The Bacterial Chromosome
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Chapter 20

The RecA Protein

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The RecA protein of *Escherichia coli* has established the paradigm for a nearly universal class of proteins that facilitate some of the central steps in recombination. After the discovery of the *recA* gene in 1965 by Clark and Margulies (26), *recA* mutants were found to have a complex pleiotropic phenotype that has fascinated and challenged researchers ever since. Many aspects of RecA action are still not understood despite over 3 decades of intensive research.

The heart of RecA function, and the one activity shared by all proteins in this class, is DNA strand exchange. In the simplest and most common version of these reactions, RecA protein and its homologues bind to single-stranded DNA, forming a helical nucleoprotein filament. A homologous duplex DNA is then taken up, and one strand of the duplex is transferred from the duplex to the complementary single strand originally bound. The other strand of the duplex, the one identical to the strand originally bound, is displaced. This general reaction plays a central role in recombinational DNA repair, recombination during conjugation and transduction in bacteria, meiotic recombination in eukaryotes, and many other processes.

The RecA protein is found in essentially all bacteria (17, 178). The only apparent exceptions involve bacteria (*Buchnera* sp.) that have a greatly reduced genome size, possibly arising from their endosymbiotic relationship with aphids (142, 227). Bacterial RecA proteins are highly homologous to each other, having similar sequences, sizes, and domain structures (17, 178). Every bacterial RecA protein in a survey of 64 examples had at least a 49% sequence identity to the *E. coli* RecA protein (178). In eukaryotes, the important RecA homologues are the Rad51 and Dmc1 proteins (9, 16, 71, 123, 196, 206). In archaea, the RadA proteins provide the same recombination functions (186). This chapter focuses on the bacterial RecA proteins, which have at least three major roles.

The first function involves a direct participation in the central steps of recombination, via the DNA strand exchange activity already described. These reactions have a classical role in the recombination that occurs during conjugation, but current evidence indicates that RecA did not evolve to promote the generation of genetic diversity. In bacteria, the most important role of recombination proteins, including RecA, is in the nonmutagenic repair of stalled replication forks. Under normal aerobic growth conditions, a large fraction of bacterial replication forks, perhaps most of them, are halted by encounters with DNA damage or other barriers (30, 31, 33, 36, 89, 102, 103). Recombination represents the primary path to repair of these events. An encounter with a strand break can create a double-strand break in which one branch of the fork is detached (Fig. 1A). An encounter with an unrepaired DNA lesion can result in a stalled fork in which the lesion is left in a single-strand gap (Fig. 1B). There are probably numerous other structures that can result from a collapsed fork. Classical paths of DNA repair, such as excision repair, rely on the presence of an undamaged DNA strand to repair against, something which does not exist in either of the situations in Fig. 1. Recombination provides a nonmutagenic path to repair of these structures (30, 31, 33, 36, 89, 102, 103), and the RecA protein plays a central role in these processes. From this standpoint, the function of RecA and other recombination proteins in recombination during conjugation and transduction is quite incidental to bacterial DNA metabolism.

Second, RecA protein has a role in regulation. As a regulatory function, the RecA protein facilitates the autocatalytic cleavage of the LexA repressor and certain other proteins to induce the SOS response to DNA damage (113, 114, 154, 194). The LexA repressor regulates the expression of over 40 genes encoding enzymes and proteins involved in DNA repair and control of cell division. A current view of

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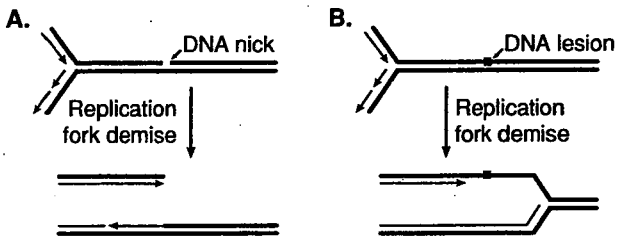


Figure 1. Replication fork demise at the sites of DNA damage. (A) Encounter with a strand break leads to a double-strand break and dissociation of one arm of the fork. (B) Encounter with an unrepaired DNA lesion can result in the creation of a gap at a stalled fork. In either case, repair pathways involve recombination.

SOS induction can be summarized briefly. When the cell is subjected to high levels of DNA damage, single-strand gaps form in the DNA, leading to the binding and activation of RecA protein to the DNA. In this bound form, RecA filaments interact with the LexA repressor, leading to the autocatalytic cleavage and inactivation. This activity of RecA is often called a coprotease function. As the levels of active LexA repressor drop, the SOS genes are induced.

Finally, the RecA protein participates in yet another type of repair process. Late in the SOS response, especially when DNA damage levels are particularly high and nonmutagenic DNA repair is insufficient to get replication restarted, a need arises to restart replication via lesion bypass. This is something of a desperation measure for the cell, since it inevitably leads to mutation. The RecA protein participates directly in the replicational bypass of DNA lesions (48, 61, 209). Mutagenic lesion bypass is mediated by a specialized class of DNA polymerases, represented in *E. coli* by DNA polymerases IV and V. The RecA protein participates directly in the lesion bypass reactions promoted by DNA polymerase V by a mechanism that is still under intensive investigation.

The known biochemical activities of the RecA protein parallel these cellular roles. These include binding to DNA, ATP hydrolysis, filament formation, DNA strand exchange, and the coprotease activity. In this chapter, I try to provide a fairly thorough and current overview. A series of recent reviews can be consulted for details (15, 32, 92, 178). Each of these activities is replete with complexity that has made the protein a focus of over 2 decades of research. Several themes wind through the continuing discussion. RecA protein functions as a filament in all of its known activities, and this filament provides an excellent platform for the central process of aligning homologous DNA sequences and switching DNA strands. The hydrolysis of ATP confers properties on RecA protein that suggest the presence of a motor function. Also, the RecA homologues found in other classes of organisms do not have all of the RecA functions, and even the shared functions can be very different in their details. This is making it increasingly clear that each of these proteins is highly adapted to a very different cellular milieu. The Rad51, Dmc1, and RadA proteins will be compared and contrasted with RecA protein wherever such comparisons may provide some insight.

STRUCTURE

The RecA protein of *E. coli* is a polypeptide chain with 352 amino acid residues with a combined molecular weight of 37,842 (37,711 after the initiating methionine is removed). This is quite average for a bacterial RecA protein. Molecular weights of other bacterial RecAs are similar, ranging from 34,344 (318 amino acid residues including the initiating methionine) for the RecA of *Bacteroides fragilis* (67) to 41,949 (388 amino acid residues including the initiating Met) for the RecA of *Streptococcus pneumoniae* (122). Bacterial strains engineered to produce the RecA protein at very high levels are widely available. Purification is relatively simple (28, 39, 69, 99, 192), and good protocols have been developed for the purification of many different mutant RecA proteins as well as the RecA proteins from a variety of bacterial species. The bacterial RecA proteins are generally quite soluble in aqueous buffers, and are stable for many months if stored at −70°C. The pI of the purified *E. coli* RecA protein has been measured in at least six studies, giving values from 5.0 (198) to 6.2 (70). Averaging all the measurements (21, 65, 70, 94, 156, 198) gives a representative pI of 5.6. In solution, the protein has a tendency to aggregate into oligomers, filaments, and bundles of filaments (19, 20, 94, 164, 210, 230). The aggregation state of a given solution of the protein is affected by pH, salt concentration, and temperature. Concentrated solutions of the protein often appear opalescent as a result of light scattering by filamentous structures.

The structure of RecA protein without DNA bound has been determined at 2.3-Å resolution (204, 205). The crystal packing features a continuous spiral filament, with six monomers per right-hand helical turn (Fig. 2). These results are consistent with other studies showing that RecA protein forms a helical nucleoprotein filament on DNA, also with six monomers per helical turn. In the electron microscope, the contiguous filaments have a striated appearance (Fig. 2). The filament exhibits a deep helical groove, where DNA binding and DNA pairing take place. The structure was solved in two forms, one with

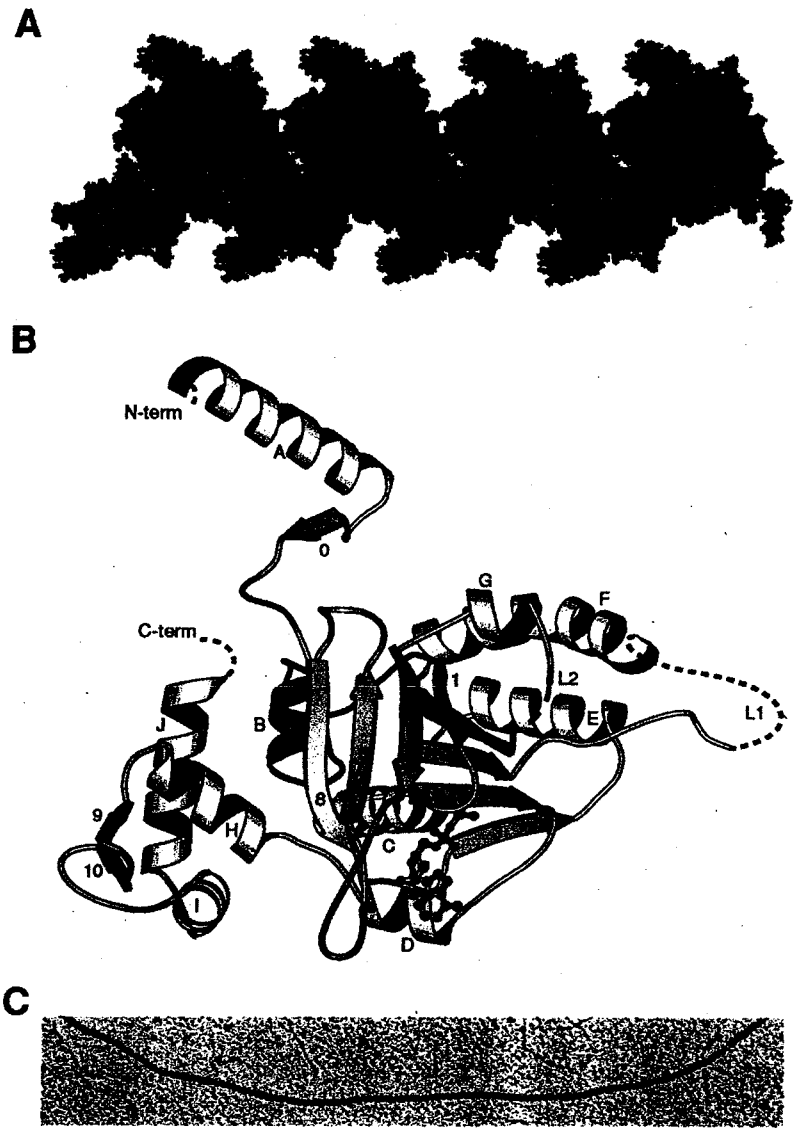


Figure 2. RecA protein structure. (A) A RecA filament is shown, with 24 RecA monomers, based on the 1992 structure by Story and Steitz (204) (see text). One monomer is colored in a darker gray. (B) A RecA monomer, with bound ADP. (C) An electron micrograph of one segment of a RecA filament formed on DNA.

bound ADP (204) and the other with no nucleotide (205). No crystal form with RecA bound to DNA has been reported. The filament seen in the crystal is not as extended as that observed on DNA in the presence of ATP, and hence the structure may reflect an inactive form of the protein (53, 54, 59, 157, 237).

In each monomer, there is a central core domain flanked by two smaller subdomains at the N and C termini. Many parts of the core domain are highly conserved among the bacterial RecAs, the eukaryotic Rad51 and Dmc1 proteins, and the archaeal RadA protein (17, 178). In contrast, the C-terminal subdomain of RecA is unique in this class of proteins (Fig. 3). Conversely, the N-terminal subdomains of Rad51, Dmc1, and RadA are not found in the bacterial RecA proteins (Fig. 3). The 20 to 30 amino acids at the C terminus of most bacterial RecA proteins, including that of *E. coli*, feature a high concentration of acidic residues. This segment of the protein is otherwise among the most variable regions of the bacterial *recA* sequences (178). The N-terminal domains of Rad51, Dmc1, and RadA proteins also feature stretches of acidic amino acid residues, suggesting that these subdomains might have the same (currently unknown) function as the RecA C-terminal subdomain (17, 178).

Many sequences of *recA* genes and the genes of *recA* homologues are available. This has led to

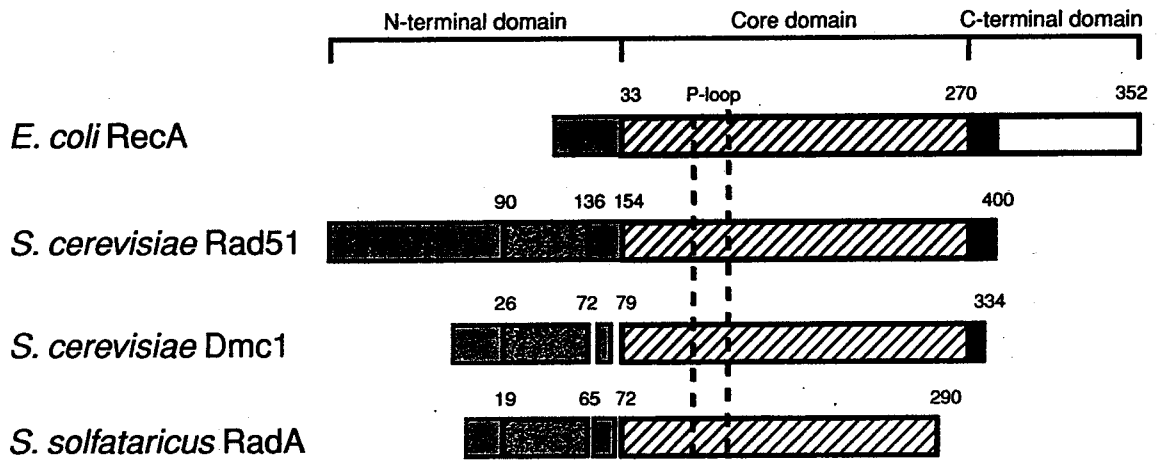


Figure 3. Domain structures of RecA protein and its homologues in *Saccharomyces cerevisiae* and *Sulfolobus solfataricus*. The open box is the core domain shared by all four proteins. The RecA C-terminal domain is unique to bacterial RecA proteins. Homologies among other domain elements are indicated by shading patterns.

extensive sequence alignment efforts and detailed structural analyses (17, 82, 177, 178). The RecA proteins from bacteria are all closely related, with none having less than a 49% amino acid sequence identity to the *E. coli* RecA protein. In a comparison of 64 bacterial *recA* genes (178), there were 59 invariant residues and another 100 that could be classified as chemically conserved. The protein has a binding site for ATP, and less well defined binding sites for up to three strands of DNA within the helical groove. Many of the conserved residues are involved in the binding of DNA or ATP, or are at the monomer-monomer filament interface. In general, the Rad51, Dmc1, and RadA sequences are more similar to each other than any of them is to a bacterial RecA sequence (17, 178).

The RecA protein of certain mycobacteria is expressed as a larger precursor containing a large, self-splicing intein (64, 98, 140, 181, 195). The intein is found in about 20% of mycobacterial species. While initially thought to be restricted to pathogenic species, such as *Mycobacterium tuberculosis* and *Mycobacterium leprae*, evidence now suggests a more general invasion of the mycobacteria with the inteins (181). The inteins are comparable in size to the RecA proteins themselves (98). The inteins are not spliced when the mycobacterial genes are cloned into *E. coli*, but are spliced when cloned into mycobacterial species that otherwise lack the *recA* intein (64).

Most of the central core domain of RecA protein, from residues 61 to 246, exhibits an intriguing structural similarity to the F1-ATPase, even though the two proteins share very little sequence similarity (239). The same structural folding pattern is seen in hexameric helicases and a number of other proteins, most involved in nucleic acid metabolism (4, 14, 51, 239).

DNA BINDING

RecA protein binding to DNA is a multistep process. The first step is nucleation, involving the binding of a monomer or small oligomer. Additional protomers are added in an extension phase to create and lengthen a filament. RecA protein filaments both assemble and disassemble in a unidirectional and end-dependent manner, with protomers added at one end and subtracted from the other (Fig. 4) (110, 187). This is true on both single-stranded DNA (ssDNA) and double-stranded DNA (dsDNA). The oligomeric species that is added and subtracted has not been defined for *E. coli* RecA protein. However, work with the RecA protein from *Thermus thermophilus* indicates that monomeric RecA protein is an intermediate in filament assembly on ssDNA (124).

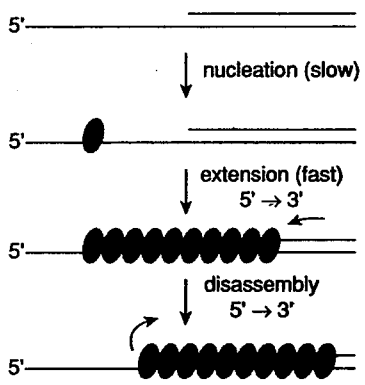


Figure 4. Assembly and disassembly pathways for RecA filaments. After nucleation, filament extension proceeds 5′ to 3′ relative to the ssDNA, and can encompass adjacent duplex regions. RecA dissociation occurs from the opposite filament end, and proceeds also 5′ to 3′.

Without nucleotide cofactor or with ADP, RecA protein binds to ssDNA in a compact form called a "collapsed" filament, with a helical pitch of 64 Å and an axial rise of 2.1 Å per nucleotide (74, 202). An extended right-hand helical filament is formed when ATP or dATP is added. Alternatively, the ATP analogue ATPγS [adenosine 5′-O-(3-thio)triphosphate] or ADP•AlF_4^- can support extended filament formation. Both analogues are bound by RecA protein, but not readily hydrolyzed. The extended filament has 6 to 6.1 RecA monomers per turn, a pitch of 95 Å, and a diameter of 100 Å (45, 55, 155, 240). The single strand of DNA binds deep within the filament groove and near the filament axis (57). The DNA is bound along the ribose-phosphate backbone, with the DNA bases displayed in the filament groove (46, 47, 105). The same extended filament can be observed when RecA is bound to dsDNA. In this case the DNA is underwound to approximately 18 bp per turn, removing either 43% (in the presence of ATPγS [201]) or 39.6% (in the presence of ATP [166]) of the helical turns in the DNA.

The structure of RecA-bound DNA has been studied by nuclear magnetic resonance. The experiments revealed a novel deoxyribose-base stacking in which the 2′-methylene moiety of each deoxyribose was positioned above the base of the neighboring residue (152, 153). Adjacent bases were not stacked as in DNA in solution. The deoxyribose-base stacking led to a base spacing of about 5 Å, as expected from other measurements. This structure has been proposed to facilitate base flipping (152).

The nucleation of RecA protein on ssDNA is slowed considerably if the DNA is bound by the *E. coli* single-strand DNA-binding protein SSB (120, 187). This inhibition is overcome in at least some contexts by other proteins. The RecO and RecR proteins form a complex that greatly facilitates RecA nucleation on SSB-bound ssDNA (219). Also, the RecBCD protein prepares duplex DNAs for RecA binding by trimming the 5′-ending strand more than the 3′-ending strand to generate a 3′ single-strand extension. The RecBCD protein also directly loads RecA protein onto the prepared DNA substrate (6, 25).

RecA binding to ssDNA is generally nonspecific with respect to sequence, although the protein exhibits an enhanced affinity to certain homopolymers such as poly(dT) (5, 22, 128). RecA also exhibits a higher affinity for a range of GT-enriched sequences, among them the recombination hotspot chi (216, 217). Optimal binding of wild-type RecA protein to poly(dT) generally occurs only with polymers more than 50 nucleotides in length (18), although somewhat shorter polymers can be employed in concert with the addition of ATPγS.

RecA protein binding to ssDNA is cooperative (92, 134). Cooperativity is also manifested in the ATP hydrolytic activity, as the binding of ATP or ATPγS to individual filament subunits can stimulate nucleoside triphosphate (NTP) hydrolysis in neighboring subunits (106, 136). Binding to ATP induces a conformation change in which the RecA protein is activated and bound DNA is extended and (if duplex) underwound. Monomer-monomer interactions help to maintain the entire filament in an extended active state.

In the assembly process, nucleation of filament formation is rate-limiting (91, 163, 165). Nucleation is much faster on ssDNA than on dsDNA. Slow binding of RecA to dsDNA at neutral pH and above is due to slow nucleation (91, 163, 165). Faster nucleation on dsDNA is seen at pHs below 6.5 (163, 165). Nucleation on dsDNA is facilitated by DNA treatments that tend to unwind the DNA. The most effective nucleation site is a ssDNA gap (91, 163, 165), although nucleation is accelerated if the DNA is supercoiled, linearized, or nicked (163). Nucleation is not enhanced by DNA damage as has been reported (86, 87, 118, 225), but by the perturbations in DNA structure (in particular DNA unwinding) that are caused by DNA damage (163).

The assembly of an active RecA filament requires the binding of ATP, but not hydrolysis. Extended filaments are formed in the presence of ATPγS. On ssDNA, the filament is extended uniquely 5′ to 3′ (168, 187). In a ssDNA gap, the extension of the filament continues into the adjoining dsDNA, continuing until the available contiguous DNA or RecA protein is depleted.

End-dependent RecA filament disassembly occurs on the end opposite to that at which assembly occurs (110, 187), and is coupled to ATP hydrolysis. ATP is hydrolyzed by RecA monomers uniformly throughout RecA filaments (18), and there is no evidence for enhanced rates at either filament end. The hydrolysis of ATP by interior monomers does not generally result in dissociation, and under some conditions ATP hydrolysis can proceed with no evident dissociation of RecA monomers (151, 187, 190). Thus, ATP hydrolysis occurs everywhere, apparently resulting in dissociation only for monomers at the disassembling end (7). Dissociation at that end occurs with a probability that is some function of reaction conditions. Some exchange of RecA protein between free and bound forms can be detected in the interior of RecA filaments under some conditions (190). This is most easily explained by end-dependent dissociation or association processes at filament discontinuities, although some dissociation of fully integrated interior monomers under some conditions has not

been ruled out. On ssDNA, the maximum observed rate of end-dependent disassembly (seen above pH 7.5) is 60 to 65 monomers per end per min (7).

Filament dynamics can also be studied with the aid of mixed filaments of wild-type RecA protein and a mutant (190). Mixed filaments are formed with wild-type RecA protein and the mutant protein RecA K72R, which binds but does not hydrolyze dATP (190). When the proteins are added together, proportions of mutant and wild-type proteins in the resulting mixed filaments are the same as the proportions in the overall experiment. The presence of a mutant affects the observed levels of dATP hydrolysis. If the mutant protein is added after wild-type filaments are formed on ssDNA, little exchange of mutant protein into the filaments is observed. On dsDNA, there is a rather facile exchange of mutant protein into the filaments. In general, the filaments on dsDNA are more dynamic with respect to monomer exchange than are those on ssDNA (190).

In a RecA filament, there is one RecA monomer per three bound nucleotides or base pairs of DNA. A few titration experiments have provided a stoichiometry twice as high (104, 133, 135, 141). The apparent higher site size reflects the binding of a second DNA strand to another DNA binding site within the filament (56, 57, 157, 203, 244). RecA filaments can actually bind up to three DNA strands within the filament groove, with three distinct DNA strand-binding sites (95, 100, 101, 211, 212). The sites are usually called simply I, II, and III (95, 100, 101, 211, 212). Site I has the highest affinity for a DNA strand and is generally the site at which ssDNA is bound to RecA protein. Site II is the site generally occupied by a strand complementary to that in site I, although heterologous sequences are tolerated. Site III would then be the site occupied by a DNA strand displaced during DNA strand exchange. The numbering of the sites varies somewhat from research group to research group. When strands of identical ssDNA are added successively to a RecA filament, site III actually binds to the DNA with an affinity higher than that of site II (when sites are identified by the system used here), and it is therefore sometimes referred to as site II.

In a competing formalism, the filament groove is described by some workers to have two DNA binding sites, each of which can bind to either a single- or double-stranded DNA (125, 127, 145, 170). Since no more than three total strands can be bound at one time, the two sites as defined this way presumably overlap.

On dsDNA, the two strands of the DNA are bound asymmetrically. The strand occupying the binding site normally occupied by ssDNA (site I) is protected from nuclease digestion 2 to 3 times better than its complement (site II) (24, 111). The strand bound in site I determines the orientation of the entire filament, with assembly processes proceeding 5′ to 3′ relative to that strand.

The RecA protein filament has been the paradigm for DNA strand exchange proteins, and similar filaments are formed by the eukaryotic Rad51 protein (157) and the archaeal RadA protein (186). The extent of structural similarity in these filaments, and the similar extents to which DNA is extended within them (50), is remarkable. Notably, the eukaryotic Dmc1 protein has not formed filaments in any experiment reported to date, and appears to function as an octameric ring (158). The mechanism by which such a structure can promote even the relatively weak DNA strand exchange reactions so far observed for Dmc1 protein provides a fascinating experimental challenge.

ATP HYDROLYSIS

RecA-mediated ATP hydrolysis is almost entirely DNA dependent. The measured monomer k_{cat} is about 30 min^{-1} on ssDNA, decreasing to 16 to 20 min^{-1} on dsDNA. The maximum reported value for k_{cat}/K_m at 37°C is about 2×10^4 M^{-1} s^{-1}, well below the diffusion-controlled limit of 10^8 to 10^9 M^{-1} s^{-1}. The kinetics are complicated by cooperativity, and the K_m is more accurately reported as $S_{0.5}$. RecA-mediated ATP hydrolysis in the absence of DNA is slow, with a maximum k_{cat} of 0.1 min^{-1} observed at about pH 6.0 (226). The rate is stimulated markedly by high (1.5 to 2 M) concentrations of a wide range of salts (164). The salt appears to induce a conformation change that to some degree mimics that induced by the binding of DNA to RecA protein (96, 234).

A variety of rNTPs and dNTPs are hydrolyzed by RecA protein, including dATP, UTP, PTP (purine ribonucleoside triphosphate), ITP, CTP, dCTP, GTP, and dUTP (90, 137, 226). Only ATP, dATP, and PTP (those with a measured $S_{0.5}$ below 100 μM) serve as cofactors in the DNA strand exchange reaction (90, 137, 138, 226).

The DNA-dependent ATPase activity exhibits no dependence on pH between 5.5 and 9.0 (226). The effects of temperature between 25 and 45°C on ssDNA-dependent ATP hydrolysis produce a linear Arrhenius plot, from which an Arrhenius activation energy of 11.8 ± 0.3 kcal mol^{-1} can be derived (13) for the reaction. The ATP hydrolysis occurs uniformly throughout the RecA filament, with no enhancement at filament ends (18, 91, 182). When

longer DNAs are used as cofactors, the relationship between ATP hydrolysis and DNA binding is sufficiently constant that ATP hydrolysis can be used as an indirect measure of DNA binding under many conditions (7, 187). However, this method of estimating DNA binding levels is obviously indirect and should not be used without first determining the k_{cat} for ATP hydrolysis and confirming that the k_{cat} is constant under all conditions of a given experiment.

ATP is hydrolyzed to ADP and P_i. ADP acts as a competitive inhibitor of ATP hydrolysis. As already noted, the ATP analogue ATPγS, which is bound but not appreciably hydrolyzed by RecA protein, also acts as a potent competitive inhibitor. The inhibition patterns in both cases are greatly complicated by additional effects of these two nucleotides (106, 107). Mixtures of ATP and ADP result in collapse and dissociation of RecA filaments from both ssDNA and dsDNA when the ADP/ATP ratio approaches 50% (41, 106, 107). ATP and ADP tend to cooperatively stabilize different conformations of a RecA filament, and these forms are not directly interconvertible via ATP hydrolysis (107, 166, 240). Very low concentrations of ATPγS can stimulate the ATPase activity under some conditions (106).

ATP hydrolysis does not proceed to completion. RecA filaments tend to come apart when the ADP/ATP ratio reaches about 1.0 (41, 106), effectively halting ATP hydrolysis. ADP and ATPγS are antagonistic inhibitors that evidently stabilize different conformations of the protein (106). When the concentration of ADP is quite high, ATPγS can partially relieve the inhibition due to ADP (106).

The hydrolysis of dATP tends to enhance some RecA reactions. With dATP, hydrolytic rates are increased about 20% relative to ATP hydrolysis. RecA filament stability and the rates of DNA strand exchange are also enhanced (133, 190). As already noted, the RecA mutant RecA K72R will promote a limited DNA strand exchange reaction only if dATP is used as the nucleotide cofactor (169, 191). The use of dATP also prevents an end-dependent disassembly of filaments from ssDNA, as described below (187).

DNA STRAND EXCHANGE

Alignment of DNA and Strand Transfer: Reactions without ATP Hydrolysis

The fundamental process of DNA pairing and strand transfer occurs within the filament groove, an arrangement originally proposed by Howard-Flanders (77). As promoted by RecA protein, DNA strand exchange can involve either three or four DNA strands (Fig. 5). RecA protein filaments first form on

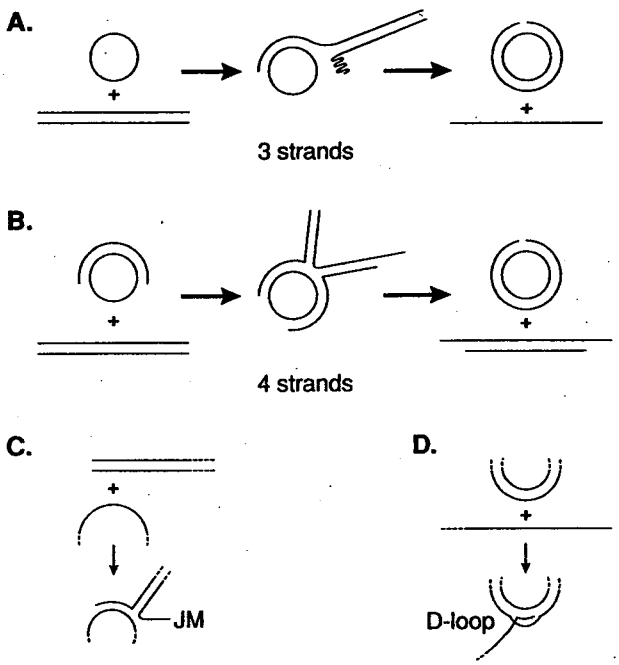


Figure 5. RecA protein-mediated DNA strand exchange reactions. (A) The most common three-strand reaction used in many studies. (B) The standard four-strand reaction. RecA protein filaments are nucleated in the gap of the circular DNA substrate, and DNA pairing is also initiated in this gap. (C) Initiation of DNA strand exchange at a free duplex DNA end. (D) Initiation of DNA strand exchange at a free single-strand (RecA-bound) DNA end.

the single-strand DNA, or on the gapped DNA substrate of a four-strand exchange reaction. The second DNA duplex is then drawn into the filament, and aligned with the first. Alignment triggers the strand switch. ATP hydrolysis is not required for the alignment or strand switch, so these basic pairing steps are presumably catalyzed by binding interactions within the filament groove (38, 83, 84, 93, 132, 169, 191). The pairing and strand switch can occur in a more or less concerted way along a region of several hundred base pairs. Thus, for reactions involving short oligonucleotides, this represents the entire process, and no ATP hydrolysis is required for any part of the reaction. When long (>1,000 bp) DNA substrates are employed, the product of these reactions is often referred to as a joint molecule (Fig. 5), a branched structure that must be extended to complete a strand exchange reaction. ATP hydrolysis is involved in certain aspects of the extended strand exchange reactions seen with long DNA substrates, and it is considered separately below.

These reactions proceed in a prescribed order, in which a single strand is bound first and the homologous duplex is drawn in second. This sequence is the same for the reactions reported for RecA and all of the homologues for which this has been examined to date. However, an active site constructed to promote this reaction should in principle be able to promote the same process in the opposite direction. An inverse reaction has been reported for the *E. coli* RecA protein, in which the duplex DNA is bound first and the single strand is drawn in (241). The reaction has been demonstrated only for quite short duplex DNA substrates (63 bp) in which RecA protein filaments are stabilized by the presence of long circular single strands contiguous with the duplex. The reaction promoted is effectively the reverse of the normal reaction, although there are some different reaction requirements that suggest it may have some unique properties (241). The DNA binding affinities of the RecA protein make it difficult to set up and observe such a "duplex-first" reaction.

The mechanism by which RecA protein aligns the bound single strand with the duplex has received a great deal of attention. Analysis of the kinetics of DNA pairing with short oligonucleotides reveals at least two steps: a rapid second-order alignment of the two homologous DNA molecules, followed by a slow first-order process (11, 12, 236). The initial alignment may involve base flipping by some bases in the duplex (especially A and T bases) to align the DNAs via Watson-Crick pairing, as revealed for the human Rad51 protein (72). In this mechanism, the slow first-order process may be a completion of the strand switch to include all remaining base pairs over an extended region. The homologous alignment does not involve a sliding of the RecA-ssDNA complex along a duplex DNA, but instead is best explained by random collision (2).

In principle, the duplex could approach the ssDNA within the filament via either its major or minor groove. Within the major-groove-first path, a novel triplex DNA intermediate, formed prior to a strand switch or base flipping, has been proposed. This triplex has been called R-form DNA (85, 243). In the alternative minor-groove-first path, homologous alignment would involve only the standard Watson-Crick base pairing provided by base flipping. As the duplex bound, it would be extended and underwound such that its bases would be free to rotate and "sample" the bound ssDNA for complementarity. The RecA and Rad51 proteins both promote DNA strand exchange readily with DNA substrates heavily substituted with base analogues that disrupt many of the interactions proposed to stabilize the R-form triplex as it has been presented (79, 173, 174). Overall, the weight of the evidence currently supports a minor-groove-first pathway for DNA pairing that excludes an R-form triplex intermediate (8, 62, 72, 97, 160, 161, 242), although arguments for a major-groove-first path have also appeared (121). The RecA filament appears to stabilize the products of DNA strand exchange, using binding energy to promote the strand switch (3).

The "search for homology" involves the transient underwinding of the duplex DNA substrate, an effect that can be observed with heterologous DNA substrates (180). In addition, the binding of a heterologous duplex DNA to a RecA-ssDNA complex "activates" the duplex for a strand exchange reaction with a homologous single strand introduced external to the filament (126). This strand exchange "in *trans*" is a much weaker reaction than the conventional strand exchange, and has been demonstrated only for short oligonucleotides. At a minimum, interesting structural changes are conferred on a duplex DNA when it binds to a RecA nucleoprotein filament, and the alterations are likely to facilitate strand exchange reactions in general.

A duplex DNA can initiate pairing at any point along the RecA-ssDNA complex. In fact, the formation of paired complexes is readily detected even when both the single-stranded and homologous duplex DNAs are circular (112, 183, 235). However, for a stable net strand exchange to occur, topology considerations dictate that at least one of the two DNA substrates undergoing DNA strand exchange must have a free end. Thus, a reaction can occur between a circular single strand and a linear duplex, or a linear single strand and a circular duplex (Fig. 5C and D).

The latter reaction is sometimes called D-loop formation or DNA strand invasion, and provides a good model for RecA protein's likely role in the repair of double-strand breaks.

If the initial DNA pairing interaction occurs away from a DNA end, the joint must migrate until a free end is encountered. This can also happen within the RecA filament and does not require ATP hydrolysis, or dissociation movement of any part of the RecA filament. Migration of such a joint can be halted by secondary DNA pairing interactions, or by other nonproductive interactions of the unreacted duplex DNA with the RecA-ssDNA complex (Fig. 6). Such interactions can limit the extent of strand exchange reactions of RecA (191), as well as Rad51 protein (197). In effect, a DNA pairing process that is too facile can restrict the extension of joints. This may be one function of ATP hydrolysis in the RecA system (191).

The four-strand reactions require a significant single-strand gap in one of the two duplex DNAs. The gap serves two purposes. It is a nucleation site for the formation of a RecA filament, which can then encompass the adjacent duplex regions. It is also the location where the DNA pairing is initiated; i.e. four-strand exchanges must be initiated as three-strand reactions (23, 27, 112). Thus, the linear duplex DNA substrate must include sequences at one or both ends that are homologous with those in the single-strand gap of the other substrate.

The four-strand reactions do not occur without ATP hydrolysis. When a gapped DNA is paired with a linear duplex in situations where ATP or an analogue is bound, but not hydrolyzed, then DNA strand exchange is initiated in the gap. However, the exchange halts at the boundary of the gap and does not extend into the region of duplex-duplex (four-strand) exchange (84, 191). Some early proposals suggested that RecA might promote the alignment of two homologous duplex DNAs, and a quadruplex recombination intermediate was entertained as a hypothesis (58, 60, 77, 92, 129, 228, 231). However, many data now indicate that four DNA strands (two duplexes) cannot be accommodated in the filament interior (29, 84, 95, 100, 101, 112, 145, 188, 191, 211, 212). Inherent ambiguities in the DNA pairing results that led to the original duplex-duplex pairing proposals have been pointed out (29, 112, 188, 233).

Reactions That Require ATP Hydrolysis

When ATP is hydrolyzed, the course of a RecA-mediated DNA strand exchange reaction with long DNA substrates follows an established pattern. The reaction begins by binding RecA protein to ssDNA, forming the extended helical filament already described. The nucleoprotein filament hydrolyzes ATP with the monomer k_{cat} of up to 30 min^{-1}. Filament assembly is cooperative, but individual monomers hydrolyze ATP independently (7). When a homologous duplex DNA is added to initiate strand exchange, a rapid decrease in ATP hydrolysis (by 30%) is observed, to a rate characteristic of filaments on

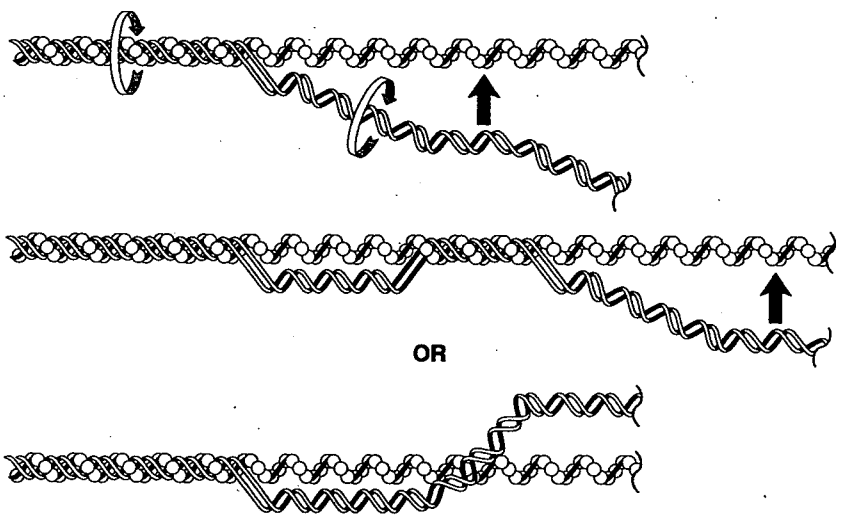


Figure 6. Unproductive complexes that can stall DNA strand exchange reactions. The formation of a joint molecule involves the uptake of a duplex DNA into the RecA filament and its alignment with the previously bound single-stranded DNA. Extension of the region of paired DNA requires a continued spooling of the duplex into the filament, as shown in the top panel. This extension can be blocked by a secondary DNA pairing involving another part of the duplex (leaving an external loop of DNA [middle panel]) or any unproductive interaction of the duplex and the filament (bottom panel) that halts the needed spooling process.

dsDNA (182). During DNA strand exchange, the RecA filaments are in a state analogous to that observed when filaments are formed on dsDNA (189). The filaments become more dynamic and monomer exchange is observed between free and bound forms, as is seen with filaments on dsDNA (189). This induced exchange between bound and free RecA monomers occurs only when a complementary strand is already paired with the ssDNA in the filament; i.e., strand exchange must be complete. It is not seen when the duplex DNA is heterologous (189), and thus has no role in the "search for homology" that must occur prior to homologous alignment of the two DNAs.

Once strand exchange is initiated, the joint molecules are extended unidirectionally (37, 81, 229), uniquely 5′ to 3′ relative to the ssDNA to which RecA protein initially binds (Fig. 5). DNA strand exchange is directed at a measured rate (380 ± 20 bp min^{-1} at 37°C) through the available homologous DNA sequences (13). The four-strand exchange reactions are also unidirectional, proceeding 5′ to 3′ relative to the single strand in the gap where the reaction is initiated (23, 188).

For the *E. coli* RecA protein, there are three properties of the DNA strand exchange reaction that require ATP hydrolysis, and a fourth that is affected by it. The three that require hydrolysis are as follows. (i) The movement of DNA branches during the late stages of strand exchange is rendered unidirectional (78, 191), with the polarity already noted. (ii) ATP hydrolysis allows the bypass of substantial DNA structural barriers (83, 179, 191). These structural barriers can include a heterologous insertion of 100 bp or more in the duplex DNA substrate, which is unwound as it is bypassed by RecA protein-mediated strand exchange. The bypass involves a generation of torsional stress, since a nick in the heterologous region blocks the bypass (80). (iii) ATP hydrolysis is required for any DNA strand exchange involving two duplex DNAs (the four-strand reaction [Fig. 5]) (84, 191). The fourth function that is affected by ATP hydrolysis is the overall efficiency of the reaction. ATP hydrolysis allows the reaction to go to completion, generating hybrid DNAs over many thousands of base pairs in high yield. As expanded upon below, this effect does not apply to the eukaryotic Rad51 proteins, and the requirement for ATP hydrolysis is only partial even in the case of RecA. In addition to these direct roles in DNA strand exchange, ATP hydrolysis is coupled to end-dependent dissociation of RecA protein from a filament on DNA, as already noted.

None of the four roles for ATP hydrolysis in RecA-mediated DNA strand exchange are observed for any of the eukaryotic or archaeal RecA homologues, and the utilization of ATP is one area where the RecA and its homologues differ greatly. The rates of Rad51-mediated ATP hydrolysis are as much as 2 orders of magnitude less than that observed for RecA protein (206), and the ATP that is hydrolyzed appears to have little effect on DNA strand exchange. The eukaryotic Dmc1 protein and the archaeal RadA protein also hydrolyze ATP more slowly than RecA by an order of magnitude or more (108, 186). The Rad51 protein does not require ATP hydrolysis to promote a robust DNA strand exchange with long DNA substrates (208). In addition, the Rad51 protein cannot promote DNA strand exchange through significant heterologous insertions (149, 207) or promote four-strand exchange reactions (P. Sung, personal communication), whether or not ATP is hydrolyzed. Like RecA, some initial reports provided evidence that Rad51-mediated DNA strand exchange was unidirectional (10, 73, 207, 208). However, some of these reports conflicted as to the direction of strand exchange, and additional reports indicated that no unique polarity to the reactions existed (147–149). The issue appears to have been a function of the structure of the DNA ends of the linear duplex DNA substrate. A single-strand overhang at the end is necessary for an efficient initiation of strand exchange by Rad51, and an overhang at either end can lead to initiation. Initiation at either end can lead experimentally to either polarity of the ensuing strand exchange as it propagates from the site of initiation (147–149). In general, there is no evidence that ATP hydrolysis plays a significant role in DNA strand exchange for any proteins in this class, other than the bacterial RecA proteins.

ATP hydrolysis is not always required for extensive strand exchange reactions to generate long hybrid DNA products. In the case of RecA protein, complete products from the reaction diagrammed in Fig. 5A are generated if the concentration of Mg ion is maintained at levels similar to the ATP concentration (191). The products are generated much more slowly (on a time scale measured in hours) and to lower extents than when ATP is hydrolyzed. The lowered Mg ion also slows the basic DNA pairing processes of the RecA filament (191). Excess Mg ion prevents the generation of complete nicked circular products. These results suggest that secondary DNA pairing events limit the extent of DNA strand exchange without ATP hydrolysis at high Mg ion concentrations, and that full product formation requires conditions that minimize these unproductive interactions between the duplex DNA substrate and the RecA-ssDNA complex. Although the Rad51 protein

does not require ATP hydrolysis to promote a strong and extensive DNA strand exchange reaction (208), it does require solution additives that weaken the basic DNA pairing process and/or eliminate other types of unproductive duplex-filament interactions (Fig. 6) (174, 197).

The capacity to promote uniquely unidirectional DNA strand exchange reactions, to bypass significant structural barriers, and to promote four-strand exchange reactions is so far unique to the bacterial RecA proteins, and all of these processes require ATP hydrolysis. These functions may also be associated with the elevated (relative to RecA homologues) levels of ATP hydrolysis seen with RecA. For Rad51, Dmc1, and RadA proteins, the slow ATP hydrolysis observed may play a role in the assembly and disassembly of functional complexes with DNA, but this has not yet been explored. These unique functions of RecA indicate that this protein, unlike the Rad51, Dmc1, or RadA proteins, clearly couples ATP hydrolysis directly to DNA strand exchange. Rates of DNA strand exchange are linked to the rates of ATP hydrolysis (13, 150), and potential mechanisms for this coupling can now be described.

Models for Coupling ATP Hydrolysis to RecA Protein-Mediated DNA Strand Exchange

Certain early models for RecA-mediated DNA strand exchange proposed that RecA filament disassembly and/or reassembly on the displaced single strand was coupled directly to the movement of the DNA branch in the late stages of DNA strand exchange (77, 88, 143). However, under optimal conditions, there is no net dissociation of RecA protein during DNA strand exchange, and the filament is found on the hybrid DNA product rather than on the displaced single strand (218). Rates of end-dependent filament assembly and/or disassembly are affected greatly by changes in reaction conditions (pH, dilution, addition of very small amounts of ATPγS) that have little or no effect on the rates of DNA strand exchange (110). No attempt has been made to explain how the proposed assembly and disassembly mechanisms would permit the bypass of DNA lesions and heterologous insertions during DNA strand exchange. Finally, most of these models envision that two duplex DNAs are both inside the filament during a four-strand exchange reaction, conferring on the RecA filament interior a binding capacity it does not appear to have. For these and other reasons, models that employ filament assembly or disassembly as the enabling process in ATP-dependent DNA strand exchange have been largely discarded. Two models remain under active investigation.

The RecA redistribution model

In the RecA redistribution model, it is proposed that RecA filaments are discontinuous, that DNA strand exchange halts at the discontinuities when ATP is not hydrolyzed, and that ATP hydrolysis serves to recycle RecA protein so as to fill in the discontinuities (93, 132, 169). This idea is subtly different from the ideas considered above, since the filament is seen to stay largely intact and bound to the hybrid DNA duplex at the end of a reaction, as consistent with observation. Also, the recycling of RecA protein need not occur at the migrating branch point of a DNA strand exchange reaction. The model can explain how strand exchange might bypass a heterologous insertion in the duplex DNA substrate (15). In brief, the RecA protein underwinds bound DNA. Also, when filaments form on circular ssDNA substrates, there are no free filament ends with the potential for free rotation. If the dsDNA substrate is bound within the filament on both sides of the insertion, then a modest dissociation of RecA protein from the filament might release underwound DNA. In the absence of free ends to dissipate the torsional stress, the released underwinding could be translated into unwinding of the DNA in the heterologous insertion to allow bypass. The exchange of RecA between free and bound forms during strand exchange (189) is generally consistent with this idea. However, two predictions of this model, that heterology bypass should be blocked in exchanges where both DNA substrates are linear, and that excess RecA should fill in the discontinuities and allow more extensive strand exchange, have not been borne out by experiment (119, 191). In addition, conditions exist in which ATP is hydrolyzed and an exchange of RecA between free and bound forms is observed, but where the presence of small amounts of a mutant RecA protein in a mixed filament completely blocks DNA strand exchange (189). Thus, RecA protein redistribution is not sufficient in itself to explain the role of ATP hydrolysis in strand exchange reactions. There has been no attempt to explain how four-strand exchange reactions might proceed with the RecA redistribution model, or why ATP hydrolysis might be required for them.

The facilitated DNA rotation model

The facilitated DNA rotation model assigns a motor function to the RecA protein (34, 35, 40, 178, 191). The filament disassembly role of ATP hydrolysis then becomes a separate function. The model proposes that without ATP hydrolysis, DNA strand exchange is halted prematurely because a discontinuous DNA



Figure 7. Model for RecA protein-mediated rotation of DNA to effect DNA strand exchange. Any duplex DNA external to the filament, perhaps as a result of the formation of external DNA loops as shown in Fig. 6, would be rotated around the outside of the filament in a reaction coupled to ATP hydrolysis. Rotation in the direction of the curved arrows will result in branch movement in the direction of the black arrows.

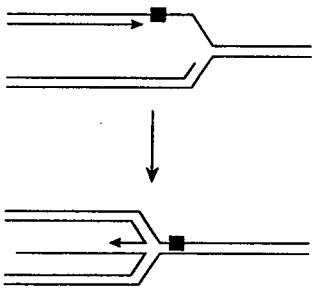


Figure 8. Fork regression as might occur at a stalled replication fork. The product of this reaction is sometimes called a chicken foot.

pairing intermediate is created by secondary DNA pairing events (Fig. 6). The discontinuities take the form of DNA loops external to the filament. The contiguous region of strand exchange that occurs in the absence of ATP hydrolysis is limited to the region between the end of the duplex DNA and the first such external loop. When ATP is hydrolyzed, the loops are resolved by rotating this external DNA around the outside of the filament, keeping the DNA itself more or less parallel to the filament axis (Fig. 7). Unidirectional rotation will bring about a unidirectional migration of the loop, with DNA spooling into the filament on one end and out on the other. The rotation is driven by an ATPase motor.

Quantitative and qualitative predictions of the facilitated DNA rotation model in three-strand exchanges have been tested, and the results conform to expectations based on the model (7, 13, 119). The model provides a basis for the requirement for ATP hydrolysis in four-strand exchanges. If four DNA strands cannot be bound within the RecA filament, then an ATP-facilitated rotation of one duplex around another (with only one bound within the filament) would allow a four-strand exchange to proceed. The four-strand exchanges also exhibit properties that conform to model predictions (188). A rotational motor working as shown in Fig. 7 would provide the energy for the bypass (and unwinding) of heterologous inserts in the duplex DNA substrate, and would render the strand exchange unidirectional. The torsional stress used to unwind the heterologous DNA would be generated by the ATP-driven rotation.

A motor function is also consistent with the structure of the core domain of RecA protein. This domain is a close structural homologue of the F1-ATPase, a family of hexameric helicases, and several other proteins that may act as motors or undergo large conformation changes in the course of their catalytic activity (1, 51, 52, 66, 215, 239).

A motor function could play a role in the recombinational DNA repair of stalled replication forks. Some of the most prominent models for the repair of stalled forks begin with a reaction called fork regression (Fig. 8) (31, 33, 36, 76, 130, 139). The replication fork is simply forced backwards, with the original template strands being re-paired and the newly synthesized strands extruded to form a "chicken foot" structure (162). There are several pathways for fork regression (33), one of which involves catalysis by the RecA protein (185). RecA protein promotes an efficient fork regression in vitro, using model DNA molecules designed to mimic the structure of the stalled fork shown in Fig. 1B (176). The reannealing of the template strands at such a fork requires the winding of one about the other to recreate the DNA helix, and such a reaction would be consistent with the proposed motor function of the RecA filament. RecA-mediated fork regression is completely dependent on ATP hydrolysis (176).

REGULATION OF THE SOS RESPONSE

In 1974, a series of earlier observations suggesting the existence of an elaborate pathway for DNA repair and mutagenesis induced by DNA damage (43, 144) were unified under the SOS hypothesis by Radman (167). RecA was implicated in the regulation of SOS, and the first activity with which RecA protein was associated in vitro was the cleavage of the bacteriophage λ repressor as a biochemical step in SOS induction (175). The LexA repressor, responsible for the in vivo repression of the bacterial SOS genes, was also soon found to be cleaved by RecA protein (115). This work led to the first purification of RecA protein (175).

A great deal is now known about the SOS induction pathway and the role of RecA protein in it (44, 63, 115, 221, 222). High levels of DNA damage cause an interruption of replication. The single-stranded

DNA created as one result of the replication halt is the primary signal for SOS induction (75). RecA protein binds to the ssDNA, assuming the extended filament conformation in the presence of ATP. However, the RecA protein is not a protease. Instead, the LexA repressor, the bacteriophage λ repressor, the UmuD protein, and a few other proteins bind to the extended RecA filament. When thus bound, these proteins undergo an autocatalytic cleavage (113, 114, 154, 194). The RecA filament simply facilitates this integrated cleavage function of the other proteins. Thus, this function of RecA protein has been dubbed the "coprotease" activity (113, 114). The cleavage of the LexA repressor results in the induction of over 40 SOS genes, including the RecA protein itself.

Facilitating the autocatalytic cleavage of LexA protein involves the binding of LexA repressor deep within the groove of a RecA filament (238), situated so as to span two adjacent RecA monomers. The RecA species involved in the coprotease activities is almost certainly identical to the extended RecA filament involved in recombinational processes (238). The propensity of RecA to bind ssDNA almost exclusively under physiological conditions serves to target RecA protein to ssDNA gaps created by the halt in DNA replication. Some RecA protein mutants bind more readily to dsDNA, leading to more indiscriminate binding in the cell. These mutants often produce an SOS constitutive phenotype (117, 214).

SOS MUTAGENESIS

Heavy DNA damage leads to a complete cessation of DNA replication. After 30 to 45 min, replication resumes. The resumption is generally referred to as replication restart (49). The SOS system induced by the replication halt is actually a staged accumulation of enzymes involved in DNA repair (42, 103, 193, 199, 200, 224). The stages reflect a measured response to different levels of damage.

There are two general paths to replication restart. Nonmutagenic replication fork repair provides one way for a fork to bypass a lesion, as already discussed. The enzymes needed for nonmutagenic fork repair are expressed under normal growth conditions, but many (including RecA protein) are also induced to higher levels in the early stages of the SOS response. The second path to restart involves a specialized system for mutagenic DNA lesion bypass that is induced in the late stages of the SOS response (44, 116, 146, 223). Induction of the enzymes needed for each of these is thus organized temporally during SOS so that nonmutagenic repair processes are induced early, followed by mutagenic processes (42, 103).

The mutagenic pathway inevitably produces some lethal mutations, and a rationale is needed for the evolution of such a system. DNA damage may simply reach levels that are beyond the capacity of the nonmutagenic systems, including recombinational replication fork repair, to handle. Thus, there may be an advantage at some point to accepting the lethality associated with mutagenic replicational bypass in order to get replication going again and rescue at least some cells in the population. Another possibility has been described by Sedgwick (184, 232): a high level of damage produces DNA lesions closely placed on opposite template strands, leading to the generation of overlapping daughter-strand gaps. With such a scenario, it may be impossible for bypass to take place via the nonmutagenic recombinational DNA repair paths. The mutagenic replicational bypass would then represent a last-ditch effort by the "stuck" cell to survive.

Mutagenic replicational bypass of DNA lesions is mediated by a special class of error-prone DNA polymerases (68, 109). In *E. coli*, this class is represented by DNA polymerases IV and V (131, 213, 220). DNA polymerase V is the enzyme primarily responsible for SOS mutagenesis. It consists of the products of the *umuC* and *umuD* genes, with the UmuD protein processed by a RecA-dependent autocatalytic cleavage to generate the active UmuD′ (154, 194). Both genes are under SOS control and expressed late in the SOS process. The DNA polymerase V is a heterotrimeric UmuD′$_2$C complex. Also required for optimal activity is the βγ complex from DNA polymerase III, the SSB protein, and the RecA protein (68, 159, 171, 172, 213). The role of RecA in this reaction may be the least-understood aspect of RecA function, although it is clear that RecA greatly activates the bypass process. The lesion bypass activity of DNA polymerase V appears to require the establishment of a RecA filament in the gap downstream from the primer that DNA polymerase V will extend in the lesion bypass process (159, 172). Such a filament would have to be displaced by the polymerase as it moves while at the same time maintaining contact with it. This displacement would take place at the 3′-proximal end of the filament, where filament dissociation generally does not occur. In addition, a filament forming in a DNA gap would extend into the adjacent duplex DNA, and thus block access to the free 3′ end that the polymerase would require for use as a primer. It has not been determined how DNA polymerase V is directed to the sites where it must act in this environment.

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