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Recombination and chromosome structure in eukaryotes

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SUMMARY

Allelic recombination frequency and pattern in fungi show strong gene-to-gene variation. At least in two fungal species, *Neurospora* and *Schizophyllum*, recombination frequencies in certain chromosomal segments are genetically determined. The possibility that chromosomal proteins and/or synaptinemal complexes may play an important role in regulation of recombination frequency and pattern is discussed.

1. INTRODUCTION

After the discovery that genetic recombination can occur between allelic mutants, the interests of geneticists have been concentrated mainly on what happens with homologous DNA segments in the course of the recombinational process. However, in eukaryotes, DNA, together with some RNA, histones and non-histone proteins, is packed into very complicated chromosome structures. In early stages of meiosis, additional protein synthesis takes place and synaptinemal complexes are formed.

Recombination occurs in prokaryotes and in somatic cells of eukaryotes. Thus neither chromosomal proteins nor synaptinemal complexes are necessary for recombination to take place.* But the question is whether or not they have any influence on this process.

The intention of this paper is to analyse the data concerning recombination in fungi which may indicate that chromosomal proteins and/or synaptinemal complexes influence recombination and perhaps participate in its fine control (see Simchen & Stamberg, 1969*b*).

2. GENE-SPECIFIC VARIATION IN ALLELIC RECOMBINATION PATTERN

Allelic recombination in various genes in fungi has many features in common, such as the occurrence of both reciprocal and non-reciprocal exchanges (conversion), polarization of conversion, clustering of exchanges over very short segments of

* If for mitotic recombination synaptinemal complexes were necessary, one would have to assume that under the influence of mutagens such complexes are formed, since many different mutagens strongly induce mitotic recombination frequency (for most complete review see Zimmermann, 1971).

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genetic material (negative interference), non-additivity in intragenic recombination frequencies, map expansion, etc. There is, however, also a pronounced variation in the expression of these features.

Most abundant evidence on intragenic recombinational events comes from studies carried out by means of tetrad analysis on *Ascobolus immersus*, using genes *46* (Rizet, Lissouba & Mousseau, 1960; Lissouba, 1960; Lissouba *et al.* 1962; Rossignol, 1964), *19* (Lissouba *et al.* 1962; Mousseau, 1967), *75* (Lissouba *et al.* 1962; Rissignol, 1967, 1969), *726* (Makarewicz, 1964), *Y* (Kruszewska & Gajewski, 1967), *84 W* (Paszewski, 1967; Paszewski & Prażmo, 1969) and *164* (Baranowska, 1970).

The heterogeneity of the behaviour of the mutants is particularly visible in the alleles of gene *75*. The frequencies of 3 mutant: 1 wild-type segregation shown by 13 mutants in crosses with the wild-type strain varied from 0·2 to 46·9 per 10^3 tetrads, and 1m:3w segregation varied from 0·6 to 38·6 per 10^3 tegrads. The 3m:1w+1m:3w segregation frequencies varied from 7·2 to 66·5 per 10^3 tetrads. Most of the mutants had very different frequencies of 3m:1w and 1m:3w segregation, so that the coefficients of inequality (frequency of 3m:1w segregation/frequency of 1m:3w segregation) varied from 18 to 0·03. In neither of the other six genes studied were such high conversion frequencies and so wide a variation of these values found. The frequencies of 3m:1w+1m:3w segregation of five *Y* alleles varied from 1 to 3·02, while these values for alleles of the remaining genes were intermediate. The highest value of interallelic recombination, up to 72 per 10^3 tetrads, was also found in gene *75*, while in genes *726*, *Y* and *164* these values did not exceed 14 per 10^3 tetrads.

Very strong polarization of 1m:3w segregation in mutant × wild-type crosses as well as conversion in the mutant × mutant crosses, and extremely rare intragenic reciprocal exchanges were found in gene *46*. These data served as a basis for working out the polaron model of recombination. In the remaining six *Ascobolus* genes studied, however, polarization was very weak if present at all, while reciprocal intragenic exchanges occurred with appreciable frequency, achieving 50% of the total numbers of intragenic recombinants in gene *164*. Thus it appears that apart from mutant specificities, and probable differences in the genetic backgrounds of the different strains studied (as suggested by Rossignol, 1969), each of the seven *Ascobolus* genes investigated had its individual features of recombination.

Preliminary results have been obtained on a newly isolated strain '28' of *Ascobolus* (Leblon & Rossignol, 1971). So far, recombination in two loci, b_1 and b_2, has been studied. All kinds of recombinational events were about ten times more frequent in b_2 than in b_1.

The studies on intragenic recombination in the presence of spanning markers by means of half-tetrad analysis in *Aspergillus* (Putrament, 1964, 1967) and tetrad analysis in yeast (Fogel & Hurst, 1967), *Podospora* (Marcou, 1969) and *Ascobolus* (Baranowska, 1970) show how far the data for *Ascobolus* discussed above are comparable with those obtained in other fungi by means of single-strand analysis.

It may safely be assumed that in the genes studied by means of single-strand

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analysis, both reciprocal and non-reciprocal intragenic exchanges occur, although from the frequencies of wild-type recombinants with non-parental spanning marker arrangements no conclusions can be drawn regarding reciprocality or non-reciprocality of intragenic events (for discussion see Putrament, Rozbicka & Wojciechowska, 1971). Polarization was very strong in some genes such as *me-2* in *Neurospora* (Murray, 1968, 1969) and *methA* in *Aspergillus* (Putrament *et al.* 1971) and less strong in others. In the *cys* gene of *Neurospora* (Stadler & Towe, 1963) most frequent was the class of wild-type recombinants with parental marker arrangement, while in *me-6* and *me-2* genes of *Neuropsora* (Murray, 1963, 1969), *adE* (Pritchard, 1955, 1960), *adF* (Calef, 1957; Martin-Smith, 1961), *pabaA* (Siddiqi, 1962; Siddiqi & Putrament, 1963) and *lys-51* (Pees, 1967) genes of *Aspergillus* the most frequent was one of the classes with non-parental marker arrangement. In *am-1* (Fincham, 1967), *his-1* (Freese, 1957; Catcheside, Jessop & Smith, 1964; Jessop & Catcheside, 1965), *his-3* (Jha, 1967, 1969), *his-5* (Smith, 1965, 1966), *pan-2* (Case & Giles, 1958) and *mtr* (Stadler & Kariya, 1969) genes of *Neurospora* polarization was very weak if noticeable at all.

The distribution of spanning markers among *his-1*$^{+}$ recombinants is strongly modified by a *rec-1* gene (Thomas & Catcheside, 1969). Similar effects are produced by *rec-3* on *am-2* allelic recombination (Smyth, 1971) and by *rec-w* and *cog* on *his-3* allelic recombination (Angel, Austin & Catcheside, 1970), while *rec-2* slightly modifies the recombination pattern between *his-5* alleles (Smith, 1966). A striking difference in the allelic meiotic and mitotic recombination pattern between the same pairs of *pabaA* mutants of *Aspergillus* was observed (Siddiqi, 1962; Siddiqi & Putrament, 1963; Putrament, 1964, 1967).

Thus as far as comparisons are conclusive, the same type of gene-to-gene variation in the recombination pattern is present in *Ascobolus*, *Neurospora* and *Aspergillus*, while in yeast and *Podospora* intragenic recombination resembles that of the three fungal species studied more extensively. Mutant specificity is independent of and superimposed on the gene-specific recombination pattern. A possibility cannot be excluded that the character of a mutant has a stronger influence on recombination pattern in those genes in which polarization is less pronounced or even absent: mutant-specificity was observed in *Y* (Kruszewska & Gajewski, 1967), *W84* (Paszewski, 1967; Paszewski & Prazmo, 1969), *75* (Rossignol, 1967, 1969) and *164* (Baranowska, 1970) genes of *Ascobolus*, but was not observed in gene *46*, in which polarization is very strong (Rizet *et al.* 1960; Lissouba, 1969; Lissouba *et al.* 1962; Rossignol, 1964).

The gene-specific recombination pattern can be modified by the genetic background of a strain (*am-1, his-1, his*-3 and *his-5* genes of *Neurospora*), and is different in the meiotic and somatic cells (*pabaA* gene of *Aspergillus*). Thus the primary DNA structure of a gene and its modifications due to mutations are not responsible for all gene-to-gene variation in allelic recombination pattern.

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3. GENETIC FACTORS INFLUENCING INTRA- AND INTERGENIC RECOMBINATION

In *Neurospora* several *rec* genes influencing allelic recombination frequencies have been identified (Angel *et al.* 1970; D. E. A. Catcheside, 1970; D. G. Catcheside, 1966; D. G. Catcheside & Austin, 1969, 1971; D. G. Catcheside *et al.* 1964; Jessop & D. G. Catcheside, 1965; Jha, 1967, 1969; Thomas & D. G. Catcheside, 1969). At least some of these and probably still other genes of the *rec* type influence intergenic recombination frequency (D. G. Catcheside *et al.* 1964; Jha, 1967; Smith, 1965, 1966; Case & Giles, 1958; Rifaat, 1969; DeSerres, 1958; Stadler & Towe, 1962).

The *rec-3* gene, which affects recombination frequency between *am-1* alleles, does not seem to affect the function of the *am-1* gene (D. E. A. Catcheside, 1968). This suggests that the *rec* genes are not involved in the regulation of gene function.

A similar system of genetic factors modifying recombination frequencies in certain definite intervals has been found in *Schizophyllum commune* (Koltlin, Raper & Simchen, 1967; Simchen, 1967; Connolly & Simchen, 1968; Simchen & Connolly, 1968; Stamberg, 1968, 1969*a*, *b*; Simchen & Stamberg, 1969*a*; Stamberg & Simchen, 1970).

The loci that influence recombination are highly region-specific. For instance, within the *A* mating-type factor, the following intervals can be distinguished: *Aα-pab-ade5-Aβ*. At least one factor modifies the recombination frequency within the first interval, and a different one alters recombination frequency in the second interval, while neither affects recombination within the third. A single factor may influence recombination in more than one region. For instance, one of the factors which in the homozygous condition increases recombination frequency in the *Aα-Aβ* interval affects in the same way recombination in the *Aβ-x15* interval. One of the factors which in the homozygous condition increases recombination frequency in *Aβ-x15* interval decreases recombination frequency in the *B* mating-type factor.

The *rec-x* and *rec-3* genes of *Neurospora* are most probably allelic. They modify recombination in two unlinked loci, *am-1* and *his-2* (D. G. Catcheside & Austin, 1971).

Genetic factors differentially affecting recombination frequencies in certain regions are present also in yeast (Simchen, Ball & Nachsohn, 1971).

Comparison of recombination frequencies at various temperatures at which meiosis took place was used in *Schizophyllum* studies as a method of differentiating the genotypes of the strains investigated. Depending on the genotypes of the strains crossed, a definite temperature at which meiosis proceeds can increase, or decrease, or have no influence on the frequency of recombination within a given interval. Other data concerning the influence of temperature on recombination are not in disagreement with this evidence (for discussion see Stamberg & Simchen, 1970). There are indications that intragenic recombination frequency and pattern can also be modified by the temperature at which meiosis and premeiotic stages

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proceeded (Stadler, 1959; Lissouba, 1960; Boucharenc, Mousseau & Rossignol, 1966; Lamb, 1968, 1969*a*, *b*; Putrament *et al.* 1971).

To sum up, the genetic factors affecting recombination (see Simchen & Stamberg, 1969*b*) have strictly localized effects. A single factor may influence recombination within several, not necessarily linked, chromosomal segments. Often the temperature at which meiosis proceeds can modify the action of these factors either in a co-ordinate or in a contrasting manner (e.g. Stamberg & Simchen, 1970, tables 3 and 9).

4. THE POSSIBLE ROLE OF CHROMOSOMAL AND SYNAPTINEMAL PROTEIN COMPLEXES IN RECOMBINATION

Recombination is mediated by enzymes which for the sake of simplicity will be called recombinases. Neither their number nor their modes of action are known. It is also not known whether all the recombinases produced by a cell or an organism are necessary for every recombinational event. However, for any recombinational event to take place two conditions must obviously be fulfilled: (*a*) the homologous DNA segments must be available for the recombinases, and (*b*) there must be close physical contact between the homolous DNA segments.

The question whether the chromosomal proteins are able to shield DNA from the recombinases cannot be answered at present, although there is some evidence concerning the action of chromosomal constituents on the availability of DNA for some other enzymes.

Histones bind with DNA non-specifically (Bonner *et al.* 1968). At least some of them (Koslov & Georgiev, 1970) interfere with the activity of RNA polymerase, probably by strengthening the hydrogen bonds between complementary DNA chains (Shih & Bonner, 1970*a*, *b*). The histone complex with unglucosylated T2 DNA is less effective as a substrate for glucosylation by alfa-glucosyl transferase than histone-free T2 DNA (Olins, 1969). On the other hand, histones only slightly interfere with DNA polymerase activity (Spelsberg, Tankersley & Hnilica, 1969).

In chromatin only some regions of DNA are transcribed, depending on the tissue from which the chromatin was isolated (Bonner *et al.* 1968). Chromatin reconstituted after denaturation serves as a template for synthesis of RNA very similar to or identical with that synthesized in the presence of native chromatin from the same organ (Paul & Gilmore, 1968; Gilmore & Paul, 1969; Bekhor, Kung & Bonner, 1969; Huang & Huang, 1969). Chromosomal RNA (Bekhor, Bonner & Dahmus, 1969; Sirolap & Bonner, 1970) or non-histone proteins (Kleinsmith, Heidema & Carroll, 1970) are responsible for masking the DNA in a highly specific manner characteristic for a given organ, so that only the unmasked parts of the DNA are available for transcription.

The number of different types of histones is very limited (Fambrough & Bonner, 1969), so that the same species of histone must be associated with many non-identical DNA segments, as suggested by Bloch (1966). The number of different species of non-histone proteins has not yet been established. However, it does not

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seem unreasonable to assume that the same species of non-histone protein can also be associated with several non-identical segments of DNA. This seems to apply also to fungi, although in their chromosomes no histones were found (Leighton *et al.* 1971).

The evidence presently available indicates clearly that in meiosis homologous chromosome pairing is mediated by the proteinaceous structures of synaptinemal complexes in fungi (Rossen & Westergaard, 1966; Westergaard & von Wettstein, 1966, 1968, 1970; Engels & Croes, 1968; Lu & Raju, 1970) as well as in higher plants and animals (Moses, 1968, 1969; Moens, 1970).

Synaptinemal complexes consist of a central component and lateral components which merge with chromatin. Westergaard & von Wettstein (1970) suggest that the lateral component of one chromosome must carry the information for the specific site-to-site recognition and pairing with the lateral component of the homologous chromosome. The material in the central component could operate in mediating the site-to-site recognition of the lateral components.

It is not yet clear whether the synaptinemal complexes are built of proteins which are normally associated with chromosomal DNA or of different protein species. In any case they must provide for a contact between homologous chromosomes as precise as is the regulation of transcription. Otherwise intragenic recombination would be impossible.

The synaptinemal complex stabilizes the homologous pairing, but apparently it also restricts the contact between the homologues. In a given region only a small fraction of DNA from each homologue can be present in the central component of the complex (Moses, 1969; Westergaard & von Wettstein, 1970). It is not known so far whether the same DNA segments are present there throughout the entire time of synapsis or whether the DNA double chains undergo movement so that at the beginning of pairing, e.g. A–A′, segments are within the central component, then successively B–B′, etc.

Thus, the present knowledge of the structure of synaptinemal complexes suggests the possibility that various segments of chromosomes have an unequal probability of being brought sufficiently close together for recombination to take place. In other words, the probability of a gene being involved in an effective pairing segment may be unequal for different genes. Perhaps this might account for the gene-to-gene differences in the conversion frequencies found in *Ascobolus*.

The possibility cannot be excluded that within some, but not all, chromosomal regions, homologous DNA segments come into contact consecutively, so that mutant sites on one side of a cistron have a greater probability of entering into the recombinational process (and eventually being converted) than mutant sites on the other side of the cistron. This perhaps may account for polarization of intragenic recombination.

The chromosomal structural proteins as well as those of synaptinemal complexes must be coded by their structural genes which can mutate. Judging from the amazing uniformity of histones in eukaryotes (Fambrough & Bonner, 1969) one can conclude that there must be a strong selection which eliminates individuals

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carrying mutations in the structural genes of chromosomal proteins (Bonner *et al.* 1968). Still, it seems possible that missense mutations of some synaptinemal complexes and chromosomal structural proteins do not disturb the chromosome metabolic activities, and lead only to changes in recombination frequencies in certain chromosomal regions. The *rec* genes identified in *Neurospora* may, in fact, be mutants of structural genes of these proteins. The same mutant protein molecule may be responsible for increased or decreased recombination frequencies in various chromosomal segments with which it is bound, depending on other chromosomal components present in each segment. This assumption could possibly account for the previously summarized *Schizophyllum* data.

It is well known that the conformation of proteins is easily modified by temperature. Perhaps temperature-induced modifications in a particular protein conformation may lead to modifications of recombination frequencies in those segments of chromosomes with which this protein is associated. The final result, i.e. increased or decreased recombination frequency, will largely depend on other chromosmal constituents.

Of course, temperature may influence recombination in many ways – for instance, by influencing the synthetic processes which take place in premeiotic and early meiotic stages (Stern & Hotta, 1969), or by influencing the duration of synapsis, or, as suggested by Lamb (1969*b*), temperature may affect the level of activators of an enzyme responsible for breakage of DNA. None of these alternatives, however, can account for the genetically determined effects of temperature on recombination within strictly localized chromosomal segments, as was found in *Schizophyllum*. In particular, Lamb's assumption that different recombinases operate in various chromosomal segments calls for an additional assumption, namely that the recombinases are strictly compartmentalized. But then the most probable factors restricting the action of the recombinases are once more chromosomal proteins.

The assumption that chromosomal proteins can modify recombination frequencies is not incompatible with the hypothesis (Angel *et al.* 1970) that there are endonucleases capable of recognizing groups of similar sequences of nucleotides in DNA molecules (*cog* regions), and of causing initiation of recombination. It seems, however, that if as a rule there were regions of preferential DNA incisions initiating recombination, then polarization of intragenic recombination would be always observed, which is not the case.

It appears that on the basis of all these assumptions only a few predictions can be advanced.

In intragenic recombination, polarization will be locus-specific, i.e. strong in some genes and weak in others, even when a set of mutants identical in character (e.g. AT–GC transitions) is intercrossed, as long as the genetic backgrounds of the strains crossed are identical (cf. Rossignol, 1969).

Allelic recombination frequency and pattern will be modifiable by temperature and by other factors which modify protein conformation, such as increased osmotic pressure of the crossing medium (Hawthorne & Friis, 1964). Recombination will be liable to modification only in some genes, some combinations of mutants crossed,

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and in some strains, since it depends on the structure of the chromosome segment, the properties of which, in turn, are genetically determined.

Intergenic recombination frequencies will also be modifiable by all factors which modify protein conformation without being toxic. More instances will be found where a single genetic factor modifies recombination frequency in several intervals, linked or unlinked either in a co-ordinate or in a contrasting manner.

No genetic factors modifying recombination frequencies in several intervals either in a co-ordinate or in a contrasting manner will be found in prokaryotes.

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