MARKER-DEPENDENT RECOMBINATION IN T4 BACTERIOPHAGE. I. OUTLINE OF THE PHENOMENON AND EVIDENCE SUGGESTING A MISMATCH REPAIR MECHANISM

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ABSTRACT

In standard crosses, some *rIIB* mutants of T4 phage were found to be susceptible to an extra recombination mechanism to which the other mutants were much less susceptible. The following observations were interpreted as evidence for the mismatch-repair nature of the phenomenon: (1) Marker-dependent recombination generates exclusively double exchanges at both sides of the marker. (2) Marker-dependent recombination is highly sensitive to DNA base sequence at the site of the marker and to that at the corresponding site on the chromosome of the other parent. (3) Within certain limits, the contribution of the marker-dependent mechanism to the total recombination frequency is distance-independent and thus constitutes a constant component.

HYBRID DNA molecules with complementary strand sections derived from different parents are generally believed to arise in genetic recombination. A genetic marker falling within such a hybrid region generates a mismatch that might be repaired.

The most convincing support for the notion of mismatch repair comes from studies on co-conversion in the fungi *Ascobolus immersus* (LEBLON and ROSSIGNOL 1973) and *Schizosaccharomyces pombe* (GUTZ 1971), and from experiments on transfection by DNA heteroduplexes with mismatches at four sites in phage λ (WAGNER and MESELSON 1976).

In T4 phage, some genetic phenomena such as high negative interference (CHASE and DOERMANN 1958) and ultrafine-structure map expansion (TESSMAN 1965), as well as the loss of heteroduplex heterozygotes after prolonged incubation of phage-infected *Escherichia coli* cells under nonreplicating conditions (BERGER and PARDOLL 1976), can be interpreted as originating from mismatch repair. However, evidence for the involvement of mismatch repair in T4 general recombination remains scanty.

The length of a single-strand DNA segment excised upon the repair of

mismatched *rII* mutations in normal T4 phage crosses seems not to exceed about 10^1 bases, whereas the maximum frequency of recombination attributable to mismatch repair is on the order of 10^{-3} (TOOMPUU and SHCHERBAKOV 1980). This permits us to focus on recombination frequencies in the range of 10^{-4} to 10^{-3} when specific manifestations of mismatch repair are sought in formal recombination analysis.

Proceeding from this consideration, we carried out a large series of two- and three-factor crosses between closely linked T4 *rII* mutants. Six of the 20 markers studied were found to be susceptible to an extra recombination mechanism to which the other markers were much less susceptible. Below is a summary of several experimental approaches resulting in evidence for mismatch repair in marker-dependent recombination, whereas the companion paper (SHCHERBAKOV et al. 1982) deals specifically with quantitative implications of the phenomenon.

MATERIALS AND METHODS

Bacteriophages: The *rII* mutants of T4 phage used in this study are shown in Figure 1. The wild-type T4D strain was kindly supplied by K. EBISUZAKI; the mutants HE122, FC1, UV375, 360, X511, FC9, FC0, UV357, FC21, FC40, and UV200 were obtained as a generous gift from S. P. CHAMPE; the mutant H72 was a contribution of Yu. P. VINETSKI.

The remaining mutants were isolated by us. The opal mutants *op360* and *opUV357* were derived from the ochre mutants 360 and UV357, respectively, as a result of spontaneous transitions (ochre → opal) selected by plating on an opal-suppressing *E. coli* strain. Similarly, the amber mutants *amUV200*, *amUV375*, *am360* and *amUV357* were derived from the appropriate ochre mutants as a result of spontaneous transitions (ochre → amber) selected by plating on an amber-suppressing *E. coli* strain. The plus frameshift mutations β_1 and β_8 and the minus frameshift mutations β_9 and β_{10} were selected as intragenic suppressors of FC1 and β_8 , respectively, whereas the plus mutation β_{11} was selected as an intragenic suppressor of β_9 . In all cases in which the mutations were isolated in a T4B background, they were made isogenic by incorporating them into a T4D background by six backcrosses against T4Dr⁺ at multiplicities of mutant and wild-type phages equal to one and nine, respectively.

The mutations were aligned on the basis of two- and three-factor cross data. The sequence of the mutants HE122, FC1, UV375, 360, X511, FC9, FC0, UV357, FC21, and FC40, as well as of the barriers (terminating codons located out of phase) b_1 (ochre), b_2 (opal), and b_3 (ochre), agrees with that in the maps of BARNETT et al. (1967) and KATZ and BRENNER (1975).

Bacteria: *E. coli* strains BB, 594(λ), K223(λ), CA167(λ) (received from the Institute of Genetics of Microorganisms, Moscow), CA244(λ), CA180(λ), and CA265(λ) (a generous gift of F. W. STAHL) were used. Strain BB was used as a host in all phage crosses, in preparing phage stocks, in phage titration, and in measuring the total phage yield in the crosses. Strains 594(λ)su⁻ and CA244(λ)su⁻ are nonpermissive for all *rII* mutants. Strain K223(λ)su⁺ is permissive for *rII* mutants of the opal type and nonpermissive for other *rII* mutants. Strain CA167(λ)su⁺ is permissive for ochre and amber mutants and nonpermissive for other *rII* mutants. All the strains used are permissive for T4r⁺.

Media: L broth: 1% Difco tryptone, 0.5% Difco yeast extract, 0.1% glucose, and 1% sodium chloride, pH 7.0; used for growing liquid *E. coli* cultures and for standard crosses. Beef-peptone broth: 5% Hottinger broth, 0.5% sodium chloride, and 1% bacto-peptone (Spofa), pH 7.0; used for weekly *E. coli* cultures. Peptone broth: 1% bacto-peptone (Spofa), 0.8% sodium chloride, 0.2% sodium citrate, and 0.1% dextrose, pH 7.0; used for phage dilution. Beef extract agar: 5% Hottinger broth, 0.5% sodium chloride, 1% bacto-peptone (Spofa), and 2% Difco agar; used for *E. coli* slant cultures. Peptone agar: 1% bacto-peptone (Spofa), 0.8% sodium chloride, and 2% agar (U.S.S.R.), pH 7.0; used for phage plating (bottom agar). Soft agar D: 1% Difco tryptone, 0.23% Difco yeast extract, 0.47% glucose, 0.77% sodium chloride, and 0.7% Difco agar, pH 7.0; used for phage plating (top agar).

Management of bacterial cultures: A colony of the bacterial strain was transferred to a beef extract agar slant and grown for 24 hr at 33°. Bacteria from one slant were suspended in 10% sucrose

FIGURE 1.—Map of *rII* mutations of T4 bacteriophage. The intervals on the basic map were determined by the mapping function of TOOMPUU and SHCHERBAKOV (1980). The localization procedure for the mutations in the magnified segment is described in the companion paper (SHCHERBAKOV *et al.* 1982). Phase-shift mutations are marked with the superscripts + or - to show the direction of the phase shift in reference to that of *FC0* as + (BARNETT *et al.* 1967); amber, ocher, and opal mutations are labeled with the superscripts *am*, *oc* and *op*, respectively. The barriers *b*₁, *b*₂ and *b*₃ correspond to the terminating codons, UAA, UGA and UAA, respectively, engendered by plus-sign phase shift (BARNETT *et al.* 1967; KATZ and BRENNER 1975). Arrows show the approximate sizes of the chromosome segments involved in a single mismatch repair event.

plus 1% gelatine, distributed over a large number of ampules, freeze-dried, and sealed under vacuum. Approximately once a month one of the ampules was opened and subcultured on a beef extract agar slant. The slant was stored at room temperature and used to inoculate beef extract broth. The resulting culture was incubated overnight at 33° without aeration and stored at 4° for 1 week (weekly culture). An aliquot of the weekly culture was diluted 100-fold into L broth and incubated overnight at 33° (overnight culture). The overnight culture was diluted 100-fold into L broth and incubated in glass fermenters at 37° with vigorous aeration. The bacterial suspension in the log phase was stored at 0° until used.

Standard cross procedure: A method analogous to that described by CHASE and DOERMANN (1958) was used. A sample of *E. coli* BB overnight culture was diluted 100-fold into L broth and aerated at 37°. At a cell concentration of 1×10^8 per ml, the suspension was cooled to 0°, pelleted by

centrifugation, resuspended in cooled L broth, and adjusted to a density of 4×10^8 cells/ml. To 0.5 ml of the cooled BB suspension 0.1 ml of 0.02 M sodium cyanide was added, the suspension was held for 1 min, and then a mixture of phage parents in a volume of 0.5 ml (the multiplicity of each parent being 5) was added. The infected cells were incubated for 10 min at 33°, diluted 1000-fold into L broth, incubated at the same temperature for another 80 min, and cell lysis was completed by the addition of 0.3 ml of chloroform.

In all the crosses examined, the adsorption efficiency was higher than 95% and the phage yield exceeded 100 particles per cell. In a number of cases the ratio of parental types in the lysate was determined. This ratio never fell outside the limits of 0.4–0.6.

Determination of phage titer: *E. coli* BB was used to determine the total titers of lysates from crosses. Wild-type recombinants were determined on CA244(λ) or 594(λ); those with amber or opal phenotypes were determined on CA265(λ) and K223(λ), respectively.

To determine the plating efficiency, concurrent with the basic experiment, we plated control samples of phage on the indicator strains. A total of about 1500 plaques was scored on each strain (on six plates). The plating efficiency was determined as the ratio of control phage titer on the λ-lysogenic strain to that on BB.

RESULTS

Comparison of mutations localized at the same site: We concentrated upon recombination particulars of 10 base-substitution mutations and 10 frame-shift mutations localized within a short proximal segment of the *rIIB* gene (magnified segment in Figure 1). From the frequencies of wild-type recombinants observed in two-factor crosses, we inferred the following clusters of mutations with extremely low frequencies of wild-type recombinants ($\leq 1.9 \times 10^{-5}$) measured in intracluster crosses: FC1/UV375/amUV375, UV375/amUV375/360/op360/am360, X511/β8, FC9/β9/β10, UV357/opUV357/amUV357/FC21, and FC21/FC40.

In crosses against more distant markers, all the mutations of the same cluster appear to behave as if occupying the same site. This makes it possible to compare recombination ability of the mutations a' and a'' of the same cluster a pairwise in crosses against the same set of markers i . Examples are given in Figure 2 where the frequencies of wild-type recombinants ($R_{A'I}$) are plotted against the similar frequencies $R_{A''I}$.

The mutations studied can be tentatively divided into two classes: those of high recombination ability (HR-mutations) (FC1, op360, am360, β8, β9 and amUV357) and those of low recombination ability (LR-mutations) (β1, HE122, UV375, amUV375, 360, X511, FC9, β10, FC0, FC21, UV357, opUV357, FC40 and β11). As will be shown in subsequent paragraphs, this classification is substantiated by distinct recombination patterns of the two types of mutations.

When HR-mutations a' are compared with their LR-type homoalleles a'' in crosses against LR-type test markers i (full circles in plots a–f of Figure 2), a typical regularity can be observed: as the distance between site a and site i increases, the difference $R_{A'I} - R_{A''I}$ grows to a certain value and then levels off. In contrast, no systematic deviation from the line of equivalence in the same coordinates is revealed when the mutations a' and a'' are both of the LR-type (plots g and h, Figure 2).

As opposed to LR-mutations, mutations of the HR-type are unfit as test markers i , since they give rise to a heavy scatter of points (open circles in the

plots a-f of Figure 2). We speculate on the origin of this phenomenon in the DISCUSSION.

The fact that the difference $R_{A'I} - R_{A''I}$ becomes constant suggests that it arises as a result of the involvement of an extra mechanism of recombination (the contribution of which is independent of distance for all but very short intervals) rather than as a result of magnification of the pre-existing basic mechanism by the presence of an HR-marker.

FIGURE 2.—Examples of pairwise comparison of homoallelic mutations a' and a'' as studied in crosses $a'I \times A'i$ and $a''I \times A''i$. The following pairs of homoalleles (a'/a'') are compared: (a) $FC1/amUV375$, (b) $op360/360$, (c) $am360/360$, (d) $\beta 8/X511$, (e) $\beta 9/\beta 10$, (f) $amUV357/opUV357$, (g) $amUV375/UV375$, (h) $opUV357/UV357$. Test-markers i are of the LR-type (●) or of the HR-type (○).

Crosses	Frequencies of wild-type recombinants
$34.1 \cdot 10^{-4}$
$14.0 \cdot 10^{-4}$
$40.6 \cdot 10^{-4}$
$17.1 \cdot 10^{-4}$
$21.8 \cdot 10^{-4}$
$0.85 \cdot 10^{-4}$

FIGURE 3.—Marker-specific effects in two- and three-factor crosses: the comparison of homoallelic mutations $\beta 8$ and X511.

Although the HR-mutation $\beta 8$ and the LR mutation $ocX511$ both occupy the same site, the former shows definitely higher frequencies of wild-type recombinants than does the latter when tested in two-factor crosses against the flanking mutations $HE122$ and $\beta 11$ (Figure 3). In the three-factor crosses of $HE122 \beta 11$ with $\beta 8$ or X511, we found a similar inequality. The differences between the frequencies of wild-type recombinants in the two pairs of two-factor crosses ($34.1 \times 10^{-4} - 14.0 \times 10^{-4} = 20.1 \times 10^{-4}$ and $40.6 \times 10^{-4} - 17.1 \times 10^{-4} = 23.5 \times 10^{-4}$) are equal to one another and to the difference between the frequencies of wild-type recombinants in the corresponding three-factor crosses ($21.8 \times 10^{-4} - 0.85 \times 10^{-4} = 21.0 \times 10^{-4}$). This striking fact indicates that the extra recombination events to which the HR-mutation $\beta 8$ rather than the LR-mutation X511 is susceptible are just the double exchanges occurring at both sides of $\beta 8$ within the short gene segment delimited by the mutations $HE122$ and $\beta 11$.

An interesting peculiarity of HR-mutations as opposed to LR-mutations was observed in the series of three-factor crosses designed so as to keep both the side marker a and the central marker b unchanged and so as to vary only the second side marker i . Such a series enables one to study the relationship between the frequency of double exchanges and one of the genetic intervals, all the other parameters of the system being kept constant.

The results of two such series are shown in Figure 4. In all the crosses $opUV357$ was used as marker a and the mutations $am360$, $amUV375$, $HE122$,

amUV200, and H72 were consecutively used as markers *i*, whereas $\beta 8$ (of HR-type) or X511 (of LR-type) served as the central marker *b* in the full- or open-circle series, respectively.

Evidently, the frequency of double exchanges responds differently to the lengthening of the interval *b-i* in the two series, even though $\beta 8$ and X511 occupy the same site. In the case of $\beta 8$, the frequency of double exchanges increases rapidly to the highest value and then ceases to grow. The same behavior was observed in a similar series of crosses involving other HR-mutations (*FC1* and $\beta 9$, not shown) as *b* markers. In contrast, when X511 or other LR-mutations (*UV375* and *FC9*, not shown) were used as the central markers, the frequencies of double exchanges grew continuously with increasing length of the interval *b-i*.

Sensitivity of marker-dependent recombination to base sequence: Marker-dependence of recombination implies sensitivity to the DNA structure at the site of the marker. A salient illustration was given by the recombination behavior of the mutations affecting the site *UV357*. The original ochre mutation *UV357* (the triplet TAA/ATT) is of the LR-type; its transition to the opal triplet TGA/ACT does not alter recombination significantly (Figure 2h), whereas its transition to the amber triplet TAG/ATC gives rise to a drastic increase in recombination ability (Figure 2f).

We have also attempted to reveal the effect of base substitutions not in the

FIGURE 4.—Relationship between the frequency of wild-type recombinants and the length of one of the intervals in three-factor crosses: the comparison of homoallelic mutations $\beta 8$ (●) and X511 (○) used as the central markers.

FIGURE 5.—Silent-marker effects on recombination. The frequencies of wild-type recombinants (abscissa) from the two-factor crosses of FC40 (●) or FC21 (○) against the test-markers *am360*, *amUV375* and *HE122* are plotted vs. corresponding frequencies (ordinate) determined in the identical crosses but in the presence of the silent marker *opUV357*. Note the absence of any silent marker effect on recombination of FC21 and the strong stimulatory effect on recombination of FC40.

mutant locus itself, but at the site opposite it in the chromosome of the other parent. We replaced the wild-type allele *A* in the chromosome of one of the parents by the suppressible allele *A^s*. To determine the frequency of recombinants of the type *A^sB* resulting from the cross *aB* × *A^sb*, we plated the lysate on the appropriate *E. coli* *su⁺* strain on which the extra mutation *A^s* was not expressed (the silent marker). Comparison of the frequencies R_{A^sB} and R_{AB} observed in the presence and absence of the silent marker, respectively, showed that in some instances alteration of the base sequence at the site opposite the mutant locus modified the recombination behavior of the system.

The effect of the silent marker *opUV357* on recombination of FC40 is striking (full circles in Figure 5). It is of interest that both *opUV357* and FC40 are of the LR-type in themselves (i.e., when lying opposite the wild-type alleles) whereas their combination results in a sharp increase of recombination ability of FC40. At the same time, the silent marker *opUV357* shows no effect on recombination of the homoallelic mutation FC21 (open circles). Hence, the recombination ability of a mutation appears to depend on the base sequence both at the mutant site itself and at the corresponding site in the chromosome of the other parent.

DISCUSSION

Mismatch repair is a plausible hypothesis: The results of two- and three-factor crosses presented in this paper suggest an extra recombination mechanism to which different *rIIB* mutants of T4 phage are susceptible to a variable degree. This marker-dependent recombination manifests a pattern suggesting the repair of mismatches in recombination intermediates:

(1) The marker-dependent recombination generates closely linked exchanges at both sides of the marker. The contribution of marker-dependent recombination reaches a maximum when the distance from the adjacent markers is as short as 10 to 20 base pairs (see below). Mismatch repair seems to be a plausible mechanism to generate such closely spaced double exchanges.

(2) The marker-dependent recombination is highly sensitive to DNA base sequence at the site of the marker and to that at the homologous site on the chromosome of the other parent. This property implies the involvement of a heteroduplex repair target composed of DNA strands originating from both parents.

(3) A mismatch repair model readily accounts for the particular relationship in three-factor crosses between the frequency of wild-type recombinants and the length of one of the intervals. The initial steep rise of the upper curve in Figure 4 reflects the increase in the probability of independent repair of the central marker *b*. The highest value of the frequency of double exchanges is attained when the interval *b-i* becomes equal to the length of the chromosome segment involved in a single repair event. The subsequent plateau, or even a decreasing trend in the frequency of double exchanges, can be explained as described below.

In the crosses under consideration, the interval *a-b* (the distance between *opUV357* and *X511/β8*) is as short as about 5% of the hybrid region. When the interval *b-i* is also small, the three markers will usually fall into the same hybrid region. With an increase in the interval *b-i*, the probability that all the markers will be in the hybrid region declines, whereas the probability of the formation of the double heterozygotes including the markers *a* and *b* proportionally increases.

In terms of the outcome of mismatch repair, the replacement of the triple heterozygotes by the double ones is not neutral; both of the reciprocal triple heterozygotes are capable of generating a wild-type DNA strand as a result of repair of the central marker *b*, whereas only one of the reciprocal double heterozygotes can yield the wild-type DNA strand via repair of *b*. Superior to the triple heterozygotes, the double ones will generate the wild-type strand by means of repair of *a* in one-half of the cases. This advantage is offset, however, by making *a* an LR-type marker (*opUV357*), thereby making negligible its repair contribution to the total frequency of wild-type recombinants. As a consequence, an almost twofold final decrease should be expected in the mismatch repair contribution as the *b-i* intervals exceed the length of the hybrid region, i.e., when only double heterozygotes become possible. In conformity with the upper curve in Figure 4, the wild-type frequency is expected to fall from about 1×10^{-3} to 5×10^{-4} . The fall is partly disguised by a simultaneous increase in

the probability of marker *b* alone to be captured by the hybrid region. Assuming markers *opUV357* (*a*) and *X511* (*b*) not to be repaired, one can use the lower curve in Figure 4 to estimate this increase, i.e., the lower curve may be interpreted as an integral non-mismatch-repair component of the upper curve. The final point in this component (3×10^{-4}) is slightly lower than the expected twofold decrease in the mismatch repair component (to about 5×10^{-4}). Thus one should expect some decrease in the net frequency of wild-type recombinants with the increase in the interval *b-i*, which, is in fact, seen on the upper curve in Figure 4. Two similar series of crosses with the readily repairable central markers *FC1* or $\beta 9$ reveal the same regularity (data not shown).

The length of the repair region: The length of the chromosome segment involved in a single repair event can be inferred from the two-factor cross data plotted as full circles in Figure 2a-f. As the distance between the sites *a* and *i* grows, the difference $R_{A'I} - R_{A''I}$ initially increases steeply and then reaches a constant level. The growth phase reflects the increase in the probability of *a* alone to be repaired without involving *i* in the same repair event. Map expansion occurs in the growth phase (data to be presented elsewhere) as expected for distances about equal to a modal co-correction distance (FINCHAM and HOLLIDAY 1970). In contrast, the constant level corresponds to distances large enough to guarantee independent repair in the overwhelming majority of events. Hence, the length of the chromosome segment involved in the repair event initiated at the site *a* can be judged from the point where the slope of the empirical curve in coordinates $R_{A'I}$ vs. $R_{A''I}$ becomes unity. The determination accuracy will be better the higher the final value of the difference $R_{A'I} - R_{A''I}$ and the closer within the inflection area *i* markers are spaced.

In Figure 1 the arrows specify the intervals involved in the repair events initiated at the positions of the HR-mutations *FC1*, *op360*, *am360*, $\beta 8$, $\beta 9$, and *amUV357*. Since we had no test markers located between *HE122* and *FC1*, the left repair boundaries for *FC1*, *op360*, *am360*, $\beta 8$, and $\beta 9$ were determined rather roughly: one could only argue that they do not overlap the *HE122* site. To the same approximation, the right boundary of the repair region initiated at *amUV357* appears just to overlap the $\beta 11$ site.

As deduced from positions of genetic landmarks in the *rII*B DNA sequence (PRIBNOW et al. 1981), the distance between the extreme nonsense mutations of our segment, *HE122* and *UV357*, is 50 base pairs. Hence, the length of the repair intervals, which cover only a fraction of this distance, can be assessed at about 10 to 20 nucleotides.

Marker interference: To compare the recombination capabilities of homoallelic HR- and LR-mutations, we used only the crosses involving LR-mutations as test-markers *i* (full circles in Figure 2a-f). Inclusion of test-markers of the HR-type violates the continuity of the relationship $R_{A'I}$ vs. $R_{A''I}$ and diminishes the absolute values of the differences $R_{A'I} - R_{A''I}$ (open circles in Figure 2a-f). We call this phenomenon "marker interference," implying that if two readily repairable mismatches occur closely enough in the same hybrid region, the probability of their co-correction will be higher than it would be for a cross between readily and poorly repairable mismatches at the same separation. The extension of the repair region in the presence of two readily repairable mis-

matches seems to account for the difference. In part, however, the marker interference arises on simple statistical grounds, as is pointed out in the companion paper (SHCHERBAKOV *et al.* 1982).

CONCLUSIONS

An excision-type mismatch repair mechanism readily accounts for all the characteristics of marker-dependent recombination depicted in this paper. Among conceivable alternatives, HR-mutations acting in the heterozygous state as specific terminators of hybrid region formation can most closely simulate features of mismatch repair in two-factor crosses. However, there is no reason to believe that the premature termination of hybrid region propagation would lead exclusively to double exchanges.

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