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The bacterial RecA protein: structure, function, and regulation

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Abstract

The bacterial RecA protein is the prototypical recombinase, promoting the central steps of DNA pairing and strand exchange in genetic recombination and recombinational DNA repair. RecA homologs are present in virtually all organisms from bacteria to humans. RecA is a multifunctional protein. As a recombinase, the protein binds to DNA in the form of a helical filament, and exhibits a DNA-dependent ATPase activity. As a nucleoprotein filament, RecA promotes a series of easily monitored DNA strand exchange reactions *in vitro*. In addition to its role as a recombinase, the *E. coli* RecA protein is also a key component of the regulatory system that controls the induction of the SOS response, and it plays a direct role in the UV mutagenesis promoted by DNA polymerase V. RecA protein is subject to multiple layers of regulation. RecA is autoregulated by its own C-terminus. Many other proteins, including the RecF, RecO, RecR, DinI, RecX, RdgC, PsiB, and SSB proteins, have either a demonstrated or probable role in modulating where and when RecA-mediated recombination events occur.

1 The role of recombination in DNA metabolism

In bacteria, the major function of homologous genetic recombination is the recombinational DNA repair of replication forks that have stalled or collapsed at the site of an encounter with DNA damage (Kuzminov 1999, Cox et al. 2000, Kowalczykowski 2000, Cox 2001b, Cox 2002). Replication fork demise occurs often even under normal growth conditions in bacteria (Cox et al. 2000, Cox 2001b, Cox 2002). Estimates of the frequency of recombinational DNA repair under normal growth conditions vary. Studies with a variety of *rec* mutants suggest that at least 10-20% of all replication forks originating at the bacterial origin of replication are halted by DNA damage and must undergo recombinational DNA repair (Zavitz and Marians 1992, Kuzminov 1996, Cox 1998, Kuzminov 1999, Cox et al. 2000, Cox 2001a, Cox 2001b, Cox 2002, Michel et al. 2004, Friedberg 2005, Heller and Marians 2005, Kreuzer 2005). Following repair, additional systems act to restart replication (Marians 2000b, Marians 2000a) and deal with the dimeric chromosomes sometimes produced by recombination (Barre et al. 2001).

There are at least two major pathways for recombinational DNA repair of stalled replication forks. If the replication fork encounters an unrepaired DNA le-

sion, a gap in the DNA is generated. Repair can occur via regression (backward movement) of the stalled fork to create a distinctive Holliday junction sometimes dubbed a "chicken foot" (Postow et al. 2001). The chicken foot can be processed in several different ways (Dillingham and Kowalczykowski 2001, Michel et al. 2001, Cox 2002, McGlynn and Lloyd 2002, McGlynn 2004, Michel et al. 2004, Friedberg 2005, Heller and Marians 2005, Kreuzer 2005). If the replication fork encounters a break in one strand (as might be the case where a lesion was undergoing repair), a double strand break is generated. In this situation, the classic RecBCD pathway predominates, processing the broken end and promoting strand invasion to reconstitute a fork structure (Dillingham and Kowalczykowski 2001, Michel et al. 2001, Cox 2002, McGlynn and Lloyd 2002, McGlynn 2004, Michel et al. 2004, Friedberg 2005, Heller and Marians 2005, Kreuzer 2005). There are multiple variants of these repair pathways and recombination enzymes can be considered an assemblage of activities that can be adapted to the damage situation.

DNA damage may also be bypassed by a replication fork, leaving the lesion behind in a DNA gap. This would bring into play a form of postreplication DNA gap repair (Rupp and Howard-Flanders 1968, Smith 2004). Recent *in vitro* work demonstrated that de novo priming of both leading and lagging strand synthesis downstream of non-coding lesions in the template DNA enables replication forks to re-initiate and continue replication with limited hindrance, leaving gaps in the nascent strands to be filled in by recombination (Heller and Marians 2006). This suggests that postreplication gap repair might comprise a substantial fraction of the fork-related recombinational repair in bacterial cells. However, the *in vitro* model system employed may not adequately mimic the sensitivity of forks *in vivo* to DNA damage. Heavy DNA damage, from UV or other sources, halts DNA replication (when the experiment is controlled to prevent DnaA-dependent replication initiation from *oriC*) and induces the SOS response (Setlow et al. 1963, Courcelle and Hanawalt 2003, Courcelle et al. 2004). Cellular replication forks can be halted by at least some types of damage, and a complete picture of the situation *in vivo* is not yet available.

2 The RecA protein of *Escherichia coli*

2.1 Overview

The RecA protein of *E. coli* (M_r 37,842; 352 amino acids) is a multifunctional protein, with roles in the induction of the SOS response to DNA damage, SOS mutagenesis, and general recombination processes such as recombinational DNA repair (Brendel et al. 1997, Roca and Cox 1997, Cox 1998, Cox 2001a, Cox 2001b, Lusetti and Cox 2002). In the context of SOS induction, filaments of RecA protein formed on DNA facililtate an autocatalytic cleavage of the LexA repressor (Little 1991). In SOS mutagenesis, RecA is required to stimulate DNA polymerase V in its lesion bypass function (Pham et al. 2001, Pham et al. 2002, Schlacher et al. 2005, Schlacher et al. 2006).

This chapter focuses only on the role of RecA protein in recombination and recombinational DNA repair. RecA protein promotes a DNA strand exchange reaction *in vitro* that mimics the postulated central steps in homologous genetic recombination *in vivo*. The reaction is stimulated by the single-stranded DNA binding protein of *E. coli* (SSB). RecA is also a DNA-dependent ATPase, and some aspects of the DNA strand exchange reaction require ATP hydrolysis. The RecA protein is found in virtually all bacteria, with certain endosymbionts being the only apparent exceptions (Moran and Baumann 2000, Tamas et al. 2002). An activity of this type has been a part of bacterial physiology for over 1.5 billion years (Roca and Cox 1990, Brendel et al. 1997, Roca and Cox 1997). Structural and functional homologs of RecA have been found in bacteriophage (the T4 UvsX protein; Jiang et al. 1993), in archaeae (RadA; Sandler et al. 1996b, Seitz et al. 1998, Seitz et al. 2001), and in eukaryotic cells (Rad51 and Dmc1; Shinohara et al. 1992, Ogawa et al. 1993, Bishop 1994, Sung 1994, Gupta et al. 1997, Baumann and West 1998, New et al. 1998, Passy et al. 1999, Gupta et al. 2001, Sehorn et al. 2004) For a description of the important eukaryotic homolog Rad51, see the chapter by Heyer in this volume.

2.2 Structure

The bacterial RecA protein is a highly conserved polypeptide chain. Primary sequence alignments of the RecA proteins from many scores of bacterial species have been published (Karlin and Brocchieri 1996, Brendel et al. 1997, Roca and Cox 1997). The EcRecA protein consists of 352 amino acid residues (Mr 37,842). With the EcRecA as a reference, the percent of identical amino acid residues in bacterial homologs range from 49% for *Mycoplasma pulmonis* to 100% for *Shigella flexneri*.

The number of reported x-ray crystal structures of bacterial RecA proteins has been increasing, including four from *E. coli* (Story and Steitz 1992, Story et al. 1992, Xing and Bell 2004b, Xing and Bell 2004a), two from *M. tuberculosis* (Datta et al. 2000, Datta et al. 2003a), one from *Deinococcus radiodurans* (Rajan and Bell 2004), and two from *Mycobacterium smegmatis* (Datta et al. 2003b, Krishna et al. 2006). These include several complexes with nucleotide cofactors, and a range of collapsed and extended filament forms. Structural information has been enriched by the solution of the structures of RecA homologs from archaeans and eukaryotes (Conway et al. 2004, Wu et al. 2004, Qian et al. 2005, Wu et al. 2005). Notably, none of the structures includes bound DNA, leaving open many critical questions about how RecA and its homologs interact with DNA. A 24 monomer filament based on the EcRecA structure of Story and Steitz (Story et al. 1992), along with a ribbon representation of a RecA monomer, are presented in Fig. 1. In the crystals, monomers tend to pack so as to form a right-handed helical filament with six monomers/turn (Fig. 1). The filament revealed in the earliest

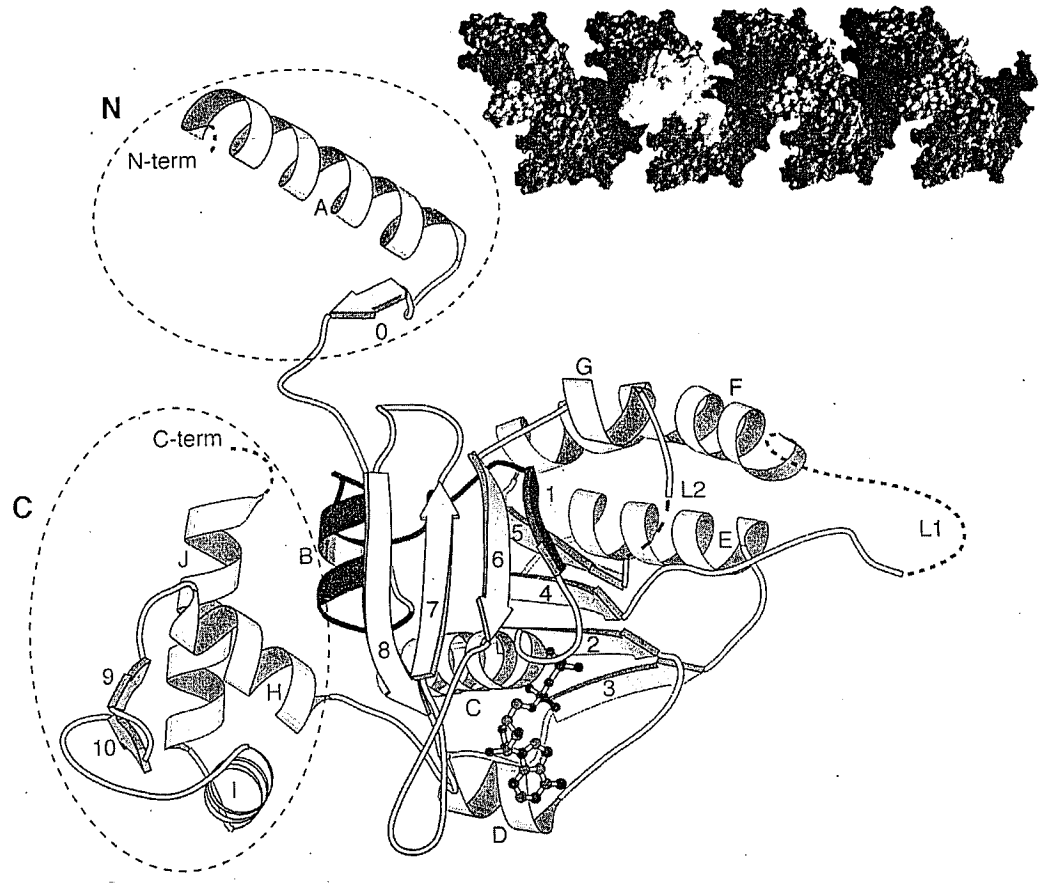


Fig. 1. Structure of RecA protein. A monomer is shown in this ribbon diagram. The domain labeled N and denoted by a dashed line circle is the N-terminal domain. The C-terminal domain is similarly outlined and denoted with a C. The remainder of the protein is the core domain, and a bound ADP molecule (in ball and stick representation) is also evident. The structure is based on that reported by Story and Steitz, 1992. A 24 monomer segment of a RecA filament based on the same structure is shown in the inset at upper right, with one of the subunits colored white.

crystal structures were not as extended as the active filaments visualized by electron microscopy, and likely represented an inactive conformation. EM image reconstructions have provided a glimpse of the active filament (Egelman 1993, Egelman and Stasiak 1993, Yu et al. 2001). The structural information garnered from electron microscopy has suggested a revised monomer-monomer interface in the active filament (Egelman 1993, Egelman and Stasiak 1993, Yu et al. 2001), one that is consistent with recent published structures of RecA homologs (Conway et al. 2004, Wu et al. 2004).

The RecA structures have revealed a central core domain and two smaller domains at the amino (N) and carboxyl (C) termini (Fig. 1). The core domain of the RecA protein (residues 34-269) is the part most highly conserved among bacterial species, and is also structurally homologous to several proteins to which it bears very little to no sequence similarity. The structural units of hexameric helicases

are RecA-like domains (Bird et al. 1998, Egelman 2000). Furthermore, 120 α-carbon atoms of the core domain of RecA can be spatially aligned with the mitochondrial F_1-ATPase and the cobalamin nucleotide loop assembly protein CobU, with an RMSD of less than 2 Å (Story et al. 1993, Thompson et al. 1998). The core domain region of residues 47-74 is especially well conserved with 14 invariant residues. The *E. coli* sequence GPESSGKT matches the consensus Walker A box (Walker et al. 1982)(also referred to as the P-loop) amino acid consensus sequence (G/A)XXXXGK(T/S) found in a number of NTP-binding proteins. The RecA K72R mutant protein is ATPase deficient while retaining nucleotide binding and DNA pairing function (Rehrauer and Kowalczykowski 1993, Shan et al. 1996).

Within the RecA structure, there are two regions implicated in DNA binding, consisting of residues 151-176 and 190-227. These loops, disordered in most of the available structures, are commonly referred to as L1 (residues 157-164) and L2 (residues 195-209). Both of these regions are well-conserved among bacterial RecA proteins, although the conservation does not extend to the archaeal and eukaryotic homologues. The loop L1 residues are ordered in one MtRecA structure and, are oriented into the groove (Datta et al. 2000). Detailed mutagenesis of loops L1 and L2 have been carried out by the Knight (Nastri and Knight 1994) and Camerini-Otero (Hortnagel et al. 1999) groups, respectively. DNA cross-linking studies support a role for these loops in DNA binding (Malkov and Camerini-Otero 1995, Wang and Adzuma 1996). Residues outside of these regions, such as Tyr103 (Morimatsu and Horii 1995), Lys183 (Morimatsu and Horii 1995, Rehrauer and Kowalczykowski 1996), and in the region of residues 233-243 (Rehrauer and Kowalczykowski 1996) have also been shown to cross-link to DNA. Many details of the RecA-DNA interaction remain to be elucidated.

The C-terminal domain (residues 270-352) exhibits the least amount of sequence conservation. This domain is positioned distal to the filament axis in the polymer structure (the dark lobes in Fig. 1). Egelman and co-workers have observed C-terminal domain movement relative to the core domain that may be responsible for (or diagnostic of) the "active" or "inactive" state of the RecA filament (Yu et al. 2001). The last 25 residues of the RecA protein are disordered in most of the crystal structures, with one of the likely numerous conformations being visualized only in a recent structure of *M. smegmatis* RecA protein (Krishna et al. 2006). This region includes a high concentration of negatively charged residues, a characteristic shared by many but not all bacterial RecA sequences (Roca and Cox 1997). Other ssDNA binding proteins such as SSB of *E. coli* (Williams et al. 1983) and the gene 32 protein of phage T4 (Lonberg et al. 1981) also have highly negatively charged C-terminal regions that modulate DNA affinity and protein-protein interactions (Lonberg et al. 1981, Williams et al. 1983, Benedict and Kowalczykowski 1988, Tateishi et al. 1992, Genschel et al. 2000, Lusetti et al. 2001, Witte et al. 2003, Cadman and McGlynn 2004). The negatively charged C-terminus of RecA autoregulates all aspects of RecA function, as detailed in section 3.

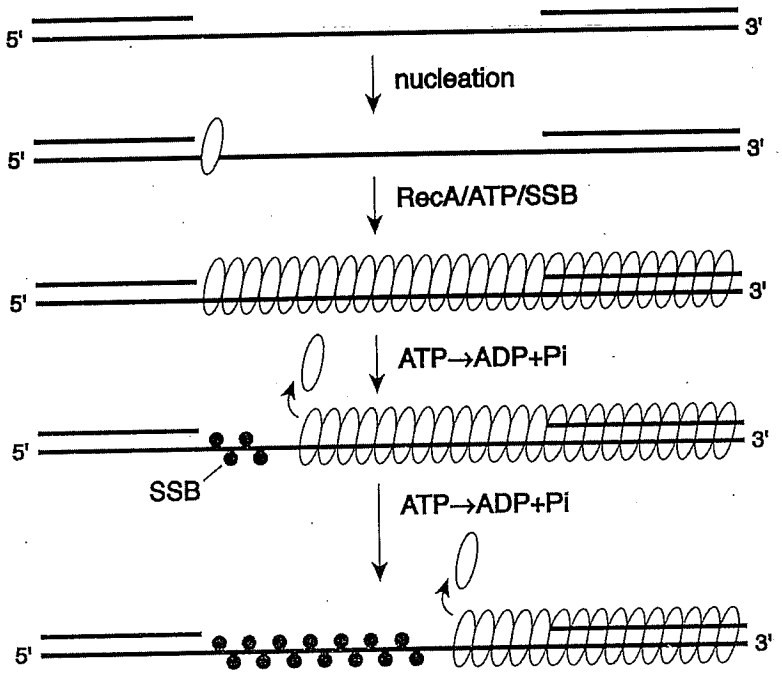


Fig. 2. A multistep pathway for the binding of ssDNA is shown. RecA protein first nucleates on the DNA, a step that may involve more than the one subunit depicted. The filament is then extended 5' to 3' when ATP is present, and the extension can continue into any contiguous duplex DNA. ATP hydrolysis leads to disassembly at the opposite end. Vacated ssDNA is bound by SSB.

2.3 Binding to DNA

RecA protein filaments both assemble and disassemble in a largely unidirectional (5' to 3') and end-dependent manner, with monomers added at one end and subtracted from the other (Fig. 2) (Register and Griffith 1985, Lindsley and Cox 1990b, Shan et al. 1997, Arenson et al. 1999, Bork et al. 2001b). This is true on both ssDNA and dsDNA. The unidirectionality has been inferred in experiments in which ATP has been actively hydrolyzed at some point in the protocol. Filaments formed in the presence of ATPγS are very stable, and the polarity of assembly with this non-hydrolyzed (or very weakly hydrolyzed) analogue is now being examined in several laboratories using single-molecule protocols. Without ATP hydrolysis, there is no reason, in principle, for the assembly process to favor one or the other end of a RecA filament. The monomer-monomer interfaces should be identical at both ends.

The DNA within a RecA filament is extended about 1.5-1.6X and underwound by about 40% (Stasiak and Di Capua 1982, Pugh et al. 1989). One RecA monomer binds to 3 nucleotides or base pairs of DNA. The helical filament thus has 18 bp and 6 monomers per right-handed turn (6.2 monomers per turn as seen in the electron microscope (Yu et al. 2001)). NMR studies have revealed a new conformation of DNA within the extended RecA filament, one in which the 2' methylene

group of each nucleotide stacks on the adjacent base (Shibata et al. 2001). The assembly of a RecA filament is limited by a slow nucleation step (Kowalczykowski et al. 1987, Pugh and Cox 1987, Pugh and Cox 1988, Lavery and Kowalczykowski 1990). The subsequent extension of the filament is relatively rapid, although good rate constants are not yet available.

RecA filament disassembly can occur in two ways. First, if ATP is not regenerated and ADP levels are allowed to build up, there is a rapid dissociation of the RecA filament from DNA when the ADP/ATP ratio nears 1.0 (Cox et al. 1983, Lee and Cox 1990, Ellouze et al. 1999). A more ordered, demonstrably end-dependent, and largely unidirectional disassembly of filaments is seen when ATP hydrolysis occurs in the presence of a regeneration system and with ATP concentrations sufficient to operate at V_{max} (Lindsley and Cox 1990b, Shan et al. 1997, Arenson et al. 1999, Cox et al. 2005). For RecA filaments bound to ssDNA, the rate of end-dependent (5' to 3') filament disassembly is 60 – 70 monomers min^{-1} (Arenson et al. 1999) On dsDNA, the rate of disassembly increases to approximately 120 monomers min^{-1} at neutral pH (Cox et al. 2005). The different rates reflect different filament states operative on ssDNA vs dsDNA, as described in the next section.

2.4 ATP hydrolysis and RecA filament states

RecA protein is a DNA-dependent ATPase, with a K_m for ATP that varies with conditions and cofactors but is often on the order of 50-100 μM. At ATP saturation, the k_{cat} is about 30 min^{-1} on ssDNA, and 20 min^{-1} on dsDNA (Lusetti and Cox 2002, Cox 2003, Cox et al. 2005). Also hydrolyzed efficiently is dATP, with measured k_{cat} values slightly higher than ATP (Menetski and Kowalczykowski 1989). Whereas the rates of ATP/dATP hydrolysis observed with RecA protein are not particularly robust, they are up to two orders of magnitude higher than the rates observed for the archaeal and eukaryotic homologues of RecA.

ATP is hydrolyzed throughout a RecA filament, with all filament subunits participating. There is no increase in ATP hydrolytic rates for RecA monomers near a filament end (Brenner et al. 1987). In general, this means that only a very small fraction of the ATP hydrolytic events that occur in a contiguous RecA filament – those that occur on the disassembly end – are coupled to RecA dissociation from the DNA. In RecA filaments that are bound to circular single-stranded DNAs, such as ϕX174 viral DNA, there are typically 2-3 breaks where RecA dissociation and replacement are occurring, based on challenge experiments where the RecAK72 R is available in excess to replace any dissociated monomers (Shan and Cox 1996, Lusetti et al. 2004b). The RecA protein monomers at all other locations in these filaments are hydrolyzing ATP at 2-3 per second without dissociating.

It is clear that ATP hydrolysis is important for RecA protein function *in vivo*. Two mutant RecA proteins that bind but do not hydrolyze ATP have been described, K72R (Rehrauer and Kowalczykowski 1993, Shan et al. 1996) and E96D (Campbell and Davis 1999). In both cases, the altered RecA protein is functional

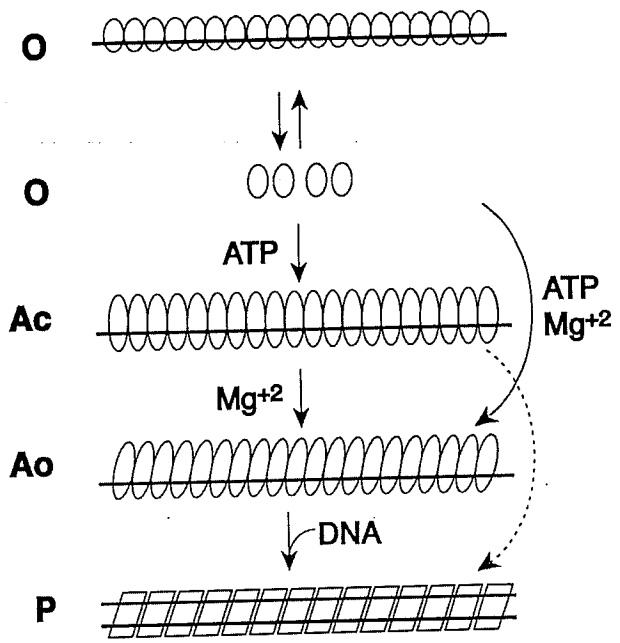


Fig. 3. RecA has at least four different filament states. In the absence of DNA or nucleotide cofactor, or in the presence of ADP, the RecA forms collapsed filaments designated O. When bound to ssDNA, in the presence of ATP or its weakly hydrolyzed analog ATPγS, RecA forms an extended filament in a state designated A. With minimal Mg ion present, the Ac form is present, with a limited capacity to promote DNA strand exchange. Addition of free Mg ion converts this into the Ao state, with an enhanced capacity to promote DNA strand exchange. Addition of a second DNA strand converts the filament to the P state, a filament state characterized by higher levels of cooperativity, lower levels of ATP hydrolysis, and more rapid rates of filament disassembly.

for many key activities, forming nucleoprotein filaments and promoting DNA pairing and facilitating the autocatalytic cleavage of LexA protein. In both cases, some aspects of DNA strand exchange function are compromised by the mutation, as described in detail later. In both cases, the mutant gene delivers a phenotype equivalent to a complete *recA* deletion or null mutation (Konola et al. 1994). The situation is quite different for the eukaryotic homolog Rad51. The K191R mutation in the yeast Rad51 protein, which corresponds to the K72R mutation of *E. coli* RecA, yields an altered Rad51 that is functional for recombinase functions both *in vitro* or *in vivo* (Sung and Stratton 1996), although overexpression of the altered protein is needed for full biological function (Shinohara et al. 1992, Sung and Stratton 1996). The situation is similar for the human Rad51 protein (Morrison et al. 1999).

The different rates of ATP hydrolysis observed when the *E. coli* RecA protein is bound to ssDNA and dsDNA again reflect different filament states. Evidence has accumulated for at least four distinct filament states (Fig 3) (Shan et al. 1996, Cox 2003, Haruta et al. 2003). In the absence of DNA, or when ADP levels are high, a state designated O is observed. This is a collapsed and inactive filament

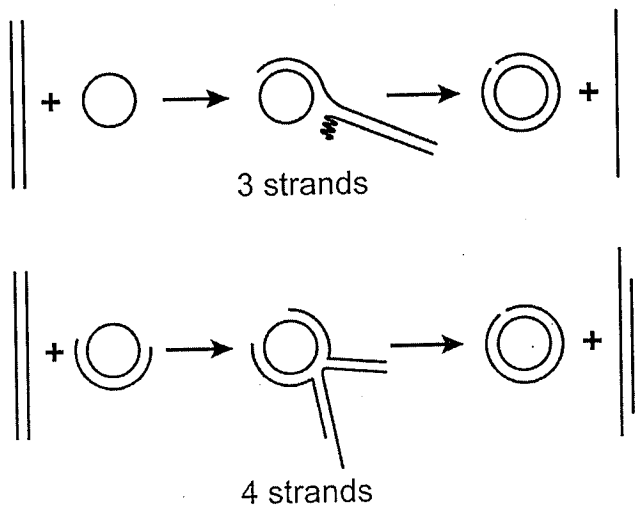


Fig. 4. Model DNA strand exchange reactions promoted by the RecA protein. The form of the DNA substrates is chosen for convenience in these widely-used reactions. RecA protein forms a filament on the ssDNA, or the duplex DNA with a gap. DNA strand exchange begins when the second DNA molecule (the linear duplex) is aligned with homologous sequences in the first, and initiates a strand exchange. The strand exchange proceeds unidirectionally around the DNA circle until it is completed.

state. When ssDNA and ATP is added, the O state must disassemble (Lee and Cox 1990, Yu and Egelman 1992) and RecA then re-assembles a filament on the ssDNA in a state designated A. There are two forms of state A that depend on the level of Mg ion present (Shan et al. 1996, Lusetti et al. 2003a). At low Mg ion (little or none in excess relative to the ATP present), the Ac state is observed, characterized by a limited capacity to promote DNA strand exchange. When 6-8 mM Mg ion is added in excess to the ATP present, the Ao state is observed, characterized by a more robust capacity to promote DNA strand exchange with a wide array of DNA substrates. When a second DNA strand is added, as when RecA is bound to dsDNA or is promoting DNA strand exchange, the RecA protein converts to a state designated P (Haruta et al. 2003). The P state has the highest capacity for the initiation of DNA strand exchange. The different forms of the RecA filament are here described as states rather than conformations, since it is assumed that there are multiple conformations of RecA accessed during the ATP hydrolytic cycles taking place within each of the defined A and P states.

2.5 DNA strand exchange is a multi-step process

The most common model reactions used for in vitro studies of RecA protein-mediated DNA strand exchange are outlined in Fig. 4. DNA substrates are generally derived from bacteriophage DNA and the reaction can involve either 3 or 4 strands. This reaction has been well-studied (Kowalczykowski et al. 1994, Kowalczykowski and Eggleston 1994, Roca and Cox 1997, Cox 1999, Lusetti and Cox 2002, Cox 2003). A RecA helical filament first forms on the ssDNA (or the

gapped duplex DNA in B). The nucleoprotein filament then binds to a second homologous duplex DNA and aligns it with the bound ssDNA. A strand switch occurs to form a region of hybrid duplex. This process is propagated unidirectionally, 5' to 3' relative to the ssDNA within the original nucleoprotein filament, until strand exchange is completed (Cox and Lehman 1981, Kahn et al. 1981, West et al. 1981). RecA protein hydrolyzes ATP during this reaction with a monomer k_{cat} of about 20 min^{-1}, characteristic of the P state.

DNA pairing occurs within the filament, as originally proposed by Paul Howard-Flanders (Howard-Flanders et al. 1984) and confirmed many times. However, the 4-stranded DNA pairing intermediate suggested by Howard-Flanders has never been observed. Physical studies have generally demonstrated that no more than three DNA strands can be readily accommodated within the interior helical groove of a RecA filament (Müller et al. 1990, Takahashi et al. 1991, Wittung et al. 1994, Cox 1995, Kubista et al. 1996, Roca and Cox 1997). DNA pairing in an efficient 4-strand exchange reaction is always initiated within the single-strand gap; i.e. productive 4-strand exchanges must be initiated as 3-strand reactions (Conley and West 1990, Lindsley and Cox 1990a, Chow et al. 1992, Shan and Cox 1998).

The problem of DNA pairing inside a RecA filament is thus reduced to an interaction between a RecA-bound ssDNA and a homologous duplex. In principle, the duplex could approach the ssDNA via either its major or minor grooves. A minor groove-first pathway for DNA pairing is currently favored by the evidence (Kumar and Muniyappa 1992, Baliga et al. 1995, Frank-Kamenetskii and Mirkin 1995, Podyminogin et al. 1995, Podyminogin et al. 1996, Zhou and Adzuma 1997, Gupta et al. 1999, Rice et al. 2000, Xiao and Singleton 2002). In this scheme, homologous alignment involves standard Watson-Crick base pairing. As the duplex is bound, it becomes extended and underwound such that its bases would be free to flip and "sample" the bound ssDNA for complementarity (Gupta et al. 1999). Studies by Radding and colleagues indicate that the base flipping occurs mainly at A:T base pairs (Gupta et al. 1999). The RecA filament appears to stabilize the products of DNA strand exchange, using binding energy to promote the strand switch (Adzuma 1992). The fundamental DNA pairing reaction has been subjected to kinetic analysis, using simplified systems employing short oligonucleotides for DNA substrates (Yancey-Wrona and Camerini-Otero 1995, Bazemore et al. 1997). These studies have revealed that the reaction proceeds minimally in three to four steps, with a rapid second order DNA alignment followed by several slower first order process that likely involve the completion of strand exchange, perhaps some conformational changes, and removal of the displaced strand (Yancey-Wrona and Camerini-Otero 1995, Bazemore et al. 1997, Gumbs and Shaner 1998, Folta-Stogniew et al. 2004, Xiao et al. 2006).

The 1.5 to 1.6 fold extension of the DNA effected when an active RecA protein filament forms on it may play a direct role in the subsequent homology search leading to DNA pairing, as laid out in a simple but elegant model proposed by Bruinsma and colleagues (Klapstein et al. 2004). If two homologous DNAs have the same rise per base pair, placing them side by side in alignment will mean they will be in alignment at every position. Moving one of the DNAs relative to the

other by one nucleotide or base pair puts every nucleotide or base pair *out* of alignment. If, instead, one DNA is extended and the other is not, only a subset of nucleotides or base pairs in one may be in alignment with the other, but moving one DNA relative to the other now places different nucleotides or base pairs in alignment. In effect, there are many potential productive alignments every time the two DNAs come together, instead of just one (Klapstein et al. 2004). The productive alignment could be the nucleation site for pairing, extending to create a larger aligned region by spooling the second DNA into the RecA nucleoprotein filament.

The single-strand DNA binding protein of *E. coli* (SSB) facilitates DNA strand exchange, binding to the displaced single-strand product and facilitating its release from the filament (Lavery and Kowalczykowski 1992).

2.6 The role of ATP hydrolysis in DNA strand exchange

ATP hydrolysis is not required to promote the fundamental process of DNA strand exchange within the filament. RecA protein can promote limited DNA strand exchange (typically yielding up to1-2 kbp of hybrid DNA) under conditions in which ATP is not hydrolyzed. These conditions include the use of ATP analogues which are bound but not hydrolyzed by wild type RecA protein (ATPγS and an ADP•AlF_4^- complex) (Menetski et al. 1990, Rosselli and Stasiak 1990, Kim et al. 1992a, Kim et al. 1992b, Kowalczykowski and Krupp 1995), as well as the use of the mutant RecA K72R, which binds but does not hydrolyze dATP (Rehrauer and Kowalczykowski 1993, Shan et al. 1996). However, when ATP is not hydrolyzed, DNA strand exchange generally halts long before the reaction reaches completion with the bacteriophage DNAs commonly employed (Menetski et al. 1990, Jain et al. 1994, Shan et al. 1996). ATP hydrolysis allows the reaction to go to completion, renders the DNA strand exchange reaction unidirectional (Jain et al. 1994, Shan et al. 1996) and allows it to bypass substantial DNA structural barriers (Rosselli and Stasiak 1991, Kim et al. 1992a, Shan et al. 1996). These structural barriers can include a heterologous insertion of 100 bp or more in the duplex DNA substrate. In addition, ATP hydrolysis is required for any DNA strand exchange involving two duplex DNAs (the 4-strand reaction, Fig. 4) (Kim et al. 1992b, Shan et al. 1996), and for RecA-mediated regression of a model replication fork (Robu et al. 2001, Robu et al. 2004). These results imply that ATP hydrolysis is directly coupled to the later stages of DNA strand exchange.

Notably, when DNA strand exchange is initiated, RecA protein filaments are rapidly converted from the A state to the P state. The addition of the homologous dsDNA to a reaction mixture containing RecA nucleoprotein complexes bound to ssDNA and hydrolyzing ATP leads to a 30% drop in the rate of ATP hydrolysis within 2 min (Schutte and Cox 1987). The new rate, characteristic of the P state, is subsequently maintained throughout the strand exchange reaction and beyond, given sufficient ATP regeneration (Schutte and Cox 1987). The decline in rate is dependent on homology between the two DNAs. If a duplex DNA with half the homology is added to the reaction, the drop is half of that observed with full

length dsDNA. If a longer DNA is added that is partially homologous to the ssDNA, the drop is proportional to the length of homology that exists. In effect, the RecA nucleoprotein filament senses all of the available homology at a very early stage of DNA strand exchange, even though the exchange itself may not be completed for another 15 – 20 min (Schutte and Cox 1987).

NTPases can generally be classified according to one of three biological functions: motor proteins, molecular timing devices, or recycling functions (Alberts and Miake-Lye 1992). The ATPase activity of RecA is often portrayed as a recycling function (Alberts and Miake-Lye 1992, West 1992, Kowalczykowski et al. 1994, Kowalczykowski and Eggleston 1994), causing the dissociation of RecA monomers from the filament after DNA strand exchange has occurred. ATP hydrolysis is indeed coupled to the end-dependent disassembly of RecA filaments (Arenson et al. 1999, Cox et al. 2005). However, ATP hydrolysis is also coupled to DNA strand exchange, in such a way as to allow it to overcome significant barriers and proceed at predictable rates (Kim et al. 1992b, Kim et al. 1992a, Jain et al. 1994, Bedale and Cox 1996, Shan et al. 1996, MacFarland et al. 1997, Shan and Cox 1998, Cox et al. 2005).

The role of ATP hydrolysis in RecA-mediated DNA strand exchange has been a subject of controversy for over 20 years. Since RecA filaments can remain on the heteroduplex product of typical DNA strand exchange reactions with SSB binding to the displaced single strand (Lindsley and Cox 1990b, Ullsperger and Cox 1995, Lusetti and Cox 2002), the early notion that net RecA filament disassembly, and/or filament reassembly on the displaced single strand, played a mechanistic role in the movement of the DNA branch (Howard-Flanders et al. 1984, Konforti and Davis 1992, Morel et al. 1994) has been largely discredited. There are two additional models that attempt to explain the coupling between ATP hydrolysis and DNA strand exchange. The first is the RecA redistribution model (Menetski et al. 1990, Rehrauer and Kowalczykowski 1993, Kowalczykowski and Krupp 1995). This model begins with discontinuities in the RecA filament, where DNA strand exchange halts when ATP is not hydrolyzed. ATP hydrolysis serves to recycle RecA protein so as to fill in the discontinuities. The filament may stay largely intact and bound to the hybrid DNA duplex at the end of a reaction as consistent with observation.The second model envisions a RecA-facilitated DNA rotation, coupled to ATP hydrolysis (Cox 1994, Shan et al. 1996, Roca and Cox 1997, Cox 2003, Cox et al. 2005). This model depicts the RecA ATPase as a motor activity with RecA recycling being a secondary function. ATP hydrolysis is organized throughout the filament and coupled to DNA rotation so as to effect branch movement during strand exchange or fork regression. ATP hydrolysis throughout the filament is thus coupled to DNA strand exchange, and not simply the ATP hydrolysis that occurs at a filament end or discontinuity. Tests of both models have been reviewed (Cox 2003) and are continuing (Cox et al. 2005).

3 Regulation of RecA function

Recombination plays a critical role in DNA repair and genome maintenance. However, it is equally critical to regulate where, when, and how recombination takes place. When unregulated, recombination can lead to genome instability and carcinogenesis. Meiotic recombination in eukaryotes is under tight regulation, ensuring the proper spacing and complete chromosomal coverage of the recombination events that are needed for proper chromosome segregation (Thompson and Schild 1999, Cohen and Pollard 2001, de Massy 2003, Hillers and Villeneuve 2003). Defects in many recombination functions result not only in DNA repair defects, but also in more general genomic instability. Much of this is associated with stalled replication forks (Chakraverty and Hickson 1999, Myung et al. 2001, van Gent et al. 2001, Venkitaraman 2001, Bjergbaek et al. 2002, Kolodner et al. 2002, Myung and Kolodner 2002, Osborn et al. 2002, Thompson and Schild 2002). Regulation determines which pathway is used to correct a double strand break in DNA in eukaryotes (Haber 2000, Lieber et al. 2003, Slupphaug et al. 2003, Aylon and Kupiec 2005, Jeggo and Lobrich 2005, Yurchenko et al. 2006). Humans with mutations conferring a hyperrec phenotype have an increased risk of cancer (Bishop and Schiestl 2003). Mitotic recombination is regulated at least in part by the mismatch repair system in eukaryotes (Datta et al. 1996, Chen and Jinks-Robertson 1998). In many cases, the operative regulatory mechanisms are not well defined.

The pattern is not limited to eukaryotes. Mutations in some bacterial recombination proteins reduce homologous recombination and associated repair processes, but can produce large increases in illegitimate recombination (Lovett and Sutera 1995, Hanada et al. 1997, Hanada et al. 2000, Lovett et al. 2002). Much of this genomic instability is again associated with stalled replication forks (Bierne and Michel 1994, Hanada et al. 1997, Hyrien 2000).

The activity of RecA protein, and presumably all related recombinases, is regulated on at least three levels. First, *recA* gene expression is controlled within the SOS regulon (Foster 2005, Friedberg et al. 2005, Kreuzer 2005). Second, RecA protein is subject to autoregulation. Its activities are suppressed, to degrees that vary with conditions, by the C-terminus (and perhaps other parts) of the protein. Third, the activity of RecA protein is modulated by a growing array of other proteins. The second and third modes of regulation are addressed here.

3.1 Autoregulation by the RecA C-terminus

The C-terminal 25 amino acid residues of RecA protein represent only a small part of the C-terminal domain. This will be referred to here as the C-terminus (as opposed to the entire domain). Over half of these terminal 25 residues have side chains that are either negatively charged (seven of the last seventeen are Glu or Asp residues) or contain hydroxyl groups (six Ser or Thr residues). Positively charged amino acid side chains are absent. Sequence conservation in this part of the protein is quite limited even when comparisons are limited to other bacterial

RecA proteins. The major feature of the primary structure, found in most but not all bacterial RecA sequences, is the preponderance of negatively charged residues in this region. A few RecA proteins, notably from *Bacteroides* and *Mycoplasma* species, lack this protein segment altogether (Roca and Cox 1997). In a few other species, particularly *Streptomyces*, the C-terminus is lengthened and exhibits a preponderance of positively charged residues (Roca and Cox 1997).

In the first two decades of RecA research, several C-terminal deletion mutants of the *E. coli* RecA protein were characterized. Ogawa and colleagues described RecAΔC25 (RecA5327) (Tateishi et al. 1992), and Kowalczykowski and colleagues described a RecA mutant in which a fragment of the protein, approximately the C-terminal 15% of the of the RecA polypeptide, had been spontaneously proteolyzed during storage (Benedict and Kowalczykowski 1988). These altered proteins exhibited a faster nucleation of filament formation on dsDNA, reducing the long lag in dsDNA-dependent ATP hydrolysis observed with wild-type RecA (Pugh and Cox 1987, Pugh and Cox 1988). Both C-terminal deletion mutants were shown to be proficient in the key RecA protein reaction of DNA pairing. Shorter C-terminal deletions of RecA protein were also constructed and characterized. A 17 residue C-terminal deletion mutant does not affect UV resistance, induction of the SOS response, or Weigle reactivation (Larminat and Defais 1989). There is a small effect on conjugational recombination only when the wild-type and mutant proteins are both present *in vivo* (Larminat and Defais 1989). Removal of about 18 residues from the C-terminus produces a substantial conformational difference in RecA filaments bound to dsDNA as seen in electron micrographs (Yu and Egelman 1991).

A more complete picture of the function of the C-terminus was revealed in the study of a set of C-terminal deletions involving the removal of 6, 13, 17, or 25 amino acid residues (Eggler et al. 2003, Lusetti et al. 2003a, Lusetti et al. 2003b). This work revealed that the C-terminal 17 amino acid residues of RecA protein (a region that includes all 7 of the negatively charged residues) act more broadly as a kind of autoregulatory flap. Removal of 17 C-terminal amino acid residues (RecAΔC17) enhances a wide range of RecA activities beyond binding to dsDNA. The deletion mutant no longer requires free Mg^{2+} ion for optimal strand exchange activity, indicating that access to the Ao state is regulated to some extent by the C-terminus (Lusetti et al. 2003a). The pH-rate profile for the DNA strand exchange is shifted sharply upwards in in the C-terminal deletion mutants (Lusetti et al. 2003b). Whereas bound SSB protein represents a barrier to the nucleation of wild type RecA protein, RecAΔC17 rapidly displaces SSB on single-stranded DNA even without the assistance of a mediator protein (e.g., the RecOR proteins described later). This indicates an intrinsic capacity of RecA to displace SSB that is modulated by the C-terminus. It also suggests that RecOR may not act by displacing SSB and creating a nucleation site for RecA, but instead may interact with the RecA C-terminus and facilitate the intrinsic process of SSB displacement by RecA. The non-recombination functions of RecA are also enhanced by the C-terminal deletions. The LexA protein is cleaved more rapidly when interacting with RecAΔC17 bound to duplex DNA (S. Lusetti and M. Cox, unpublished re-

sults). RecAΔC17 is also more effective in stimulating the activity of DNA polymerase V (Pham et al. 2002, Schlacher et al. 2005, Schlacher et al. 2006). Thus, the C-terminal peptide appears to modulate virtually every RecA function. As such, it is a logical interaction point for other proteins that modulate RecA function.

3.2 Proteins that modulate RecA function

Classically, the RecF, RecO, and RecR proteins (often abbreviated RecFOR) have been highlighted as functions necessary to load RecA protein onto SSB-coated DNA at single-strand gaps (Umezu et al. 1993, Umezu and Kolodner 1994, Sandler 2001). The RecBCD helicase/nuclease has a RecA loading function on the single-strand segments it creates at DNA ends (Anderson and Kowalczykowski 1997, Churchill et al. 1999, Arnold and Kowalczykowski 2000, Spies et al. 2005, Spies and Kowalczykowski 2006). These functions seemed sufficient to target RecA filaments to the locations requiring them, yet recent work has shown that RecA regulation is much more complex. The RecF protein may have multiple functions (Sandler 1996, Rangarajan et al. 2002). Several additional proteins play important roles. We now turn to a description of the activities of these proteins. For a description of RecBCD, see the chapter by S. Kowalczykowski, this volume.

3.3 The single-strand DNA binding protein (SSB)

SSB plays a complex role in RecA reactions. RecA filament nucleation is inhibited, and under some conditions blocked entirely, if SSB is allowed to coat the DNA prior to RecA addition (Kowalczykowski et al. 1987, Lavery and Kowalczykowski 1990, Umezu and Kolodner 1994, Shan et al. 1997, Bork et al. 2001a). This inhibition of binding nucleation is overcome in the bacterial cell by the mediator proteins, RecO and RecR (Umezu and Kolodner 1994, Shan et al. 1997, Bork et al. 2001a). However, Wt EcRecA protein does not bind well to secondary structure in ssDNA, and addition of SSB after RecA protein disrupts the secondary structure and allows RecA to form a contiguous filament on the DNA (Kowalczykowski and Krupp 1987). As already mentioned above, SSB also facilitates DNA strand exchange by binding to the displaced DNA strand.

3.4 The RecFOR proteins

Mediator proteins are as ubiquitous as recombinases, ensuring the targeted assembly of recombinase filaments. In *E. coli*, the RecF, RecO, and RecR proteins function in this capacity, and perhaps have other functions as well.

3.4.1 The RecF protein

The *recF* gene was discovered (Horii and Clark 1973) as a UV sensitive, recombination-deficient mutant in a *recBC sbcBC* background. Although it has never been implicated in replication, the gene is contained in an operon that also includes the *dnaA*, *dnaN*, and *gyrB* genes. The sequenced *recF* gene encodes a 357 amino acid polypeptide (40.5 kDa). The RecF protein has been purified and characterized *in vitro* (Griffin and Kolodner 1990, Madiraju and Clark 1991, Madiraju and Clark 1992, Umezu et al. 1993, Umezu and Kolodner 1994, Webb et al. 1995, Webb et al. 1997, Webb et al. 1999). It binds to ssDNA with an apparent stoichiometry of 1 RecF monomer per 15 nucleotides (Madiraju and Clark 1991). In the presence of ATP, the RecF protein also binds to dsDNA (Madiraju and Clark 1992, Webb et al. 1995). The protein contains a consensus nucleotide-binding fold (Walker A box). The protein binds ATP, and has a weak dsDNA-dependent ATPase activity (k_{cat} about 1.0 min^{-1}) (Webb et al. 1995, Webb et al. 1999). ATP hydrolysis leads to RecF dissociation from DNA (Webb et al. 1999).

3.4.2 RecO protein

The *recO* gene (Kolodner et al. 1985) is situated in an operon with the *rnc* gene, which encodes ribonuclease III, and the *era* gene, which encodes a GTP-binding protein with sequence similarities to the yeast RAS proteins (Ahnn et al. 1986). The sequenced *recO* gene encodes a protein with 242 amino acids (26 kDa) and includes a Walker A box (Morrison et al. 1989, Takiff et al. 1989). The purified protein binds to both ssDNA and dsDNA and behaves as a monomer in solution (Umezu et al. 1993, Luisi-DeLuca and Kolodner 1994, Umezu and Kolodner 1994, Luisi-DeLuca 1995). It promotes an ATP-independent renaturation of complementary DNA strands (Luisi-DeLuca and Kolodner 1994). Binding or hydrolysis of ATP has not been reported. The protein forms a functional complex with the RecR protein, as described below.

The structure of the *D. radiodurans* RecO protein has been determined (Makharashvili et al. 2004). The protein has three structural domains, including an N-terminal domain which features an OB-fold, a novel α-helical domain, and an unusual zinc-binding domain. Sequence alignments indicate that this structural pattern is found in other bacterial RecO proteins.

3.4.3 RecR protein

The *recR* gene (Mahdi and Lloyd 1989a, Mahdi and Lloyd 1989b) is cotranscribed with the *dnaX* gene and shares an operon with a small open reading frame of unknown function called orf-12. The *recR* gene encodes a 201 amino acid protein (22 kDa). The sequence includes two putative DNA-binding motifs (helix-turn-helix and zinc finger) (Alonso et al. 1993). The purified protein has been examined *in vitro*, where it was studied in concert with the RecF and RecO proteins (Umezu et al. 1993, Umezu and Kolodner 1994, Webb et al. 1995, Shan et al. 1997, Webb et al. 1997). There is no indication that the *E. coli* RecR protein alone

binds directly to DNA, although the RecR proteins from *D. radiodurans* (Lee et al. 2004) and *B. subtilis* (Alonso et al. 1993) do. The *E. coli* RecR protein is a dimer in solution (Umezu and Kolodner 1994).

The structure of the *D. radiodurans* RecR protein (44% identity with EcRecR) has been determined (Lee et al. 2004). The protein crystallizes as a tetrameric ring with a central hole large enough to accommodate a molecule of dsDNA (Lee et al. 2004). The mechanistic implications of this structure have not yet been explored.

Of the RecFOR proteins, RecR is the most common protein in bacterial genomes (Rocha et al. 2005). RecF is the least common.

3.4.4 Interaction of RecF, O, and R proteins

Several lines of evidence indicate that these 3 proteins function at the same stage of recombination, and tie them to a role in displacing SSB and modulating RecA filament assembly. The phenotypes of mutations in the 3 genes are very similar, defining them as an epistatic group (Smith 1989, Clark and Sandler 1994). Mutations in all three genes are suppressed by *recA*441 (E38K, I298V), *recA730* (E38K), and *recA*803 (V37M) mutations (Wang et al. 1993). *In vitro*, the same RecA441 (previously tif) and RecA803 proteins exhibit an enhanced capacity to displace SSB and bind ssDNA (Lavery and Kowalczykowski 1988, Madiraju et al. 1992). In addition, a gene in bacteriophage λ called *ninB* or *orf* (described further below) has been identified which can replace *recF*, *recO*, and *recR* functions in lambda recombination (Sawitzke and Stahl 1992, Sawitzke and Stahl 1994). *In vivo*, mutant bacteria missing any of the *recFOR* functions exhibit a delayed activation of the SOS response that might reflect slow formation of the RecA filaments required to facilitate LexA cleavage (Madiraju et al. 1988, Whitby and Lloyd 1995). *E. coli* strains in which SSB is overexpressed exhibit a *recFOR*-like phenotype (Moreau 1988), again suggesting that these proteins function together in overcoming the barrier to RecA filament nucleation represented by SSB.

A more detailed examination of the literature, however, shows that the roles of these proteins are not always confluent. In particular, RecF protein appears to have a distinct role that may not always intersect with that of RecO and RecR. In general, the distinctions show up in genetic studies where the underlying molecular mechanisms are poorly understood. RecF activity can be toxic to the cell at least in some contexts. The effect of RecO loss is moderated in *recOrecR* or *recOrecF* strains, suggesting that RecF and RecR are doing something deleterious to the cell in the absence of RecO. In a strain lacking the function of PriA protein (a helicase that plays a key role in restart of replication forks that stall or collapse away from the replication origin (Marians 2000b, Marians 2000a)), the additional loss of RecO is about 10 times more deleterious than the loss of either RecF or RecR (Grompone et al. 2004). In the presence of a different *priA* mutation, *recF* mutants are more deleterious than *recO* or *recR* mutants (Sandler et al. 1996a). The apparent discrepancy may be explained by the extra steps taken in the former study (Grompone et al. 2004) to avoid the appearance of suppressors in the very sick *recOpriA* strains. Both studies, however, draw a clear distinction between the effects of *recF* and *recO* mutations in the *priA* background. The RecF protein, but not

RecO or RecR, is needed for the *in vivo* function of DNA polymerase V and mutagenic TLS (Rangarajan et al. 2002). This work suggests that RecF may work with RecOR in some processes and independently in others. A number of bacterial species with sequenced genomes possess homologues of the *recF* and *recR* genes, but no *recO* gene (Sandler 2001). In *Bacillus subtilis* (which has all three genes), RecF protein recruitment to repair foci is preceded by the appearance of RecO protein (and by RecA protein) by several minutes (Kidane et al. 2004). Overexpression of RecF protein in *E. coli* reduces SOS induction, UV resistance, and viability at 42°C (Sandler and Clark 1993). The overexpression of the RecOR proteins suppresses many of the deleterious effects of either RecF overexpression (Sandler 1994) or a *recF* null mutation (Sandler and Clark 1994). These varied results suggest that the current pictures of RecFOR and RecF function require expansion.

The functional distinction between RecF and RecO proteins is also quite evident *in vitro* (Umezu et al. 1993, Umezu and Kolodner 1994, Webb et al. 1995, Shan et al. 1997, Webb et al. 1997). RecR protein forms alternative complexes with RecF and RecO protein (Webb et al. 1995, Shan et al. 1997, Webb et al. 1997, Bork et al. 2001a, Morimatsu and Kowalczykowski 2003). RecF protein generally interferes with RecOR function (Webb et al. 1995, Shan et al. 1997, Webb et al. 1997, Bork et al. 2001a, Morimatsu and Kowalczykowski 2003).

The RecOR complex stimulates RecA protein binding to ssDNA coated with SSB, in a process that is not further stimulated by RecF protein under most conditions (Umezu et al. 1993, Umezu and Kolodner 1994, Shan et al. 1997, Bork et al. 2001a). RecO and RecR proteins remain associated with the RecA filament after it is formed (Umezu and Kolodner 1994, Shan et al. 1997). In addition to stimulating nucleation of RecA filament formation on SSB-coated ssDNA, the RecOR complex prevents a net end-dependent dissociation from linear ssDNA (Shan et al. 1997), although it does not suppress RecA dissociation altogether. It is likely that the presence of RecOR leads to rapid nucleation that leads to a rapid replacement of any RecA that dissociates from ssDNA. The RecO and RecR proteins are not active independently in these processes.

There is no evidence yet reported for an interaction between the RecO and RecF proteins. With one exception (Morimatsu and Kowalczykowski 2003), there are no reports of a stimulatory effect of RecF on any RecA activity. However, the presence of RecO and RecR appears to nullify a strong inhibitory effect of RecF on RecA-mediated reactions *in vitro* (Umezu et al. 1993).

The RecF and RecR proteins form a complex in an ATP and DNA-dependent fashion (Webb et al. 1995). The RecFR complex binds primarily to dsDNA, and the complex is stable enough to halt RecA filament extension (Webb et al. 1997). The RecR protein stimulates the RecF ATPase, but reduces the rate of RecF transfer from one DNA to another (Webb et al. 1995, Webb et al. 1999).

Optimized *in vitro* reconstitution of several steps of one major pathway for recombination-dependent replication restart requires the presence of the RecOR proteins (Xu and Marians 2003). RecF protein reduces the stimulation provided by RecOR (Xu and Marians 2003). The effects of RecOR on RecF inhibition of RecA

in vitro and RecF overexpression *in vivo* (described above) may reflect a similar RecO antagonism of RecFR function.

It is always possible that the failure to detect the formation or activity of a RecFOR complex could reflect a failure to find the right reaction conditions. One recent study has provided evidence that RecF, O, and R can act together to facilitate RecA protein filament formation on SSB-coated DNA gaps (Morimatsu and Kowalczykowski 2003). The stimulatory effect of RecF is observed, however, only in the presence of levels of SSB that are in 6-8 fold excess of that required to saturate the available ssDNA. A useful overview model is that RecOR is necessary and sufficient to load RecA protein onto SSB-coated ssDNA, and that RecF plays a role in targeting this process to the ends of ssDNA gaps as proposed by Morimatsu et al. (Morimatsu and Kowalczykowski 2003). More substantiation of this model is needed. RecF protein has an additional function in antagonizing the function of RecX protein, as described below. This links the RecFOR proteins into a wider network of RecA regulation.

3.5 The DinI and RecX proteins

These two proteins are related in the sense that they have opposing activities, each antagonizing the function of the other.

3.5.1 The RecX protein

The RecX protein (19 kDa) is encoded by a widespread bacterial gene often found just downstream or even overlapping the *recA* gene (Sano 1993, De Mot et al. 1994, Papavinasasundaram et al. 1997, Vierling et al. 2000, Yang et al. 2001). In a few cases, the gene is found in another region of the chromosome (Stohl and Seifert 2001). In *E. coli*, the *recX* gene is just downstream of the recA gene, and expressed from the *recA* promoter via a 5-10% transcriptional readthrough of a hairpin sequence separating the two genes (Pages et al. 2003). In some bacterial species, RecX protein is necessary to overcome deleterious effects of overexpression of RecA protein, implying that RecX is a negative modulator of RecA expression or function (Sano 1993, Papavinasasundaram et al. 1998, Vierling et al. 2000, Sukchawalit et al. 2001). Deletion of the gene in *E. coli* produces no clear phenotype (Pages et al. 2003), although overexpression of the *recX* gene can reduce the induction of the SOS response (Stohl et al. 2003). When purified, both the *Mycobacterium* RecX (Venkatesh et al. 2002) and the *E. coli* RecX protein (Stohl et al. 2003) inhibit the ATPase and strand exchange activities of RecA protein *in vitro*. The RecX protein binds deep within the major helical groove of an AMPPNP-stabilized RecA filament (VanLoock et al. 2003).

Purified RecX blocks the extension of RecA filaments during assembly, almost certainly by capping the filament (Drees et al. 2004a). When RecA filaments have been formed on circular ssDNAs, there is generally no net dissociation and ATP hydrolysis proceeds at a constant steady state. There are generally breaks in the filaments where dissociation at a disassembly end can occur, but the resulting ends

are quickly filled in by growth of the trailing filament assembly end. When RecX protein is added at relatively low concentrations (about one RecX per 20-100 bound RecA monomers), a net disassembly of the RecA filaments occurs that takes 10-15 min to complete. Whereas RecX blocks RecA filament assembly, RecA filament disassembly proceeds unabated. The RecA C-terminus plays a significant role in the RecX-RecA interaction (Drees et al. 2004b). Mutations in the RecA C-terminus moderate the interaction (Drees et al. 2004b).

The RecF protein physically interacts with the RecX protein and protects RecA from the inhibitory effects of RecX (Lusetti et al. 2006). *In vitro*, efficient RecA filament formation onto single-stranded DNA binding protein (SSB)-coated circular single-stranded DNA (ssDNA) in the presence of RecX occurs only when all of the RecFOR proteins are present. The RecOR proteins promote RecA filament nucleation onto SSB-coated single-stranded DNA. When RecX is present, substantial RecA filament extension (after RecOR-mediated nucleation) does not occur unless RecF protein is also present (Lusetti et al. 2006). *In vivo*, RecF protein counters a RecX-mediated inhibition of plasmid recombination (Lusetti et al. 2006). Thus, a significant positive contribution of RecF to RecA filament assembly is to antagonize the effects of the negative modulator RecX, specifically during the extension phase of RecA filament assembly.

3.5.2 The DinI protein

DinI is a small (81 amino acids) protein that is induced very early in the SOS response (Kenyon and Walker 1980, Yasuda et al. 1996, Yasuda et al. 1998). Overexpression of the DinI protein in *E. coli* results in UV sensitivity and inhibits the induction of the SOS response (Yasuda et al. 1998). An early proposal suggested that DinI plays a role in bringing the SOS response to an end (Yasuda et al. 1998, Voloshin et al. 2001, Yasuda et al. 2001), but recent work calls this hypothesis into question (Lusetti et al. 2004b). DinI has been purified by several different research groups. DinI inhibits the RecA-mediated cleavage of the UmuD protein (Yasuda et al. 2001). Little effect on RecA filaments was noted in this work, and LexA cleavage was not affected to the same extent. DinI can disrupt RecA filaments (Voloshin et al. 2001), but only when very large excesses (> 20 fold) of DinI are present (Lusetti et al. 2004b). The structure of the DinI protein has been solved by NMR (Ramirez et al. 2000). The C-terminal 17 amino acid residues of DinI features six negatively charged residues, arranged much like they are in the 17 C-terminal amino acid residues of the RecA protein. Another NMR study suggested that the DinI protein binds to the core domain of RecA (Yoshimasu et al. 2003).

Rather than an inhibitor, DinI is actually a potent stabilizer of RecA protein filaments. At DinI concentrations more closely stoichiometric with RecA, DinI strongly stabilizes RecA filaments. Filament disassembly is almost completely suppressed. The effect can be seen dramatically in the electron microscope (Lusetti et al. 2004b). Further, most DNA strand exchange is not blocked by the DinI protein. In one instance (with duplex DNAs cut with restriction enzymes that

leave a 5' single strand extension), the initiation of strand exchange is slowed by DinI, but DinI has no effect on the reaction once it is initiated.

The interaction between DinI and RecA is modulated by the RecA C-terminus. Removal of the C-terminal 17 amino acid residues of RecA strongly enhances the interaction between the two proteins (Lusetti et al. 2004b). This is consistent with the C-terminus of RecA being a target for RecA modulators.

This work has led to a new hypothesis for DinI action in which DinI is a selective modulator. During SOS, DinI is induced with somewhat faster kinetics than RecA (Voloshin et al. 2001), consistent with an activator function; its concentration declines late in SOS. The only RecA function reliably suppressed by DinI is the cleavage of UmuD protein, a subunit of DNA polymerase V that is activated by a RecA-mediated autocatalytic cleavage (similar to what is seen with the LexA protein). Thus, the presence of DinI early in SOS could suppress the activation of DNA polymerase V while leaving most other RecA activities intact. This would have the effect of delaying the onset of the mutagenic phase of the SOS response. Thus, DinI may regulate the temporal course of the SOS response, allowing non-mutagenic DNA repair processes to proceed early and delaying the onset of mutagenic translesion DNA polymerase activity.

The role of DinI is distinct from that of Rec(F)OR. DinI does not affect the loading of RecA onto SSB-coated ssDNA (Lusetti et al. 2004b). Instead, DinI stabilizes RecA filaments after they are formed.

The DinI and RecX proteins each antagonize the function of the other. DinI protein stabilizes the RecA filament, and RecX destabilizes it (Lusetti et al. 2004a). With sufficient DinI protein present, a challenge with low concentrations of RecX protein has no effect on RecA filaments. (Lusetti et al. 2004a). If DinI protein is added after the RecX protein challenge, the filaments recover. High concentrations of RecX (nearly stoichiometric with RecA protein) do displace the DinI protein and destabilize the RecA filament. In addition to its capping function, the RecX protein appears to compete with DinI for binding sites in the RecA filament groove. This idea meshes well with the binding of RecX within the RecA filament groove as seen in the EM studies of Egelman and colleagues (VanLoock et al. 2003).

3.6 The PsiB and RdgC proteins

These proteins are implicated in the modulation of RecA filament formation and/or function, but have been characterized minimally *in vitro*.

3.6.1 The PsiB protein

The PsiB protein is encoded by a number of conjugative plasmids (Delver and Belogurov 1997, Sarno et al. 2002). These proteins are generally small, ~140 amino acid residues giving a molecular mass of 15-16 kDa. PsiB inhibits the induction of SOS when conjugation is taking place, presumably by interacting with the RecA protein (Bagdasarian et al. 1986). The *psiB* gene is transferred early in conjugation

and transcribed transiently (Bagdasarian et al. 1986). None of the known PsiB proteins have been studied *in vitro*.

When bacterial cells are starved, there is a transient induction of the SOS response that leads to genome-wide hypermutation. This is called adaptive mutation, and it requires RecA function both directly and for the SOS induction (McKenzie et al. 2000, McKenzie et al. 2001). In this context, DinI protein has little effect on the SOS response, but PsiB is a potent inhibitor (in cells with an F plasmid) (McKenzie et al. 2000). These results again suggest that PsiB is an inhibitor of RecA function (and reinforce the hypothesis that DinI is not an inhibitor. Also of interest, the IncN plasmid pKM101 (broad host range) encodes both a PsiB protein and a RecX protein (Delver and Belogurov 1997).

3.6.2 The RdgC protein

RdgC is a fairly abundant DNA binding protein that appears to affect the function of RecA and RecFOR. The *rdgC* gene is located near *sbcC* and *sbcD* on the *E. coli* chromosome, encoding a protein of 34 kDa (Ryder et al. 1996). A deletion of the *rdgC* gene by itself has little obvious effect. However, the same deletion in a *recBCsbcBC* background is viable only if the RecA and RecF proteins are functional (hence, recombination-dependent growth or rdg) (Ryder et al. 1996). The RdgC protein also appears to be important in a *priA* background. The poor viability of *priA* mutants is suppressed by certain mutations in *dnaC* such as *dnaC*212 These allow the DnaC protein to circumvent PriA in the pathway by which the DnaB helicase is loaded onto a repaired fork structure during replication restart (Sandler et al. 1999, Sandler and Marians 2000). Introducing an *rdgC* deletion into a *priAdnaC212* background confers a slow growth phenotype (Moore et al. 2003). Suppressors arise rapidly in these strains, and they are quite informative. First, the slow growth is suppressed by mutations that eliminate RecF, RecO or RecR function (Moore et al. 2003). This suggests that the slow growth is caused by inappropriate loading of RecA protein. It also suggests that the RdgC protein has a role in preventing this inappropriate loading or function of RecA protein. The slow growth is also suppressed by certain mutations in the *ssb* gene (R97C and Δ115-144)(Moore et al. 2003) that could define interaction points for Rec(F)OR. The RdgC protein is present at about 1000 copies per cell (compared to about 800-1700 tetramers of SSB) (Moore et al. 2003), and *in vitro* the protein binds to both ssDNA and dsDNA (Moore et al. 2003).

The *Escherichia coli* RdgC protein is a potential negative regulator of RecA function. RdgC inhibits RecA protein-promoted DNA strand exchange, ATPase activity, and RecA-dependent LexA cleavage *in vitro* (Drees et al. 2006). There is no apparent interaction between RdgC protein and RecA, and RdgC inhibition appears to involve a simple competition for DNA binding sites, especially on duplex DNA. The capacity of RecA to compete with RdgC is improved by the DinI protein. When RdgC protein is bound to the homologous duplex DNA, DNA strand exchange catalyzed by RecA nucleoprotein filaments formed on single-stranded DNA is inhibited (Drees et al. 2006). RdgC protein exists in solution as a mixture of oligomeric states in equilibrium, most likely as monomers, dimers, and tetram-

ers. In the electron microscope, the RdgC protein coats duplex DNA (Drees et al. 2006). It is not clear whether RdgC is a dedicated regulator of recombination. If the observed inhibition of RecA function *in vitro* is physiologically relevant, there must exist some interaction between RdgC and another recombination or replication protein that would serve to target RdgC to sites of recombinational activity.

3.7 The UvrD helicase

In every organism, there appear to be helicases that antagonize recombination functions. This is perhaps best characterized in yeast. The yeast Srs2 helicase negatively modulates recombination (Aguilera and Klein 1988, Aboussekhra et al. 1989). Additional work suggests that Srs2 actively removes recombination complexes or structures *in vivo* (Kaytor et al. 1995, Milne et al. 1995, Schild 1995, Chanet et al. 1996). The yeast Sgs1 protein is a helicase from the RecQ family (Gangloff et al. 1994). A combination of *srs2* and *sgs1* null mutants results in a near-lethal slow growth phenotype (Lee et al. 1999, Klein 2001, Fabre et al. 2002, Mankouri et al. 2002). Mutations in a number of recombination functions, including Rad51, Rad52, Rad55, and Rad57, alleviate the defect in the *sgs1 srs2* double mutant (Klein 2001, Fabre et al. 2002). The work indicates that Sgs1 and Srs2 are involved in the removal of toxic recombination intermediates, and can partially substitute for each other. *In vitro*, the Srs2 helicase will disrupt Rad51 protein filaments and interfere with their DNA strand exchange activity (Krejci et al. 2003, Veaute et al. 2003).

In bacteria, parallels are evident but less developed. The RuvA and B proteins displace RecA filaments *in vitro* (Adams et al. 1994), but the genetics provides only limited support for this role *in vivo*. Null mutants of the *uvrD* gene have phenotypes implicating it in recombinational DNA repair (Mendonca et al. 1995). UvrD protein is induced as part of the SOS response, and has been demonstrated to displace RecA filaments.

The Ec UvrD protein (or *E. coli* DNA helicase II) is an 82 kDa helicase protein, whose gene is located at about 84 minutes on the *E. coli* chromosome. UvrD is homologous to the somewhat smaller *E. coli* Rep helicase, and can even form heterodimers with Rep (Wong et al. 1993). Deletion of both the *rep* and *uvrD* genes in *E. coli* is lethal (Washburn and Kushner 1991). UvrD protein is a 3' to 5' helicase (Matson 1986) (as is Rep and the yeast Srs2 helicase) and unwinds duplex DNA best when there is a 3' single strand extension upon which to bind and initiate. However, UvrD also exhibits significant unwinding activity even when initiating the reaction at a nick (Runyon et al. 1990) or blunt end, and this capability could be important for repair systems designed to address strand breaks. In addition, UvrD will unwind RNA-DNA hybrids in a reaction more robust than the unwinding of DNA (Matson 1989), perhaps suggesting a role in replication fork repair on the lagging strand. The UvrD helicase functions as a dimer (Ali et al. 1999, Maluf et al. 2003), although the protein binds well to single-stranded DNA as a monomer (Mechanic et al. 1999, Velankar et al. 1999, Maluf et al. 2003).

As Rep helicase has been shown to remove proteins from the DNA (Yancey-Wrona and Matson 1992), it has been proposed that Rep might serve to remove proteins in the path of the replication fork (DNA synthesis is slowed 50% in cells lacking Rep function (Lane and Denhardt 1975)). However, UvrD is uniquely able to displace RecA protein from ssDNA *in vitro* (Veaute et al. 2005). Rep helicase has a much abbreviated capacity to displace RecA in side by side assays (Veaute et al. 2005).

The genetic studies of the *uvrD* gene generally bears out a role in eliminating RecA and perhaps other recombination proteins from sites where recombinational DNA repair is underway. UvrD plays a role in many aspects of DNA metabolism, although its detailed molecular function remains somewhat enigmatic. This helicase is involved in both methyl-directed mismatch repair (Lahue et al. 1989, Modrich 1989) and the DNA excision repair mediated by the UvrABC excinuclease (Kumura et al. 1985). A role in chromosomal replication is suggested by the constitutive induction of the SOS response that is observed in many *uvrD* mutant cells (Ossanna and Mount 1989, George et al. 1994), presumably because replication forks are stalling in these strains. Cells lacking UvrD function have a defect in recombinational DNA repair (Howard-Flanders and Bardwell 1981, Lloyd 1983, Mendonca et al. 1993). At the same time, *uvrD*$^-$ strains have a hyperrecombination phenotype, with large increases in illegitimate recombination (Washburn and Kushner 1991, Lovett and Sutera 1995). Certain alterations of UvrD can suppress the phenotypes of *ruvB* and *recJ* (Lovett and Sutera 1995) mutations, further suggesting a complex involvement in recombination processes. UvrD has a demonstrated anti-recombinase function *in vivo* that may involve the destabilization of recombination intermediates, the complexes that form them, or both (Morel et al. 1993, Lovett and Sutera 1995, Petranovic et al. 2001). In strains lacking the RecBCD pathway, *recQ* and *uvrD* null mutations are synthetically lethal (Mendonca et al. 1995). A fork-clearing role has been proposed for UvrD protein, based on the suppression of the lethality of *uvrD* mutants in DNA polymerase III ts backgrounds by mutations in the *recA*, *recFOR*, *recJ*, and *recQ* genes (Flores et al. 2005).

4 Regulation summary

Bacterial genetic recombination and recombinational DNA repair is clearly under the regulation of an elaborate network of positive and negative effectors. RecA protein appears to be the principle target of regulation. The RecFOR proteins promote RecA filament formation in various ways. The DinI protein stabilizes RecA filaments and alters their function by inhibiting UmuD cleavage. RecX protein blocks RecA filament extension. RdgC protein inhibits RecA by blocking access to duplex DNA. PsiB may be a RecA inhibitor. The UvrD helicase dismantles RecA filaments on DNA. The RecF and DinI proteins antagonize the activities of RecX. The biochemical functions of all of these proteins require further elucida-

tion. It seems likely that we do not yet have a complete picture of the regulatory network.

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