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Genetics

Topography and kinetics of genetic recombination in *Escherichia coli* treated with psoralen and light

(DNA cross-links/*recA*/DNA repair)

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ABSTRACT **Genetic exchanges appear to be involved in repair of cross-linked DNA. Kinetics for completion of repair and strand rejoining controlled by the *recA*$^+$ gene were examined in *Escherichia coli* treated with psoralen and light. The results suggest the following model for genetic recombination. After cross-linking treatment, cells in a population initiate repair in near synchrony. Removal of DNA cross-links, preparation of substrate for recombination, and initiation of the first *recA*-dependent event are completed in less than 1 min. Recombination events occur singly in each cell or chromosome, and require 2.3 ± 0.4 min at 32° for the *recA*$^+$-dependent step. After completion of the first event, subsequent recombination events occur in a sequential or progressive fashion around the chromosome or in clusters which may consist of one or more domains of the folded chromosome. The time required to proceed to successive sites is either a constant, independent of the distance on the chromosome, or is quite small compared to 2.3 min. DNA substrate for recombination decays with approximate first-order kinetics and the rate is dependent on the number of unrepaired sites. Cell survival can be expressed as a competition between completion of all repair events and the simultaneous decay of chromosomes to forms not reparable by recombination.**

Equations relating kinetics for completion of repair, the size distribution of DNA molecules, and cell survival are derived for the above model, using as parameters only rate constants for recombination and decay of substrate, and number of events per chromosome. An excellent correlation is found between experimentally determined and theoretical values.

The genetic control of recombination in phages and bacteria has been studied extensively, and substantial progress is being made on biochemical studies of this process (for excellent reviews, see refs. 1–3). Although several plausible models have been proposed, surprisingly little appears to be definite about the detailed biochemistry of how DNA strands from different chromosomes become paired and undergo exchanges and how recombinant structures are resolved. Additionally, little is known about how recombinational events at one locus influence simultaneous or subsequent events at other loci. Genetic evidence, such as interference, suggests that an exchange at a particular locus influences the frequency of events at nearby positions, but the particular order or topography of events remains to be determined.

The kinetics for formation of recombinant molecules, measured both biochemically and genetically, should indicate properties of the recombinational process. Previous studies showed that *recA*-controlled reactions in *Escherichia coli* are initiated within a few minutes, but that DNA bearing structural features that require recombination for repair may persist in cells for more than an hour (4, 5). Other measurements indicate that bacteria can complete recombination events, and express recombinant genes within 30–60 min (6–8). One difficulty encountered in biochemical studies involving DNA is the relatively low frequency and asynchrony with which recombination occurs in a population of cells.

Several agents that damage DNA induce many genetic exchanges during subsequent repair. In particular, repair of each cross-linking damage appears to require a recombinational event (9–11). The sequence suggested for this process is as follows: DNA cross-links are first recognized and removed by damage-specific endo- and exonucleases. A single-stranded region of about 700 nucleotides is opened near the site of each cross-link, and this gapped structure persists in cells. During further incubation, the gapped structure is restored to intact DNA, presumably through strand exchanges with a homologous duplex. These reactions are controlled by *recA*$^+$ and all other gene products known to influence genetic recombination (unpublished results). A desirable feature of this process is that a predetermined number of recombinational events can be induced in every cell in a relatively short period of time, and a population appears to be undergoing recombination in near synchrony (12).

In this study we have used the psoralen cross-linking of DNA in *E. coli* to induce repair involving recombination. The kinetics for completion of this process were determined both biochemically and genetically by use of a temperature-sensitive *recA*$^-$ strain shifted between permissive and restrictive conditions at various stages of repair.

MATERIALS AND METHODS

E. coli K12 derivatives were: AB1157 *arg his leu pro thr ara gal lac mtl xyl thi str* (13); and KL399 *recA200*(ts) *thi leu pro met his thy lac ara mtl xyl mal str spc* (14). Exponentially dividing cells were grown with aeration in K medium (salts, glucose, and casamino acids) with thymidine added to 10 μg/ml (K+10 medium). Treatment with 4,5′,8-trimethylpsoralen (described here as psoralen) and light has been described (15, 16). More recent and accurate determinations show that the yield of cross-links in cells increases approximately with the light exposure to the 1.5 power in the dose range of experiments described here. The number per 2.5×10^9 daltons is $(2.0 \pm 0.2) \times 10^{-4}$ times the light exposure (in J/m^2) to the 1.5 power (unpublished observations). Viable cells were determined by colony formation on plates made with K+10 medium containing 2% agar. Cell cultures were diluted serially, and 1.0 ml was mixed rapidly with 3.0 ml of 2% agar in K+10 medium at 45°, giving a final temperature of 42°. Plates were previously warmed to and maintained at 42° for colony formation. These conditions allowed temperature shifts to be completed within 10 sec. In experiments on the decay of chromosomes to forms not reparable by recombination, plates incubated for various times at 42° were cooled on bench tops, and further incubation was at 32°. Fluctuations in data from cell survival experiments

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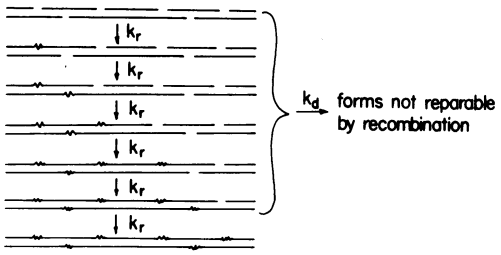

FIG. 1. The model for recombination shown here illustrates the sequence of events and types of DNA products expected. At the top is a DNA duplex with discontinuities in both strands representing substrates requiring recombination for repair (the homolog for recombination is not shown). These gaps are stable and persist until strand exchanges (jagged lines) restore the intact base sequence necessary for survival. Sites are encountered and repaired singly, and successive reactions occur in a sequential or progressive fashion as shown. Thus, subsequent reactions would appear to proceed with zero-order kinetics with rate constant k_r. By such a mechanism short segments of DNA would appear to be joined directly into high molecular weight strands. Competing with successful strand rejoining is the decay of unrepaired chromosomes to forms not reparable by recombination. This decay occurs by a first-order reaction with rate constant k_d times the number of unrepaired sites.

(caused by variations in temperature and sample size) were minimized by working in a room maintained at 42° and by use of an automatic device for sampling at time intervals of 15 or 20 sec.

DNA was labeled and prepared for sedimentation analysis as described previously (9) and in the legend to Fig. 5.

RESULTS

Results of experiments described here suggest a model for recombination in *E. coli*. The rationale and interpretations of data are facilitated by an initial description of the model and its prediction from theoretical calculations. The remarkable correspondence between calculated and experimental values strongly supports the model and eliminates several alternate possibilities.

We suggest the following model: Recombination events occur singly in *E. coli* chromosomes. Successive events occur sequentially in a progressive fashion around the chromosome or in clusters comprising about 2–3% of the chromosome. Each event requires a constant length of time, regardless of the number of previous or subsequent events or of the distance separating their loci on the chromosome. DNA substrate for recombination decays in a first-order reaction dependent on the number of unrepaired sites. Formation of viable or recombinant progeny depends primarily on a competition between completion of all required events and decay of substrate to forms not reparable by recombination. Some elements of this model are depicted in Fig. 1.

From this model, relationships derived are: (*i*) the fraction of cells completing all required recombinational events by a given time; (*ii*) the fraction of total DNA having been repaired in a population of cells; and (*iii*) the survival curve for cells treated with a DNA cross-linking agent. The derivation below, in its simplest form, does not consider distributions of damages among the multiple chromosomes per cell as a factor influencing survival. Starting at time zero, a population of cells contains an average of m damaged sites per chromosomes. Damages are distributed among chromosomes in a Poisson distribution, and each damaged site requires recombination for restoration of the intact genome necessary for cell survival. If recombination occurs as a zero-order reaction as described above, with rate constant k_r, the fraction of cells having completed all of up to $x = k_r t$ events by time t will be given by the sum of terms of the Poisson distribution,

$$P(x) = \sum_{j=0}^{j=x} \frac{e^{-m} m^j}{j!}.$$

Although this equation represents the fraction of cells having completed repair, the probability that these cells are able to form progeny depends additionally on the probability that, during repair, the chromosome remained in a form recoverable by recombination. If repair occurring at rate k_r is competing with decay at rate ik_d, where i is the number of unrepaired damages, then the probability that the chromosome is reparable until $j = k_r$ is

$$D(j) = \prod_{i=0}^{i=j} (1 + ik_d/k_r)^{-1}.$$

Accordingly, the fraction of cells having completed repair and that are able to form progeny by time t is the sum of the terms of $P(x)$, each multiplied by the latter probability, or

$$S(x) = \sum_{j=0}^{j=x} \frac{e^{-m} m^j D(j)}{j!}.$$

In liquid medium, where cells having repaired all of their damages by time t-a are able to divide with generation time a, the number of colony-forming individuals will be $S(x) + S(x - k_r a)$. Summing $S(x)$ to $j = \infty$ gives S_m, or the probability that a cell will survive m damages requiring recombination for repair.

Another parameter of interest is the fraction of total DNA that has undergone recombination in a culture. For this, the DNA of each chromosome is considered as containing m discontinuities, such that at $t = 0$ it can be dissociated at denaturation into segments having an average length of $2/m$ of the intact genome, as shown at the top of Fig. 1. During the course of repair, chromosomes are of two types: those that are still undergoing recombination and have already completed $x = k_r t$ events per individual; and genomes on which all of $j = k_r t < x$ recombination events have been completed. Dividing the sum of these two contributions by m will give the fraction of total DNA that has undergone recombination by time t. Thus,

$$F(t) = \frac{1}{m} \sum_{j=0}^{j=k_r t} \frac{j\, e^{-m} m^j}{j!} + \frac{k_r t}{m} \sum_{j=k_r t+1}^{j=\infty} \frac{e^{-m} m^j}{j!}.$$

This expression simplifies, in terms of x, to:

$$F(x) = P(x - 1) + \frac{x}{m}[1 - P(x)].$$

If the above model describes the progress and sequence of events accurately, then kinetics for the rate and completion of recombination, conversion of DNA reactants into products, size distributions of products and reactants; and the survival curve should be consistent with, and predicted by $S(x)$, $F(x)$, and S_m. The extent of completion of recombination was determined with *E. coli* KL399 *recA200*. The *recA200* mutation confers RecA$^+$ and RecA$^-$ phenotypes at 32° and 42°, respectively (14). In repair of cross-linked DNA, *recA*$^-$ strains are unable to rejoin DNA strands after cross-link removal and are killed by treatments producing about one cross-link per chromosome (9, 15). The response of KL399 to psoralen and light was determined at 32° and 42°, at which 37% survivals were found after treatments of 3.3 kJ/m^2 and 0.41 kJ/m^2 producing 39 and 1.7 cross-links per chromosome, respectively. Other wild-type and *recA*$^-$ strains survived 35–50 and 1.1–1.3 cross-links, respectively (unpublished data). Thus, KL399 behaves toward psoralen and light as RecA$^+$ and 32° and RecA$^-$ at 42°.

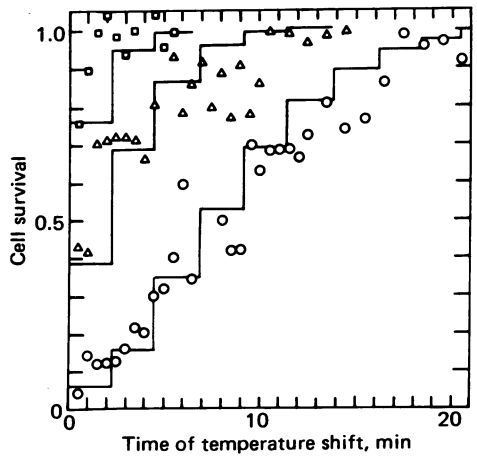

FIG. 2. Kinetics for completion of reactions requiring the *recA*$^+$ gene product in *E. coli recA200* treated with psoralen and light. Cells were grown at 32°, treated, and then incubated at 32°. At times shown on the abscissa, aliquots were warmed quickly and spread on plates at 42° for incubation at this temperature. Symbols refer to the number of cross-links per chromosome formed by the psoralen and light treatment: 0.5 (□); 1.7 (△); and 5.0 (○). Lines drawn were calculated from the model and $F(t)$ using the numbers of cross-links induced, $k_r = 0.43$ min^{-1} and $k_d = 0.001$ min^{-1}, as determined from experiments described in the text.

The time dependency for the *recA*$^+$ product in mediating cell survival was determined by growth of KL399 at 32° and treatment with psoralen and light, followed by incubation at 32° for various times. Cells were then switched rapidly to 42° and plated for colony formations. Viable cells should represent individuals that had completed requirements for the *recA*$^+$ product by the time of temperature shift.

Fig. 2 shows increases in survival of KL399 incubated for various times at 32° before the shift to 42° (RecA$^-$ conditions). At $t = 0$ and 18 min, survivals corresponded to RecA$^-$ and RecA$^+$ conditions, respectively, for the number of cross-links induced originally. After 1–2 min, for all values of m tested, survivals increased abruptly by a value corresponding to completion of repair in the fraction of cells having one damage per chromosome. For example, with $m = 0.5$, chromosomes having 0, 1, and 2 or more damages would be represented by 61, 30, and 9% of the total, respectively. Thus, more than 75% of the damaged chromosomes would have only one damage. Fig. 2 shows that survival increases dependent on RecA$^+$ were essentially completed by 2–3 min. This indicates that the rate constant for the first RecA$^+$-dependent event was about 0.3–0.5 min^{-1}. For larger m, the near constant levels of survivals seen initially suggest that repair occurs in synchrony, as might be expected with the entire population initiating this process at $t = 0$. Reactions at later times show more continuous increases in survival; the scatter in data does not permit distinction between discrete steps or continuous increases. It seems reasonable that synchrony present at the start of the repair would be lost as subsequent reactions progress.

From data similar to those in Fig. 2 for $m = 0.5$–250, and from the sedimentation analysis described later, the best fit to these data by $S(x)$ and $F(x)$ was with $k_r = 0.43 \pm 0.07$ min^{-1} and $k_d = (9 \pm 2) \times 10^{-4}$ min^{-1}. A similar value for k_d at 42° was determined directly as described below. The step functions plotted in Fig. 2 represent $S(x)$ for the different numbers of damages induced and the above rate constants. These theoretical lines were calculated with an addition suggested by other measurements. Part of the $j + 1$ term ($0.55 = e^{-1/1.7}$) was added to $S(x)$ to include the slightly higher survival of KL399 at 42°

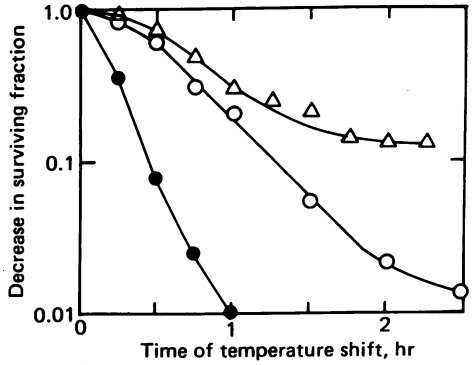

FIG. 3. Loss in colony-forming ability of *E. coli* KL 399 *recA200* treated with psoralen and 1.2 kJ/m^2 (△), 1.6 kJ/m^2 (○), and 3.4 kJ/m^2 (●) light and incubated on plates at 42° for times shown on the abscissa. The temperature was then reduced to 32° and incubation was continued for colony formation.

(1.7 cross-links) compared to other *recA*$^-$ strains tested. The latter could reflect a time for inactivation of the *recA200* protein, a residual activity at 42°, or both (14). Such considerations could also explain the apparent premature increases in survival observed after temperature shifts during the first 1–2 min (Fig. 2). These corrections are not appreciable for $m > 5$.

Values of k_r determined by this analysis will be the actual rate constant for a single reaction mediated by *recA*$^+$ product, multiplied by the number of reactions occurring simultaneously on each chromosome. The inverse rate constant, $1/k_r = 2.3 \pm 0.4$ min, reflects an average time for completion of the *recA*$^+$-dependent step throughout the course of repair. The average time for a single reaction will be some multiple of 2.3 min, which reflects the average number of reactions occurring simultaneously. Since at least one event per chromosome was evidently completed in about 2 min rather than 4.6 min, the number of simultaneous events appears to be limited to one. The remarkable correlations between predicted and observed values for both the times and magnitudes of initial increases are consistent with the model presented here. Although more complex interpretations are possible, it appears that recombination involved in repair occurs as single events.

k_r reflects the time required to complete a single reaction mediated by *recA*$^+$ product and may additionally contain a time required to proceed to successive sites on the chromosome. In the survival and strand-rejoining experiments (as described for data in Fig. 5), k_r was a constant for values of m between 0.5 and 250. This indicates that the time between recombination events at different sites on the chromosome was either a constant independent of distance or was quite small compared to 2.3 min.

The stability of DNA substrate for the reaction mediated by *recA*$^+$ product was determined with KL399 grown at 42° and then exposed to psoralen and light. At $t = 0$, cells were spread on plates at 42°, which were cooled subsequently to 32° at various times. The fraction of cells able to form colonies decreased with a half-time dependent on the number of damages induced (Fig. 3). For treatments producing between 5 and 20 cross-links, the surviving fraction decreased continually during the initial 10–20 min at 42° and with apparent first-order kinetics thereafter. For 30–90 cross-links, the decay was first order throughout the reaction. A plot of half-times against the inverse number of cross-links was linear with a slope of $(14 \pm 3) \times 10^{-4}$ min^{-1} cross-link^{-1}. Thus, the approximate rate constant for decay per cross-link is $k_d = (10 \pm 2) \times 10^{-4}$ min^{-1}.

If decay of substrate for recombination is the same under both RecA$^+$ and RecA$^-$ conditions, the survival curve should

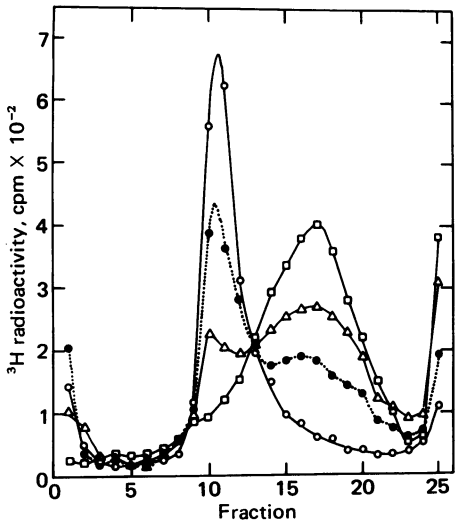

FIG. 4. Sedimentation profiles in alkaline sucrose gradients of DNA released for *E. coli* K1399 *recA200* treated with psoralen and 6 kJ/m^2 light and incubated at 32° for 20 min (□), 90 min (△), 150 min, or 210 min (○). Prior to treatment, the DNA was labeled uniformly by growth in K+2 medium containing [^{3}H]thymidine. After incubation, cells were converted to spheroplasts with lysozyme/EDTA and lysed on top of 5-ml gradients (5–20% sucrose/1.2 M NaCl/10 mM EDTA pH 12.4) for centrifugation in an SW 50.1 rotor at 40,000 rpm for 55 min at 20°. Sedimentation is from right to left; the number average molecular weight of the DNA strands in the 20-min sample was 2.5 X 10^7, based on DNA from bacteriophage T7 used as a molecular weight standard.

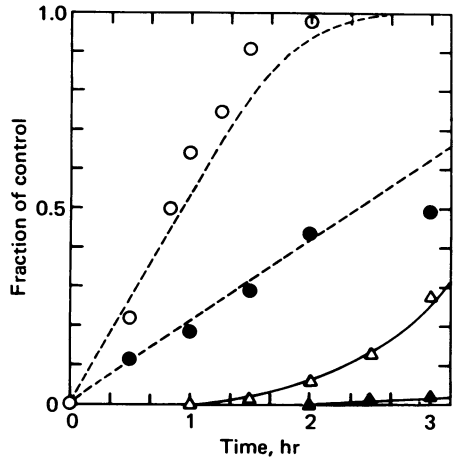

FIG. 5. A composite showing the extents of strand rejoining completed (as circles) and corresponding survivals (as triangles) for *E. coli rec200* incubated at 32° after treatment with psoralen and light, and then shifted to 42° at times shown on the abscissa. Cell survival was determined as described in the legend of Fig. 2, and the extent of strand rejoining was measured from data similar to those in Fig. 5, as described in the text. Symbols refer to treatment of 4.1 kJ/m^2 (○ and △) and 7.2 kJ/m^2 (● and ▲), producing 52 and 122 cross-links per chromosome, respectively. Lines drawn are theoretical values calculated from $F(x)$ and $S(x)$ with m = 52 or 122, k_r = 0.43 min^{-1}, and k_d = 0.001 min^{-1}.

be predicted by the model described. Values of S_m were calculated with k_d = 0.001 min^{-1}, as determined for KL399 at 42°, and k_r = 0.90 ± 0.1 min^{-1} or 0.6 ± 0.2 min^{-1}, as determined for strain AB1157 at 40° and 42° (unpublished data). The theoretical curves for 40° and 42° were within 5 and 15%, respectively, of experimental values (data not shown). This reasonable correlation suggests that survival may be expressed as competition between completion of repair and a simultaneous decay of unrepaired chromosomes.

The nature of DNA reactants and products and the kinetics of their reaction can be followed by sedimentation analysis (unpublished data). Strand rejoining does not occur in *recA*$^-$ strains (9); this was confirmed for KL399 at 42°. Strand rejoining (Fig. 4) occurred normally at 32°, at a rate similar to other wild-type strains. The treatment with psoralen and light (6 kJ/m^2) produces about 100 cross-links per chromosome. After 20 min, when cross-link removal was completed, DNA sedimented in alkaline sucrose as a distribution corresponding to a number average molecular weight of about 2.5 X 10^7, as expected (16, 17). During further incubation, DNA was joined into high molecular weight strands, and the reaction appeared completed by 210 min. Significantly, the number average molecular weight of short segments did not increase continually, as would be expected if rejoining occurred at random. Instead, short segments appeared to be joined directly into high molecular weight strands similar to those released from intact cells. Such behavior would be expected if strand rejoining occurred in a sequential or progressive fashion. For example, after completion of five to six rejoining events at t = 14 min, rejoined DNA would have a molecular weight greater than that released from control cells. Subsequent joining would be detected as an apparent conversion of short segments directly into high molecular weight strands, as was observed. Alternatively, successive reactions might occur in clusters within confined regions, such as domains of the folded bacterial chromosome (18, 19). Theoretical calculations on both models were consistent with sedimentation profiles; the best correspondence with experimental values was found using clusters within regions consisting of 2–4% of the genome.

The extent of strand rejoining as a function of time is shown in Fig. 5 for treatments producing about 52 and 122 cross-links per chromosome. Also shown are fractions of cells able to form colonies when shifted to 42° at times shown. The extent of strand rejoining is shown as the fraction of control DNA that has been restored to high molecular weight strands. These values were determined by considering sedimentation profiles, as shown in Fig. 4, to be composed of the two size classes of DNA molecules described above. Relative contributions of each were estimated by extrapolating the shape of each component (from control and 20-min samples), and determining the relative areas. As shown, the extent of rejoining increased almost linearly to 0.5 and then approached 1.0. Times required for completion were proportional to the numbers of cross-links induced. Dashed lines were calculated from $F(x)$ with k_r = 0.43 ± 0.07 min^{-1}. k_r, determined from strand rejoining data, is based on the initial slope through points in Fig. 5 or the best fit by $F(x)$. As seen with 52 cross-links per chromosome, survival did not reach 50% of the final value even when more than 95% of the DNA had been rejoined. This difference in behavior is contrary to predictions from models for recombination in which all events in a given cell are completed in a time that is short compared to that observed in the entire population. Such a mechanism could produce the bimodal distributions of DNA sizes observed, but predicts that increases in survivals will parallel extents of strand rejoining.

k_r is defined in Fig. 1 as the rate constant for completion of individual recombination events. Completion of a single event probably involves a series of biochemical reactions, of which the slow step will determine the overall rate. In the biological experiments, reactions controlled by *recA*$^+$ were taken to be rate-determining in repair promoting survival. The biochemical analysis of strand rejoining reasonably reflects completion of individual recombination events, and the extent of reaction will

also be determined by some rate-determining step. The observation that these two processes appear to proceed at the same rate suggests that both reactions share the same rate-determining step. Although the *recA*$^+$-controlled reaction, or a prior reaction, appears to determine the overall rate, the present analyses do not distinguish whether the *recA*$^+$-controlled step and strand rejoining are the same, follow closely in time, or are separated by up to 10 min.

DISCUSSION

These results are consistent with recombination in the repair of cross-linked DNA occurring as single events. Successive events appear to occur in a progressive or sequential pattern around the chromosome, as shown in Fig. 1, or in clusters such as domains of folded chromosomes. Initial recombination events appear to occur in synchrony in a population of treated cells, and at 32°, 2.3 min is required for completion of each step requiring the *recA*$^+$ gene product. DNA substrate for recombination is remarkably stable in cells and decays with a half-life of about 700 min/number of cross-links, even under RecA$^-$ conditions. This model for recombination is consistent with observed rates of single events, completion in individual cells, the kinetics of strand rejoining, and size distributions of DNA during repair. Additionally, this model predicts the survival of cells after treatment with psoralen and light. Significantly, calculated values of these parameters use only observed rate constants for recombination and decay of DNA substrate and the numbers of cross-links induced.

The genetic control and products of recombination in repair of cross-linked DNA appear to be similar to those of other recombinational processes (refs. 9–11 and unpublished data). Thus, it seems reasonable that a mechanism such as described above, or parts of it, will apply to recombination after conjugation, transduction, or transformation. Single events could be a result of a unique site for recombination within each cell and, additionally, might reflect steric factors between participants organized in forms such as folded chromosomes (18, 19). A sequential mechanism could serve in assisting synapsis between domains of folded chromosomes (20, 21) and single exchanges would limit participating DNA duplexes to two. Such features could provide safeguards by reducing errors and possible tangles among products.

recA$^+$ controls generalized recombination completely and is believed to act early in the process by mediating synapsis or strand cutting required for initiation of strand exchanges (1, 2). The *recA*$^+$ gene product has been identified as protein X (22), but its activities mediating recombination remain to be established. It has also been suggested that *recA*$^+$ regulates the synthesis of other gene products involved in repair and recombination (23). The present study shows that *recA*$^+$ was required continually at each successive site for recombination encountered throughout the repair sequence. These observations do not exclude the possibility of *recA* in a regulatory role. They show that this product has an additional activity in mediating events separated by time and distance on the genome, and that it is not involved primarily in stabilizing the DNA substrate.

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