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Review

Landscaping Crossover Interference Across a Genome

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The evolutionary success of eukaryotic organisms crucially depends on the capacity to produce genetic diversity through reciprocal exchanges of each chromosome pair, or crossovers (COs), during meiosis. It has been recognized that COs arise more evenly across a given chromosome than at random. This phenomenon, termed CO interference, occurs pervasively in eukaryotes and may confer a selective advantage. We describe here a multipoint linkage analysis procedure for segregating families to quantify the strength of CO interference over the genome, and extend this procedure to illustrate the landscape of CO interference in natural populations. We further discuss the crucial role of CO interference in amplifying and maintaining genetic diversity through sex-, stress-, and age-induced differentiation.

Meiotic COs and Interference

Meiosis, a specialized type of cell division used by sexually reproducing organisms, reduces the chromosomal complement by half to generate haploid gametes from diploid cells. During meiotic prophase, two homologous chromosomes, each from a different parent, exchange genetic material, leading to recombinant chromosomes. This phenomenon, known as crossing over, together with **independent assortment** (see Glossary) of chromosomes, constitute two important mechanisms by which meiosis promotes genetic diversity and ensures that each gamete inherits a copy of every chromosome [1–4]. Because the exchange occurs between non-sister **chromatids**, COs allow genes from each parent to intermix, and thus form new chromosomes with a different genetic complement, resulting in new traits in offspring. In most organisms the number and distribution of COs are highly regulated by a pervasive mechanism, called CO interference or genetic interference, through which a CO discourages the formation of additional nearby COs by generating some CO-discouraging signal or substance that spreads some distance along the chromosome [5]. Because of such interference, **chiasmata** are more evenly placed along the **bivalents** than would be expected by chance [5,6].

CO interference is a universal phenomenon that has received a great deal of attention since its discovery over a century ago [7]. The extent of CO interference was observed to decrease with distance between COs, while, given the same distance, it is stronger on the same chromosomal arm than on two arms [5]. The strength of interference was thought to depend inversely on the physical distance separating the COs, but a body of evidence also shows that CO interference is more crucially contingent on genetic distance than on physical distance [8]. The distribution density of interference varies among different eukaryotes; for example, interference operates in tens of kb in budding yeast, tens of Mb in mice and humans [8,9], and 46 centimorgans (cM) in

Trends

COs between two homologous chromosomes during meiosis promote genetic diversity, and are regulated by three machineries, (i) obligate CO formation, (ii) CO interference, and (iii) CO homeostasis.

CO interference, a phenomenon where the occurrence of one CO prevents the formation of another CO nearby, is detected traditionally by genetic mutation screening.

The identification of CO interference can also be through multipoint analysis. By designing various sampling strategies based on biological properties of species, this approach can be widely used to estimate and test CO interference for both experimental and natural populations.

Multipoint analysis, that is traditionally used to construct genetic linkage maps, provides a means to detect and quantify CO interference, thereby providing new insights into the mechanistic basis of genome evolution in eukaryotes.

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Drosophila [10]. Variability in CO interference within a specific chromosome region is affected by the overall size and structure of the chromosome [11]. Several studies have explored the mechanistic underpinnings of CO interference by cytogenetic and molecular approaches [12–14]. In *Caenorhabditis elegans*, CO interference is regulated by the anti-recombinase **RTEL-1 protein** through the promotion of meiotic synthesis-dependent strand annealing [2]. Anderson *et al*. [15] found that reduced CO interference results from lack of the DNA-damage-response kinase **Tel1/ATM**. A **topoisomerase II** pathway involving **SUMOylation** of **Red1 protein**, a prominent meiotic axis component, was identified to mediate CO interference in yeast and mammals [16]. de Boer *et al*. [13] reviewed the cytological analysis of CO interference by studying the chromosomal positions of protein complexes involved in CO formation.

Studies have increasingly linked CO interference with sex differences [17,18], stress-induced adaptation [19,20], and aging [21,22], identifying its multifaceted roles in mediating these biological processes. Traditional cytological and genetic screening based on interference mutants has proven to be powerful, despite being labor-intensive, for unraveling the molecular mechanisms of CO interference, but it is difficult to place various types of interference on genetic linkage maps [8] and further use these maps to elucidate how genome-wide variation in CO interference is related to biological processes. In combination with cytological approaches, multipoint genetic linkage analysis provides an alternative for landscaping CO interference throughout the genome by estimating and testing the pattern of interference and genomic distribution related to a particular biological process. Multipoint linkage analysis has been employed to estimate the extent of CO interference and related it to sexual dimorphism and evolution [17,23]. Similarly, Aggarwal *et al*. [20] pioneered the use of multipoint analysis to explore the change of recombination frequency and CO interference when *Drosophila melanogaster* was subject to directional selection for desiccation, hypoxia, or hyperoxia tolerance. By combining multipoint analysis and sex-specific genome-wide association studies (GWAS) in cattle, Wang *et al*. [22] identified a locus in the region of the ***NEK9* gene** that affects the strength of CO interference.

Here, we elaborate and expand on the usefulness of multipoint analysis as an approach to quantify CO interference from linkage mapping data. The past three decades have been fertile ones for the development and use of DNA-based molecular markers to construct high-density linkage maps for a variety of model systems and non-model species [24–27]. Although many of these maps basically cover the entire genomes of species, they have been rarely utilized to chart the CO interference landscape of a genome. By first describing how CO interference takes place during meiosis, we outline the procedure of estimating this important phenomenon through multipoint analysis. In particular, by evaluating the chromosomal distribution of CO interference over the genome, multipoint analysis can activate a further dimension of the application of linkage mapping as a routine genetic tool to investigate genome structure and organization. Although the principle of multipoint analysis was founded on controlled crosses, we show that this approach can be tailored for use in natural populations.

How CO Interference Is Characterized Cytologically

Originally, CO interference was defined genetically, but it has also been characterized by cytological approaches that study the chromosomal positions of protein complexes and chiasmata involved in CO formation [28]. The basic principle of these approaches is to choose cytological CO markers along the bivalents which are used to identify the CO positions. CO markers suitable for cytological studies of interference include chiasmata, **late recombination nodules**, and **immunofluorescent foci** of proteins involved in CO formation [5]. Based on the positions of chiasmata, the gamma model has been used as an approach for modeling the distribution of distances between different CO events along a linear axis (Figure 1) [29,30]. The strength of CO interference is described by the shape parameter (ν) of the fitted gamma