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NOTES AND COMMENTS

SYNAPTONEMAL COMPLEX AND CROSSING-OVER: STRUCTURAL SUPPORT OR INTERFERENCE?

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SUMMARY

Positive cross-over interference is attributed to the prevention of crossing-over by the growing synaptonemal complex. This conjecture is based on a report in the literature that the selection of prospective cross-over sites may actually precede a proper synapsis of homologous chromosomes during meiotic prophase. A genetic test of this notion is suggested using a properly marked trisomic configuration, applicable to a variety of organisms.

1. INTRODUCTION

THE formation of a synaptonemal complex during meiosis (in short: "synapsis") has proved to be almost as universal among eukaryotes as meiosis itself (Moses, 1968; Westergaard and von Wettstein, 1972). Its implication in meiotic recombination, in the establishment of cross-overs or chiasmata, is the widely accepted view of cytogeneticists (Gillies, 1975), although the mode of this implication remains as enigmatic as ever.

At the time when copy-choice models were entertained to explain recombination (see Pritchard, 1960), the idea that recombination is initiated before synapsis was already pondered thoroughly. Yet, the discovery that premeiotic DNA synthesis can even precede nuclear fusion, *e.g.* in *Neottiella* (Rossen and Westergaard, 1966), has reduced the possibility of copy-choice replication to no more than local episodes of repair-type synthesis, which still retains the advantage of explaining high negative interference at intragenic distances (Pritchard, 1960).

Comparative analyses of mutants defective in certain aspects of meiosis have shown that asynaptic mutants such as C(3)G in *Drosophila* (see Lindsley and Sandler, 1977) fail to undergo recombination, and that desynaptic mutants or varieties are known in several species, in which crossing-over is reduced or absent despite initially formed synaptonemal complexes. No mutants are, however, known as yet that retain a normal level of recombination in the absence of synapsis. It therefore appears that a proper complex is a prerequisite at least for the final stages of chiasma formation. Yet there is no compelling evidence that the complex is already involved in the selection of sites where cross-overs are to be established later on.

2. SYNAPSIS INITIATED AT PROSPECTIVE CROSS-OVER SITES?

In fact, Maguire (1977) has seriously challenged the latter extrapolation on the basis of cytological observations in her maize material. In structural

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heterozygotes of an inversion (19 map units = 0·38 chiasmata/tetrad), chiasma frequency within the inverted segment (bridges at anaphase I, 33 per cent) exactly matched the frequency of homologous pairing (inversion loops, also 33 per cent), whereas a reduction of the original map length by a factor corresponding to the lowered incidence of synapsis might have been expected ($0{\cdot}38 \times 0{\cdot}33 = 13$ per cent). In other words: whenever an inversion loop was formed by synapsis, it must have contained a chiasma site. Therefore it was held that a site of commitment to crossing-over was associated with each event of synaptic initiation.

3. Cross-over interference, a preventive effect of the synaptonemal complex?

Maguire's argument has far-reaching consequences indeed. Implicitly it provides a mechanism for positive cross-over interference (the lowered incidence of neighbouring double exchanges), a long-standing unsolved problem. Moreover, the general features of this interference become deducible from a few elementary assumptions, which in turn are likely to yield to experimental scrutiny more easily than other explanations hitherto suggested. These assumptions are listed below, and genetical means for their evaluation will be discussed.

As suggested by Carpenter and Sandler (1974), the term " node " will be used for the establishment of an exchange possibility. If these nodes (i) are only formed before synapsis, and (ii) serve as initiation centres at which synapsis is started, then the growing synaptonemal complex progressively removes the pre-condition (i) from the neighbourhood of the node it started from. This basically means interference. Statistically speaking, the chances of node formation are diminished around any successfully established position. As long as pairwise homologous chromosomal stretches remain unpaired, the chances are that yet another node be established between them; but, once synapsis has embraced an entire chromosome, this will be closed to additional events.

The model implies that each chromosome is given sufficient time to undergo exchange at least once. That condition is a fairly stringent requirement for the prevailing mechanism of meiotic segregation. A chromosome failing to procure any chiasma will precociously disjoin from its homologue; both partners will be distributed at random, with a 50 per cent chance of non-disjunction; and chromosomal accidents, such as Down's syndrome, will follow. (In the cases known of chromosomes regularly remaining achiasmatic, *e.g.* X/Y pairs, additional mechanisms have always been developed so as to ensure proper segregation at anaphase.)

It is obvious that the model is sensitive to variation in rate parameters for the different processes. For instance, interference should be higher the more the step of node formation becomes rate-limiting, occasionally reaching the extreme of complete interference such that each chromosomal arm recieves one and only one chiasma. At the other extreme, if a cell has usually exhausted its potential of node formation before it becomes competent for synaptic initiation, there should be no interference at all.

The basic model (i, ii) is probably too stringent to cover all the features known about interference and synapsis, and a few supplementary remarks appear advisable. (iii) There seem to exist barriers to autonomous synaptic

extension, *e.g.* the centromeres (known to terminate interference of either chromosomal arm) or the break-points of structural heterozygotes. (iv) There may be secondary centres for synaptic initiation, less favourable than the nodes as postulated, *e.g.* the telomeres attached to the nuclear envelope. Such action has been aptly illustrated for female silkworms, devoid of genetic recombination but capable of forming complexes, which tend to zip along entire chromosomal arms with no internal initiation (Rasmussen, 1977).

4. A REAPPRAISAL OF THE MEIOTIC SCENARIO

How does this concept fit into the general framework of meiotic processes? As a corollary to the synaptic interference model, node formation is viewed as being initiated by essentially random contacts of homologous chromosomal sites; yet, fewer sites remain available for further contacts the more synapsis progresses. It is held that the likelihood of such contacts occurring at random in the large eukaryotic genomes has usually been underestimated. The relevant stages, leptotene and zygotene, are particularly lengthy affairs in most organisms, during which the entire nuclear contents are turbulently moved about (as viewed by time-lapse photography). Moreover, most workers agree that synapsis proper is preceded by a recognisable alignment of homologous chromosomes. Hence, homologous sites should be capable of finding each other. Actually it is more difficult to perceive how the relatively narrow synaptonemal complex can prevent additional contacts of the surrounding lumps of chromatin. Evidently not all chromosomal sites are equally likely to engage in those random contacts effectively. Such discrimination is not, however, without precedence: (1) Hybrid DNA (widely accepted as an intermediate in molecular recombination) seems to be started from preferential "opening points" (*e.g.* Whitehouse, 1966; Rossignol, 1969). (2) In lilies it appears that a fraction of the DNA is delayed in replication until zygotene (see Stern and Hotta, 1977). This fraction is interspersed throughout the genome. If its replication is selectively inhibited, synapsis too is prevented.

A presynaptic chromosome may thus be endowed with a fringe of "recognition sites", which can participate in node formation as long as these sites are not immobilised by the synaptonemal complex. After all these sites have been fixed in the complex, the diameter of the complex (about 100 nm) may suffice to keep them effectively separate. Only the contacts previously stabilised by the postulated "nodes" can now be converted into visible "recombination nodules" (Carpenter, 1975; Lindsley and Sandler, 1977). These spherical objects are found in the central axis of the synaptonemal complex. Their numbers and distributions closely match those of chiasmata at a later stage, so that these structures may represent an intermediate phase towards mechanically strong chromosomal exchanges.

5. HOW TO TEST THE MODEL

The model, as outlined above, should have consequences amenable to testing by genetic criteria. A feasible test is suggested below, at least for organisms that allow the recovery of viable progeny from triploid meioses, or from conditions trisomic for only one of the chromosomes. The tester chromosome in the trisomic condition should be marked in a way that the

three partners of a trivalent can be identified with regard to their involvement in adjacent double-exchanges. An appropriate configuration is depicted in fig. 1. This test is based on the reasoning that there should be

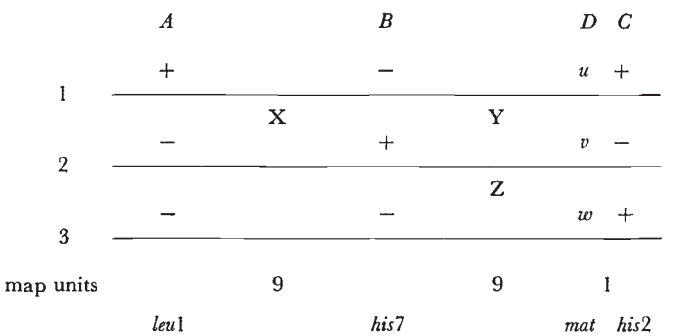

FIG. 1.—A test configuration for " trisomic interference ". Each line represents a pair of sister chromatids in a triploid (or trisomic) meiosis. Haploid progeny, selected for $A^+B^+C^+$, will be scored for the alleles *u*, *v*, or *w* of the differential locus *D*. Selection for A^+B^+ enforces an exchange from chromosome 1 to 2 at X. Selection also for C^+ requires a further exchange, either back to 1 at Y or down to 3 at Z. If exchanges at Y or Z are located between *B* and *D*, they can be differentiated by *u* or *w* respectively (the combination $v\ C^+$ will be neglected as being ambiguous). Cross-overs at Y or Z would be equally frequent if they occurred independently of the enforced exchange at X, whereas Y should outnumber Z if extended pairing-regions excluded the respective third partner over a considerable distance. The example given is based on a region of chromosome II in *Schizosaccharomyces pombe*. A leucine gene and two histidine genes are used for recombinant selection, and three different mating-type alleles (*mat*) will be used in the final scoring (E. Limpert and R. Egel, in preparation).

no preference in the second interval to the enforced crossing-over in the reference segment. Validation of the classical assumption, however, would call for a high degree of such *trisomic interference*, since continuous synapsis should normally confine the double-exchange to two partners, unless a partner switch has occurred in the test interval.

Obviously, the results from such a test will be clearer the lower the number of switches is per tetrad per map length, or the longer the stretches of uninterrupted synapsis. Therefore, this test should preferably be performed on organisms where the number of switches has already been worked out by cytological reconstruction. In the data so far available, internal initiation centres of synapsis have been observed about as frequently as chiasmata (*e.g.* 4 per bivalent in maize; Gillies, 1975). Particularly striking is the uninterrupted extension of the synaptonemal complex from any two homologous telomeres in triploid female silkworms (Rasmussen, 1977). In this case, with no crossing over, there is no internal initiation. Clearly, analogous studies in male silkworms, proficient in crossing over, would be relevant to the question.

The general conformity in distribution of chiasmata and synaptic initiation centres already provides circumstantial evidence in favour of Maguire's suggestion. The genetical test of " trisomic interference " could extend the evidence to a variety of organisms, and to fairly short genetic distances. Such supplementary information is badly needed.

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