beneficial (see the section titled Is Recombination Rate Variation Driven by Adaptive Evolution?). Yet most eukaryote species have from just one to a few crossovers per chromosome pair per meiosis, despite wide variation in physical genome size, suggesting that there may generally be selection for lower recombination rates (93, 129). However, the causes of this pattern are not entirely clear. For example, mutants that raise crossover rates by 7.8-fold in *A. thaliana* show no obvious immediate fitness or fertility consequences (50, 126). Nevertheless, though there are not always immediate effects, there is evidence that higher recombination rates might be problematic in the longer term. Modeling suggests that in some conditions recombination decreases fitness by breaking up coadapted gene blocks creating so-called recombination load that can negatively affect individual as well as population average fitness (31, 111). Meiotic recombination can also be directly mutagenic (5, 58, 62, 139). Furthermore, while strong selection is often associated with an increase in recombination, selection for higher fertility can be associated instead with a decrease in recombination rate (56). Over the long term, competing pressures may cause recombination rates to fluctuate up or down, depending on the relative strengths of different types of selection acting on a population.

THE GENETIC BASIS OF MEIOTIC RECOMBINATION RATE VARIATION

Understanding which processes can be evolutionarily modified in natural systems could provide insights into the causes and consequences of observed recombination variation and possible constraints on how systems can evolve. A number of genes have been implicated in recombination rate variation in different eukaryotes. For example, in cattle, a large genome-wide association study (GWAS) identified multiple candidate genes as potentially causal for recombination rate variation among individuals, including genes encoding proteins that process early interhomolog meiotic recombination intermediates (*MSH4*, *MSH5*, *RNF212*, and *HFM1*) and one that functions in subsequent crossover resolution (*MLH3*) (74). Recombination rate variation in Soay sheep and

red deer maps to genomic regions containing *RNF212* and the meiotic cohesin subunit *REC8*, and variants of *RNF212* are additionally associated with recombination rate variation in humans and mice (36, 71, 72, 79, 80, 106, 125, 136). Thus, *RNF212*, which is important for the formation of crossover-specific protein complexes and for linking crossover maturation with synapsis (112), is associated strongly with variation in recombination rates in a range of vertebrates. In *Drosophila*, a gene encoding another recombination modifier, mei-218, is strongly diverged between species and affects interspecies differences in recombination rate (21). Though unrelated to the genes identified in vertebrates as candidates for causing recombination rate variation, mei-218 functionally replaces the MSH4-MSH5 complex, which controls crossover maturation in other eukaryotes but is absent in *Drosophila* (78, 91).

In plants, a recent GWAS identified the gene encoding the meiotic cohesin subunit REC8 as a candidate for causing crossover rate variation between wild and domestic barley (44). *REC8* is among several meiotic genes under selection in polyploid *Arabidopsis arenosa* (140, 143), which evolved lower recombination rates likely due to a need to stabilize polyploid meiosis (16, 143). *REC8* also shows evidence of directional selection in a diploid *A. arenosa* population adapted to a distinct habitat (140). Although sequence variation in *REC8* has not yet been causally connected with altered recombination rates in *A. arenosa*, this gene has the potential to affect recombination rates by altering chromatin loop structures and thereby the length of the meiotic axes (77). In *A. thaliana*, several QTLs have been identified that influence crossover frequency between accessions (47, 84, 149). One of these has been identified as the *HEI10* gene (149), which encodes a protein required for class I crossover formation and also draws a parallel across kingdoms, as HEI10 is closely related to RNF212 (33).

Complementing the functional studies mentioned above, more hints about mechanism come from studies of the molecular evolution of meiosis genes. Across mammals, genes encoding meiotic proteins involved in synapsis and the crossover/noncrossover decision show stronger evidence of directional selection than other meiotic genes, and the evolutionary rate of one of them correlates positively with recombination rate (39). In polyploid *A. arenosa*, where selection likely favors reduced recombination rates to regularize polyploid meiosis (16), several meiotic genes with functions in cohesion, axis formation, and synapsis show strong evidence of directional selection (14, 68, 140, 143). In other cases, meiotic genes also show evidence of selection along environmental gradients, or in different habitats, in both animals and plants (4, 128, 132, 140). This may be connected to the effects that temperature or other environmental variables have on meiosis (see the section titled Meiotic Recombination Rate Plasticity and Evolution).

IS RECOMBINATION RATE VARIATION DRIVEN BY ADAPTIVE EVOLUTION?

The observations described in the previous sections indicate that there is substantial genetically controlled variation in recombination rates above the obligatory one per chromosome. The genes identified in animals and plants as directly involved in recombination rate variation, and under selection in divergent populations, point to crossover designation and processing, as well as chromatin compaction and axis structure, as prime candidates for the mechanistic basis. The question now becomes whether recombination rate variation is stochastic or a consequence of selection, and if it is the latter, then selection for what?

Extensive theoretical and evolutionary modeling work has been devoted to exploring whether, or under what conditions, recombination might be advantageous (for reviews, see, e.g., 8, 38, 48, 49). Early modeling studies suggested that recombination can accelerate evolution (see 49), but

in these optimality models, the benefit of recombination falls on the population, not individuals, making the results from these models examples of group selection (48, 49, 102), which has been a hotly debated and controversial concept in evolutionary biology (100). Using recombination modifier models in which recombination rate is affected by a locus linked to two or more other loci, it has also been shown that in some scenarios selection can favor recombination via individual selection (see, e.g., 48, 101). Two major benefits of recombination are that (*a*) it breaks down the linkage of beneficial mutations to deleterious mutations that arises due to drift [i.e., the Hill-Robertson effect (49, 67)] and (*b*) it reduces mutational load, because without recombination, a population cannot decrease load below the lowest level already present in a population (i.e., Muller's ratchet) (49). In other words, recombination can both reduce negative genetic associations and increase positive ones, the key benefit being that it thus effectively breaks the linkage between beneficial loci and deleterious alleles on the same chromosome (8, 9, 49, 101). Conversely, in models in which recombination is selected against, it is generally because it breaks up beneficial associations (7, 31, 111). Modeling studies have shown that selection favors recombination particularly strongly when there is directional selection and when linkage disequilibrium is generated randomly by mutation or drift (7, 8, 30, 101). In small populations responding to strong selection, drift is an especially powerful force that can drive selection for increased recombination (75, 101). Recently, it has also been shown that as models with larger numbers of segregating loci are considered, making them more realistic to the actual structure of genomes, recombination is favored over a greater parameter space of input assumptions (66).

Empirical studies generally support predictions from theory. For example, laboratory evolution studies show that sex and recombination can accelerate adaptation (54, 90, 114). Sequencing of evolved genomes showed that recombining populations adapting under directional selection have lower levels of genetic load and hitchhiking (the fixation of deleterious alleles due to linkage with positively selected loci) during adaptation (90). Strong directional selection also occurs in domestication, and increased recombination has been observed in domesticated species relative to their wild ancestors (119). Studies of genome-wide patterns of polymorphism and their link to recombination rate variation across the genome also support predictions from theoretical studies. For example, in multiple species, low-recombining regions of the genome have reduced diversity and often higher genetic load, while recombination rate correlates positively with increased efficiency of positive and purifying selection (e.g., 11, 29, 37, 108). For example, in maize, regions with lower recombination rates carry a higher genetic load of deleterious mutations relative to regions with elevated recombination (117). In *Drosophila*, low recombination regions are dominated by patterns of polymorphism that suggest background selection, caused by interference among linked alleles at different loci, while patterns of polymorphism in high recombination regions suggest the joint effects of biased gene conversion, selective sweeps, and demographic history (29).

Selection on Genome-Wide Recombination Rates in Polyploids

One clear example where recombination rate may be directly under selection is in autopolyploids, which arise from within-species whole-genome duplication and thus have multiple equally homologous copies of each chromosome (109). Autopolyploids can easily form multivalent associations during meiosis between more than two of the multiple available homologs, which can negatively impact chromosome segregation. Because multivalents require the formation of recombination interactions among multiple homologs, they can at least in theory be prevented by reducing the number of crossovers to just one per chromosome (16). Indeed, the majority of evolved autopolyploids with stable meiosis have reduced crossover rates relative to their diploid progenitors (reviewed in 15, 16). Interestingly, immediately after genome duplication, crossover

rates can increase, which could correlate with higher rates of multivalent formation (e.g., 42, 86, 104). Thus, an important aspect of evolved polyploid meiotic stability is likely a reduction of crossover rates relative to the neopolyploid situation. Candidate genes that mediate meiotic stabilization in autopolyploid *A. arenosa* were identified in genome scanning experiments of a diploid and an evolved tetraploid derivative (68, 143). Among the identified genes were those encoding several key meiotic proteins, including the meiotic cohesin subunit REC8, several cohesin regulators, and axis and SC components. Although these genetic variants have yet to be causally connected to a change in recombination rate, they are promising candidates.

Meiotic Drive as a Possible Driver of Selection on Recombination Rates

Genetic inheritance through meiosis is generally balanced, in that any given allele has in principle a 50/50 chance of being represented in any given gamete from a diploid heterozygote. Any genetic change that can bias this ratio in its own favor has a tremendous evolutionary advantage, effectively cheating the democratizing effect of inheritance. Selfish meiotic drive systems that bias allelic transmission have arisen repeatedly (for a detailed discussion, see 26). One major class of drive loci are genes that encode proteins or RNAs that poison competing male gametes. These systems consist of a minimum of two components: a killer locus that encodes a molecular poison and a linked antidote locus that rescues its carriers from the poison. Examples include the *t* haplotype in mice, *Segregation Distorter* in *Drosophila*, and the WTF drivers in fission yeast, all of which contain minimally two genes (26, 99). In such killer-antidote drive systems, recombination between the killer and antidote gives rise to suicide chromosomes that are rapidly selected against, and thus, researchers have proposed that increasing recombination rate can evolve as a defense against two-gene drivers (61). But this defense would likely only be temporarily effective, because in most killer-antidote systems, inversions are also present that prevent crossovers between the killer and antidote genes. Once an inversion arises, an increase in genome-wide recombination rate would no longer be an effective defense against drive systems that locally repress recombination.

In female meiosis, there is a different opportunity for drive. In many species that differentiate male and female meiosis, only one female meiotic product becomes a functional gamete (i.e., an egg). Any genetic change that increases the chance that a chromosome ends up preferentially in the egg rather than, for example, nutritive polar bodies, will be advantageous for its transmission. There are a number of female meiotic drivers known, which can involve either modifications to centromeres or formation of neocentromeres at new locations (25, 113). Modeling has shown that recombination modifiers can be selected for in female drive systems, but whether higher or lower crossover rates suppress or enhance drive depends on the particulars of the system (22). An interesting example is the *Ab10* system in maize, which consists of centromere-like heterochromatic knobs on the chromosome arms that cause drive during meiosis II (113); one (and only one) crossover event between the knob and centromere is important for drive in this system (25, 65). Thus, either higher or lower recombination rates could, in principle, suppress drive in this example.

A change in recombination rate in the context of a driver may be important for more than just suppressing drive itself. Being relatively safe from purging by selection, and effectively mimicking a locus under positive selection, drivers can dramatically affect patterns of linked neutral polymorphism (25, 34) and can cause the accumulation of linked deleterious alleles that are costly to their bearers (26, 46, 52). Just as with the case of breaking up Hill-Robertson interference, or purging genetic load in examples of classical selection, increasing recombination could help unlink drivers from nearby deleterious mutations. While this does not eliminate the driver itself, it can help improve the fitness of progeny that inherit the driver and could thus be directly advantageous

to both the driver and its carriers by reducing the cost of the driver to its carriers due to linked deleterious alleles. Drivers may be important players in recombination rate evolution, but it is important in each case to consider the genetic basis of a drive system in order to predict whether increased recombination will suppress or enhance drive and to understand whether selection on recombination might be targeting the breakup of the drive system itself or unlinking it from other deleterious mutations.
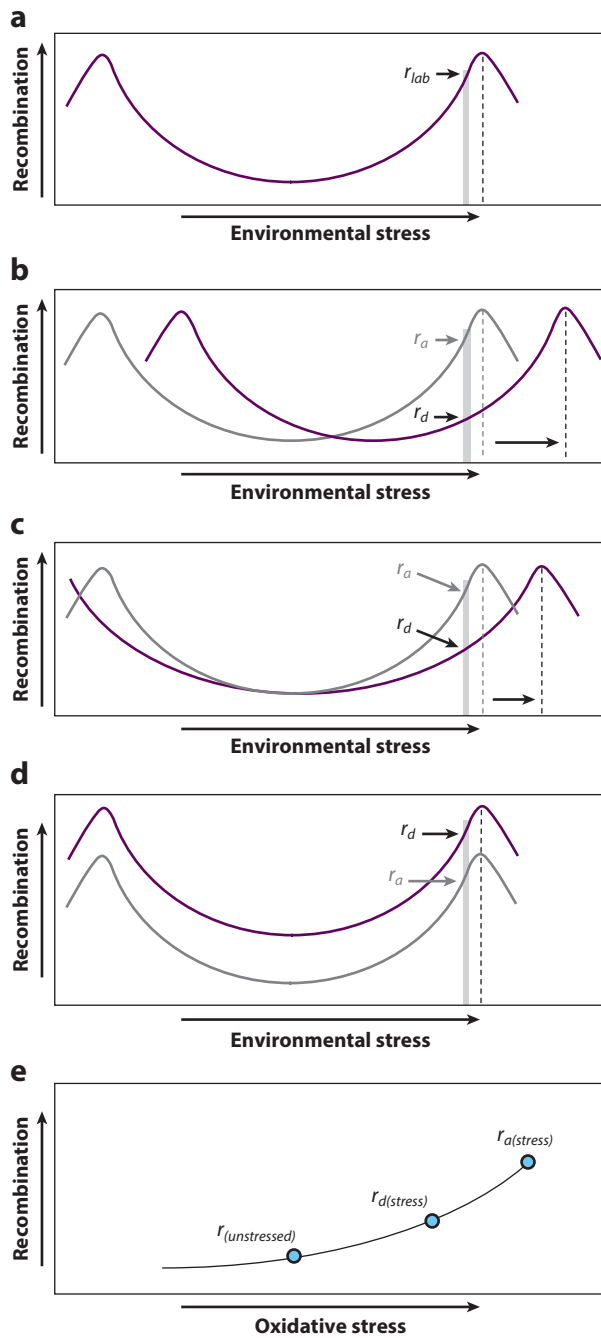
Environment as a Possible Factor in Recombination Rate Evolution

Environmental effects may be important drivers of recombination rate evolution, not only for enhancing the efficiency of adaptation, but also because environmental stress directly challenges the meiotic machinery (15, 94). Excessively high or low temperatures in particular can cause meiosis to fail outright, leading to sterility (15). Thus, as populations adapt to new environments, the meiotic machinery may need to adapt, and recombination rate variation may arise as a by-product (15, 96). Interestingly in this context, genes important for DNA repair and recombination have been found to be under selection in both animal and plant cases where populations have adapted to different climates, though whether this is causally related to environmentally driven selection on meiosis, and whether it causes recombination rate variation, remains to be tested (4, 132, 140). The biotic environment may also play an important role in recombination rate evolution. It has been proposed that pathogen challenge could favor higher recombination rates to speed adaptation to an ever-changing cast of enemies (23, 63). This type of rapid coevolution is termed the Red Queen dynamic and can, under certain assumptions, also lead to selection for increased recombination rates (23, 63, 123). One interesting prediction that has empirical support is that antagonistic coevolution between host and pathogen should raise recombination rates, but exposure to novel pathogens should not; studies of laboratory-selected lines of *Tribolium castaneum* support this conclusion (51).

MEIOTIC RECOMBINATION RATE PLASTICITY AND EVOLUTION

An intriguing feature of meiotic recombination that was recognized already in 1917 from a study in *Drosophila* is that crossover rates are sensitive to temperature (107). Since then, reversible recombination rate plasticity in response to temperature has been widely observed (for review, see 15), suggesting it is a fundamental feature of meiosis. Moreover, many different kinds of environmental factors can affect genome-wide crossover rate; whether other features of meiotic recombination, such as noncrossover events, are affected by temperature is less clear (e.g., 2, 57, 83, 98). Though there appear to be exceptions, in many species where recombination rate plasticity in response to temperature has been observed, U-shaped responses have been reported (15, 88, 94, 107) (**Figure 2a**). This means that as temperature deviates above or below an intermediate (potentially optimal) value, recombination rates rise. Whether other stressors cause the same type of U-shaped response is not known, likely because they are usually only studied in one direction (e.g., studies of dehydration stress are rarely combined with studies of overhydration, or studies of environmental toxins have zero as a lower bound).

Recombination rate plasticity may be inadvertently adaptive, but like recombination itself, it seems to be a nearly ubiquitous feature of eukaryotes, suggesting it is more deeply linked to core functions of meiosis. One argument previously presented (15, 96) is that recombination rate plasticity to temperature is functionally linked to another feature of meiosis, namely that the entire process is temperature sensitive and fails entirely above a certain temperature threshold. This failure, in many cases, can be due to protein aggregation or failures, for example, in cohesin, axis, and SC formation or in the meiotic spindle (15, 40, 41, 96). Recombination rate increases may thus

a

Recombination

r_{lab}

Environmental stress

b

Recombination

r_a

r_d

Environmental stress

c

Recombination

r_a

r_d

Environmental stress

d

Recombination

r_d

r_a

Environmental stress

e

Recombination

$r_{a(stress)}$

$r_{d(stress)}$

$r_{(unstressed)}$

Oxidative stress

(*Caption appears on following page*)

Figure 2 (*Figure appears on preceding page*)

Recombination rate curves and some possible responses to selection. (*a*) Recombination rate plasticity commonly (but not always) follows a U-shaped relationship with temperature, here generically labeled as environmental stress on the x-axis. A U-shaped curve is shown here for illustrative purposes. The curve shows the genome-wide recombination rate (y-axis) against an environmental input (x-axis), like temperature (which is the environmental stress for which U-shaped curves have been reported). U-shaped refers to the observation that, as an environmental variable goes up or down from a midpoint value, recombination rate increases. Vertical dotted lines indicate failure thresholds above or below which meiosis and recombination fail entirely and sterility ensues. The grey bar indicates a laboratory temperature at which recombination is measured, and r_{lab} indicates the recombination rate that is measured. This highlights that recombination rate should not be seen as having a single value for a given organism. (*b*) If a population experiences selection to favor increased environmental (e.g., thermal) tolerance of meiosis, selection may favor shifting the tolerance threshold upward (e.g., by changing the stability or aggregation potential of meiotic proteins themselves). If recombination rate plasticity is unaltered, the curve will also simply shift up the scale. As a result, when organisms adapted to different environments are tested in a single common laboratory condition, they will be found to have distinct recombination rates. In this example, the ancestral population would have a higher recombination rate (r_a) than the derived population (r_d), but this result depends on where along the x-axis the laboratory condition (e.g., temperature) lies. (*c*) Another way in which temperature thresholds could shift upward is if the response itself is flattened, which could occur, for example, by the expression of chaperones to prevent aggregation. Here, too, r_a and r_d differ as in panel *b*, but their relationship will remain consistent, while the magnitude of the difference between them will change depending on where along the curve sampling is done. (*d*) In some conditions, for example, strong directional selection or environmental heterogeneity, a simple increase in recombination may be favored by selection. This would merely push the response curve upward on the y-axis, and results would remain consistent across the sampling range. Note that if recombination rate can only reach a certain level before failure, the higher recombination population would have a more restricted temperature tolerance than the lower one. (*e*) In some cases, it may be that the meiotic system itself is not responding directly to an environmental variable but to the oxidative state of a cell, a readout of organism-level stress. As oxidative stress increases, recombination rate increases. $r_{(unstressed)}$ represents the unstressed recombination rate, while $r_{a(stress)}$ is the recombination rate of an ancestral (unselected) population when exposed to stress. During adaptation to that stress, the organism becomes less responsive to that stress and the oxidative state of cells is not increased as much by stress, and thus the recombination rate responds less strongly [e.g., $r_{d(stress)}$ for an imperfectly adapted population, where a fully adapted population would remain at the unstressed level].

be an early symptom of the same underlying dysfunction that ultimately causes complete failure at more extreme temperatures (15, 96). Indeed, the meiotic cohesin subunit REC8 is known to be oxidative stress sensitive, perhaps leading to stress having downstream effects on axis structure and recombination (105). Thus, the recombination rate curves across temperature ranges are likely intimately linked to the failure thresholds and likely evolve in concert with them (15) (**Figure 2***b–d*). An intriguing example of a direct link between meiotic thermotolerance and plasticity comes from grasshoppers, where there is variation both within and among species in the extent to which heat affects recombination rate, as well as a correlated change in the positions of thermal tolerance thresholds for meiosis (27, 28, 127). Because the failure thresholds are not extremely high [e.g., 15°C in *Endymion*, 24°C in temperate wheat strains, and between 30°C and 37°C in mammals (reviewed in 15)], populations will encounter them, especially as they invade warmer habitats or as the climate changes. In such situations, selection would favor the thresholds shifting in order to accommodate the new climate regimes and improve fertility. In keeping with this, there is a correlation between the temperature at which meiosis fails and the climate of an organism's origin (reviewed in 15).

How might recombination rate plasticity respond to selection for overall meiotic thermotolerance (i.e., the moving of a tolerance threshold)? Understanding how plasticity coevolves with recombination rate and meiotic stability has important implications for how we interpret reports of recombination rate variation observed among populations or species. Specifically, if

the recombination rate curves are in fact linked to meiotic temperature tolerance thresholds, as seems likely (96), the curves may shift as populations adapt to novel habitats (**Figure 2b,c**). Then individuals sampled from two populations would have the same degree of recombination rate plasticity but with distinct low points on the response curves (**Figure 2b**). When individuals from these populations are then tested in a single laboratory condition, they may be observed to differ in recombination rate because they are effectively being tested along different points of a response curve that has shifted sensitivity to temperature (**Figure 2b**). Functionally, this may mean that individuals with different adaptations may experience different levels of stress in a single laboratory condition, with recombination rates responding accordingly. This is in line with the concepts of fitness-dependent recombination and the cellular stress hypothesis, both described below. We propose that genetic variations identified in meiotic cohesin, axis, and SC proteins are strong candidates that could modify recombination rate in response to the environment (i.e., demonstrate plasticity), including temperature.

There is empirical evidence to support the idea that recombination rate and habitat adaptation are indeed linked, perhaps via plasticity. For example, variation in crossover rate observed among *Drosophila* derived from populations in distinct habitats was interpreted as a compensatory response that returns crossover rates to a genome-wide optimum in the context of a plastic response (124). This may also relate directly to a phenomenon described as fitness-dependent or fitness-associated recombination. This concept refers to the observation that genotypes adapted to particular stresses show a weaker response to that stress than sensitive genotypes (2, 121, 122). A demonstration of this comes from *Drosophila* selected for desiccation tolerance. Resistant lines evolved a higher recombination rate than sensitive ones when tested in non-stress conditions, perhaps as a by-product of strong directional selection. However, the recombination rate of resistant lines responded far less to desiccation than that of sensitive ones, leading the authors to conclude that recombination rate plasticity is fitness-dependent, as less fit genotypes respond more strongly in terms of recombination than more fit backgrounds (2). This highlights an important point about the concept of fitness-dependent recombination: It is not a trait that ensures that in a certain environment a certain recombination rate is observed; rather, it relates to the fitness of individuals in a particular environment, such that stressed individuals have higher recombination rates than non-stressed individuals (121) (e.g., **Figure 2e**). This serves as a reminder that recombination rate is not a fixed parameter in a given environment but rather a response to the state of that individual.

The observations described above may all be explicable by the same underlying mechanism, namely that recombination rate plasticity arises as a consequence of dysfunction of meiotic proteins when experiencing cellular stress. Populations that are adapting to novel, initially stressful habitats should at first have higher recombination rates, but as they evolve to mitigate cellular stress and/or make their protein machinery more stress resilient, recombination rate would decline as a by-product (15, 95) (e.g., **Figure 2e**). The idea that plasticity relates to cellular stress is also supported by the observation that stress, manifested as the oxidative state of the cell, directly affects REC8, which is involved in chromatin compaction, and recombination rate by affecting the length of the meiotic axes and perhaps other recombination processes (105). Thus, for a particular stress that causes recombination rate to rise, a less stressed genotype (a resistant one in a certain condition) will show less plasticity and/or a lower recombination rate, because the oxidative state of its cells is lower than that of a sensitive genotype (**Figure 2e**). Another, not mutually exclusive, model could be that temperature affects the fluidity of the synaptonemal complex, perhaps leading to altered dynamics of crossover maturation and thus altered recombination rates (118). Thus, fitness-dependent recombination and recombination rate variation tested in common conditions could both be readouts of the degree of cellular or protein homeostasis stress an organism experienced during meiosis. Importantly, the cellular stress hypothesis also fits with the observation

noted above that a wide range of environmental factors can affect recombination rates, since these factors can all cause cellular stress. Among the stresses that affect recombination, temperature may be, to an extent, special. Temperature is one of the most commonly reported factors causing recombination rate plasticity, although this could represent a testing bias. However, temperature seems to be unique in that it can also cause the outright failure of meiosis beyond specific thresholds (15). Such complete failure of meiosis has not, to our knowledge, been reported for other types of cellular stress.

We might expect that populations adapted to novel temperature regimes could adapt meiosis in two ways: (*a*) by evolving general resistance and thus reducing cellular stress (**Figure 2***e*) and/or (*b*) by reducing the propensity of proteins to aggregate, via either changes in those proteins themselves or upregulation of, for example, chaperones that prevent protein aggregation (**Figure 2***b,c*). It is thus intriguing that populations adapted to distinct habitats, in at least some cases, show evidence of the amino acid sequences of recombination and repair proteins being targeted by selection (e.g., 4, 128, 132, 140). That this variation might drive the adaptation of meiosis to habitat by altering protein resilience to temperature is an intriguing, but as yet untested, hypothesis.

IS RECOMBINATION RATE PLASTICITY, OR ITS STRENGTH, ADAPTIVE?

The observation of recombination rate plasticity has led researchers to explore, via modeling, whether or not plasticity could be selected for as an on/off trait. One argument is that it could be beneficial for organisms that are poorly adapted to their environment to produce more recombined offspring. But is producing more highly recombined offspring in stressful situations beneficial? Modeling studies vary on this point, and while in haploids condition-dependent recombination appears to be beneficial under a wide range of scenarios (e.g., 59), in diploids it is much harder to find conditions in which it is beneficial (3). Though they would commonly place stress on existing genotypes, even strongly fluctuating conditions do not favor recombination rate plasticity (2). In another series of models, plasticity can be beneficial relative to the absence of plasticity via an indirect effect in which selection acts on a modifier locus, due to the association of the modifier with the beneficial genotypes it creates (121). Alternatively, a direct mechanism may occur where the modifier is selected for by breaking down its own association with no-longer-beneficial alleles (i.e. the so-called abandon ship model) (3, 59).

Thus, the modeling literature is inconclusive as to the overall benefits of recombination rate plasticity. But as discussed above, plasticity is likely an unavoidable consequence of the aggregation-prone protein interactions that underpin meiotic chromosome structure and recombination (96). Therefore, plasticity likely cannot really be eliminated, but it could be quantitatively modulated. Upregulation of chaperones, for example, could potentially reduce recombination plasticity by preventing the protein aggregation that may contribute to temperature-associated meiotic failure. Similarly, the evolution of stress tolerance could indirectly mute plastic responses by reducing cellular stress. Interestingly, recombination rates of heat-resistant tomato respond less to heat than they do in cold-resistant tomato and vice versa, while F_1s between the two types show very broad tolerance and little response of recombination to temperature (discussed in 121). One way to interpret this result is that heterozygosity is protective because at each temperature, the plant has one optimized set of proteins from one parent or the other. Whether heterozygosity is similarly protective in other systems will be interesting to explore. The grasshopper system mentioned above also shows that the strength of the plastic response can evolve (27, 28, 127). All of these cases could be explained by the need of parental genotypes to evolve not recombination rate plasticity per se but stress tolerance in their habitats of origin. Thus, an important question about

the evolution of recombination rate plasticity now becomes not whether it exists in particular species but under what scenarios its strength might be increased or decreased by selection.

CONCLUSIONS

Recombination rate variation has long fascinated evolutionary biologists and its near ubiquity is sometimes difficult to explain from a purely theoretical viewpoint. Modeling has shown that recombination is, under certain scenarios, directly beneficial for its role in breaking up linkage and allowing selection to act more efficiently, while in others, it is selected against because it breaks up beneficial combinations. Mechanistically, we know that in the majority of species recombination rates cannot drop below one per chromosome, although between any two given loci, they can drop to zero. Yet above this chromosome-level minimum of one, recombination rates vary widely among species and within them. Conditions that can, in some cases, select for increases above the minimum recombination level seem to be particularly strong in situations with a changing environment, strong directional selection, and finite populations where drift is a factor. Linking theory with mechanism has lagged to some extent, but increasingly we are beginning to understand the mechanisms underlying recombination rate variation, and it is likely that this can soon be connected with understanding how they might relate to selection and perhaps environmental adaptation.

In the future, it will be important to consider plasticity in models of recombination rate evolution, since recombination rate plasticity could presumably influence the dynamics of the evolution of modifier loci. Importantly, the near ubiquity of recombination rate plasticity negates the idea that there is a single recombination rate that can be assigned to an individual or species, and highlights that organisms may instead have ranges of possible recombination rates (as pointed out in another context in 116). With regard to recombination rate plasticity itself, more theory and empirical studies are needed to better understand this phenomenon. However, it seems to be unlikely that plasticity is a trait that could easily be toggled on and off or that it exists purely to produce more recombined offspring when needed. It also seems that the strength of the plastic response can respond to selection, and this may connect back to environmental adaptation and recombination rate evolution, which will be important to consider in both theoretical and empirical studies. Importantly, recombination rate plasticity is not independent of meiotic thermotolerance, and both are likely to respond to selection in a correlated fashion. Important new insights will likely arise if the environmental sensitivity of meiosis and recombination is more regularly accounted for in models and empirical studies of recombination rate evolution.

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