RecA Protein

Advanced article

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The RecA protein of *Escherichia coli* is the prototypic deoxyribonucleic acid (DNA) strand exchange protein. It assembles on single-stranded DNA to form a helical nucleoprotein filament that is the active species for all RecA protein-dependent functions. This protein–DNA complex is responsible for three mutually exclusive functions: DNA recombination, induction of the DNA-damage SOS response and SOS-induced mutagenesis.

Article Contents

doi: 10.1038/npg.els.0003925

Introduction

The RecA protein of *Escherichia coli* is a multifunctional protein that is essential to three distinct, but related biological processes: (1) general genetic recombination; (2) regulation of the coordinated expression of over 40 unlinked genes in response to deoxyribonucleic acid (DNA) damage, known as the SOS response; and (3) the error-prone replicative bypass of DNA lesions, resulting in a highly mutagenic repair of DNA. Not surprisingly, mutations in *recA* are pleiotropic, affecting not only recombination, but also DNA repair, mutagenesis and cell division (Bianco *et al*., 1998).

To mediate this broad spectrum of biological events, RecA protein possesses three major biochemical activities: (1) the homologous pairing and exchange of DNA; (2) adenosine triphosphate (ATP)- and DNA-dependent coproteolytic processing of effector proteins; and (3) interaction with specialized DNA polymerases to facilitate error-prone DNA synthesis past DNA lesions.

The DNA-strand exchange activity is characteristic of a ubiquitous class of proteins that are essential to genetic recombination, a biological process in which two homologous DNA molecules pair and exchange regions of their DNA strands. These proteins facilitate the ATP-dependent exchange of single strands of DNA between the participating DNA partners. The RecA protein of *E. coli* is the prototypic member of this family of functionally and genetically similar proteins. **See also**: Evolutionary developmental biology: homologous regulatory genes and processes

Coprotease activity is another unique property of RecA protein. This activity is the highly specific catalysis of the self-cleavage of proteins (LexA repressor, UmuD mutagenesis factor and phage repressor proteins), which is dependent on both ATP and single-stranded DNA (ssDNA) binding.

The third activity of RecA protein is its direct participation in the replication-dependent bypass of mutagenic lesions in DNA. This function requires the binding of the processed mutagenic complex $Umu(D')_2C$, comprising DNA polymerase V, to the RecA protein filament that has assembled at the site of the DNA lesion, thereby enabling DNA synthesis beyond the lesion.

Each of these processes is discussed in more detail below.

The Structure of RecA Protein

For RecA protein to function in these processes, it must assemble on ssDNA to form a nucleoprotein filament known as the presynaptic complex (Story *et al*., 1992). This filament is an adaptable structure, capable of performing three separate functions (**Figure 1**): homologous recombination (interaction with double-stranded DNA, dsDNA), SOS induction (cleavage of the LexA repressor) and SOS mutagenesis (interaction with the processed $Umu(D')_2C$ complex (DNA polymerase V)) (**Table 1**). **See also**: Single-stranded DNA binding proteins

The active nucleoprotein filament is a helical complex of RecA protein monomers wrapped around ssDNA at a stoichiometry of three nucleotides per monomer and about six monomers per turn (**Figure 2a**–**d**). Under certain conditions, RecA protein will also form filaments on dsDNA. Filament assembly is highly cooperative and occurs in the $5'\rightarrow3'$ direction relative to the ssDNA to which it is bound. The resulting filament has a regular, right-handed, helical structure, and the prominent feature is a large helical groove (**Figure 2a**). One side of the groove is smooth, while the other is penetrated by the protrusion of the individual monomers (**Figure 2b**). This groove is the binding site for the LexA repressor and is proposed to be involved in the binding of dsDNA. The binding of the LexA repressor and dsDNA to the nucleoprotein filament is competitive, indicating that they bind at the same, or overlapping site, on the filament. **See also**: Protein–DNA complexes: nonspecific

The nucleoprotein filament can exist in two forms: active and inactive. The inactive filament is formed in the absence of a nucleoside triphosphate (NTP) cofactor and exists in a collapsed conformation with a helical pitch of approximately 6.5 nm. The binding of an NTP cofactor (typically

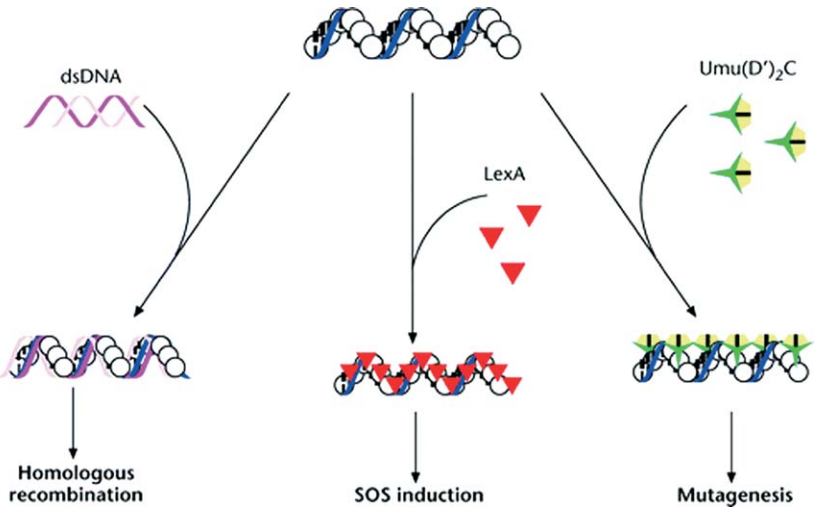

Figure 1 Roles of the RecA nucleoprotein filament in DNA metabolism. A schematic showing the three mutually exclusive functions of the RecA protein filament. Adapted from Rehrauer *et al.* (1998).

Table 1 Requirements for RecA protein-dependent processes

Requirement	Homologous recombination	SOS induction	Mutagenesis
[RecA protein]	Basal level	Initially, basal level later, induced levels	Only induced levels of RecA protein
Stoichiometry in the first site	3:1 (nt: RecA)	3:1 (nt: RecA)	3:1 (nt: RecA)
Stoichiometry in the second site	3:1 (bp:RecA monomer)	1:2 (LexA monomer:RecA monomers)	1:2 ($Umu(D')_2C$ complex:RecA monomers)
Cofactor requirement	NTP binding and hydrolysis	Only NTP binding	Only NTP binding
Competition (at the second site)	dsDNA binding excludes LexA or $Umu(D')_2C$ binding	LexA binding prevents dsDNA or $Umu(D')_2C$ binding	$Umu(D')_2C$ binding excludes dsDNA or LexA binding

ATP or 2′-deoxyadenosine 5′-triphosphate (dATP)), converts RecA protein to a high-affinity ssDNA-binding state, which is the active conformation of RecA protein. This active form of the filament has an extended conformation with a helical pitch of approximately 9.5 nm. It is this extended conformation that is the active species in RecA protein-promoted reactions. **See also**: ATP binding motifs

Within the active form of the nucleoprotein filament, the conformation of ssDNA and dsDNA differs significantly from that of B-form DNA. The bound DNA is extensively stretched (to approximately 150% the length of B form) and, in the case of dsDNA, the helix also has a lower twist. Electron micrographic analysis and neutron scattering reveal that the DNA is located near the axis of the nucleoprotein filament. **See also**: DNA topology: fundamentals

DNA strand exchange proteins isolated from a wide variety of organisms including bacteriophage, archaea and eukaryotes (Ogawa *et al.*, 1993; Yang *et al.*, 2001) are very similar (**Figure 3**), and assemble into nearly identical nucleoprotein filament structures, highlighting the importance of the nucleoprotein filament in RecA protein function. Thus, the assembly of RecA protein on to ssDNA promotes the formation of the nucleoprotein filament that is the central structure in RecA protein function. This unique structure (the filament) has the capacity to bind dsDNA and catalyse the exchange of single strands of duplex DNA, to bind and cleave repressors and proteins important for mutagenesis, and also to bind and target DNA polymerase V to DNA lesions, thereby facilitating SOS-induced mutagenesis. **See also**: Rad51 and eukaryotic recombination proteins

The Role of RecA Protein in DNA Strand Exchange

RecA protein promotes the exchange of single strands of DNA between two homologous DNA molecules (Shibata *et al.*, 1979). The functional form of RecA protein in this

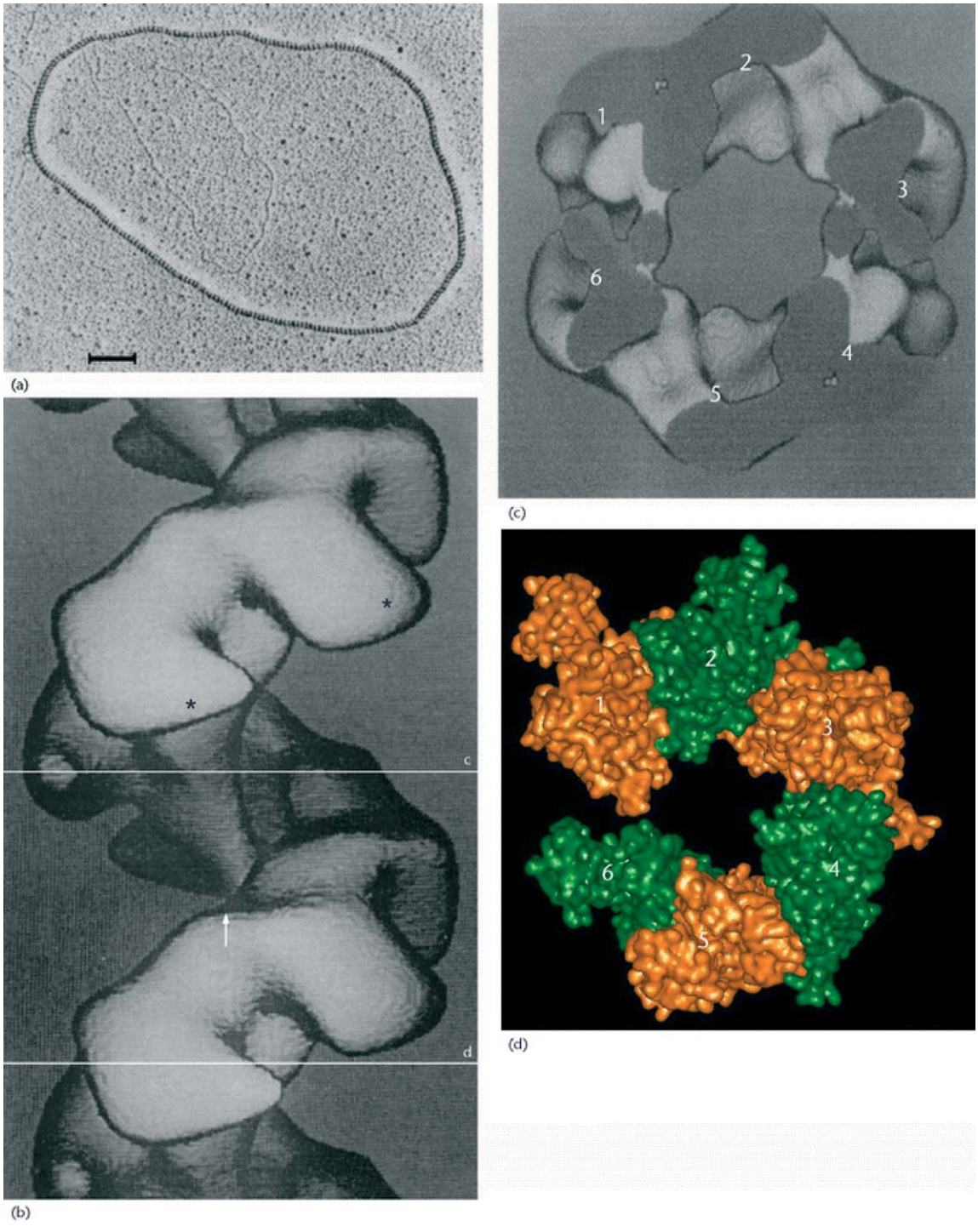

Figure 2 The nucleoprotein filament formed by RecA protein. (a) A filament formed on dsDNA with ATPγS as cofactor (from Stasiak and Egelman (1988)). The striations in the filament indicate the groove discussed in the text. Scale bar 0.1 nm. (b) Closeup of the filament (the DNA is not visible) shown in (a). The asterisks indicate the lobes of monomers that protrude into the groove and the white arrow indicates the smooth surface of the groove. (c, d) Cross-sections of the filament showing a single turn. (b,c) Three-dimensional reconstructions of electron micrographs of RecA filaments formed on dsDNA with ATPγS. (d) Single turn of the RecA filament as seen in the crystal structure (Story *et al.*, 1992). The individual monomers are coloured alternately in orange and yellow. The numbers in (c,d) indicate the six monomers making up the turn in the cross-section; the DNA would be located in the central hole, but is not shown.

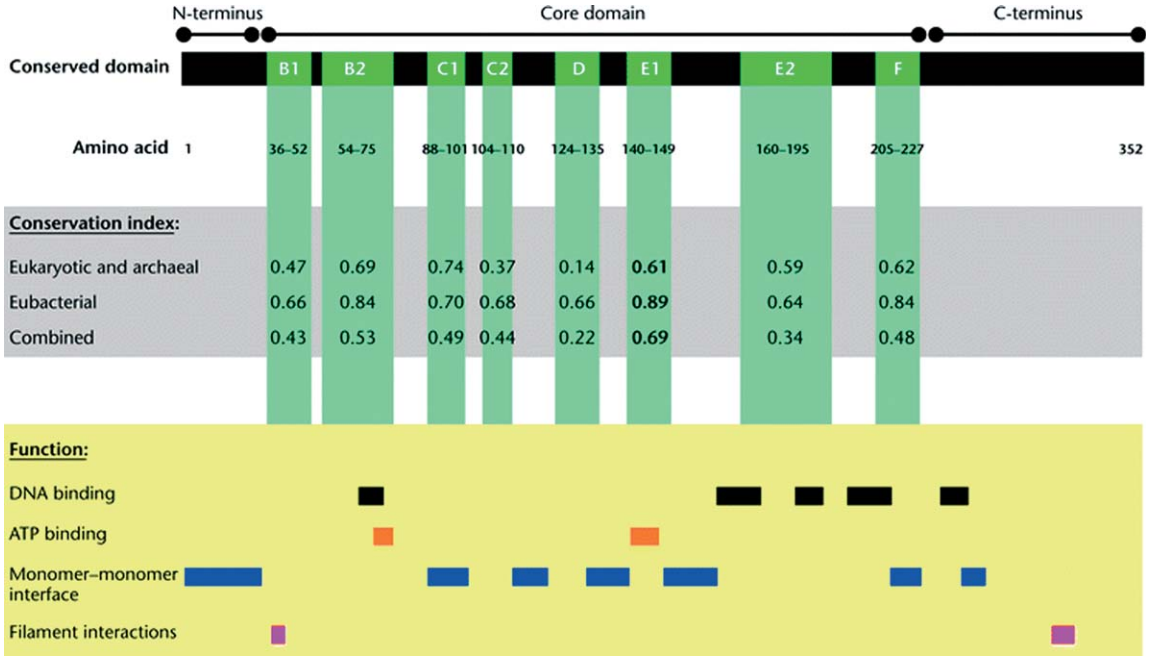

Figure 3 Functional map of the RecA protein. RecA protein is presented as a linear amino acid sequence. There are eight highly conserved subdomains found in all RecA protein homologues. These are highlighted in green, and the amino acids corresponding to each domain are shown at the top of each domain. The conservation index (CI) for each subdomain is shown in the grey box. A CI = 1.00 indicates that this region is invariant in all RecA protein homologues. The combined index is a combined analysis of all RecA protein homologues and the number shown is not an average CI of the eubacterial, eukaryotic and archaeal conservation indices. The functional domains of RecA protein are highlighted in the peach box. The regions involved in DNA binding (black), ATP binding (orange), the monomer–monomer (M–M) interface (blue) and filament–filament interactions (cerise) are displayed.

reaction is the extended, presynaptic filament assembled on ssDNA. The nucleoprotein filament possesses two DNA-binding sites: the primary site, which is required for assembly and is in contact with the ssDNA, and the secondary site, which is constituted only upon filament formation and is located outside the central axis of the filament. The secondary site is responsible for binding both the incoming dsDNA and, following DNA strand exchange, the displaced ssDNA product of this reaction. **See also**: Homologous genetic recombination during bacterial conjugation

DNA strand exchange catalysed by RecA protein is the paradigm for homologous pairing processes *in vitro* (**Figure 4**). The most widely studied substrates are circular ssDNA (isolated from ϕX174 or M13 phage) and linear dsDNA (usually the linearized, replicative forms of these phages). Many pairs of substrates can be used, provided that one of them is at least partially single-stranded. The products of the complete exchange of DNA strands are nicked, circular dsDNA and linear ssDNA.

DNA strand exchange can be divided into three experimentally distinguishable steps: (1) presynapsis; (2) synapsis; and (3) DNA heteroduplex extension (**Figure 4**; Cox and Lehman, 1981). In presynapsis, RecA protein assembles on to ssDNA to form the nucleoprotein species that is active in the homology search. Synapsis is a complex step, conceptually composed of random nonhomologous contacts occurring between the presynaptic complex and naked dsDNA; the search for DNA sequence homology; and base-pair switching, all resulting in the formation of a plectonemic, joint molecule intermediate. DNA heteroduplex extension then completes the reaction by migrating the nascent DNA heteroduplex joint in a polar fashion.

Presynapsis

In this stage of the reaction, RecA protein assembles in an ordered fashion on to ssDNA to produce the active nucleoprotein complex. Due to limitations imposed by DNA secondary structure, RecA protein is unable to form a contiguous nucleoprotein filament. The single-stranded DNA-binding protein (SSB protein) of *E. coli* is an accessory factor whose role is to remove the secondary structure; the SSB protein is then displaced by further binding of the RecA protein. Assembly of RecA protein on to the ssDNA is facilitated by other recombination proteins (RecBCD and RecFOR) that catalyse the loading of RecA protein on to the SSB–ssDNA substrate (Umezu *et al.*, 1993; Anderson and Kowalczykowski, 1997; Morimatsu and Kowalczykowski, 2003). Formation of a contiguous nucleoprotein filament results in the generation of a second DNA-binding site. This second DNA-binding site exists only in the complete nucleoprotein filament, is vacant, and is used to bind a second

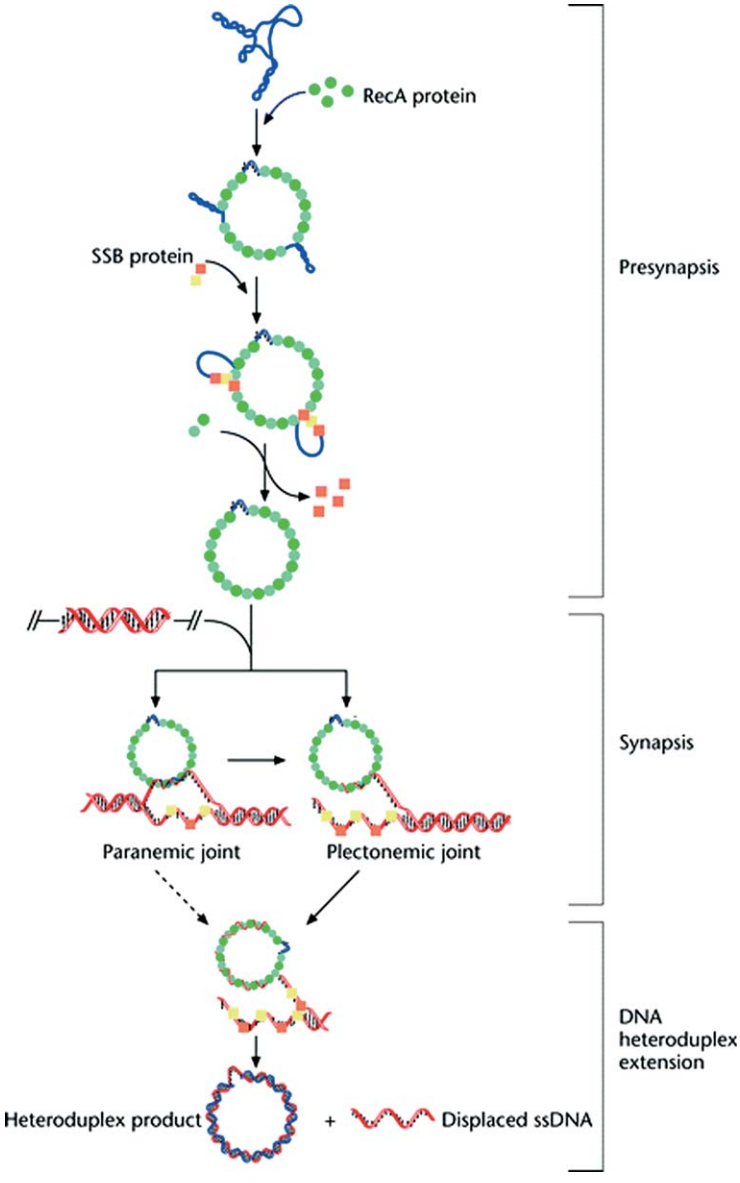

Figure 4 The DNA strand exchange reaction promoted by the RecA protein. RecA protein is represented as round dots and ssDNA-binding (SSB) protein as squares. The three stages shown are presynapsis, synapsis and DNA heteroduplex extension. Adapted from Bianco *et al.* (1998).

DNA molecule (either ssDNA or dsDNA) (Howard-Flanders *et al*., 1984).

Synapsis

During this stage of the reaction, dsDNA binds to the filament and, upon homologous recognition, a plectonemic joint molecule intermediate is formed (defined below). The second DNA molecule binds to the secondary DNA-binding site of the nucleoprotein filament in a sequence-independent fashion. Once bound, a search for homology takes place. The search is rapid, occurring within minutes, and requires that the binding of dsDNA to the secondary site be both weak and transient. The problem of the homology search is analogous to the problem that sequence-specific DNA-binding proteins face in locating their target sequence. However, for RecA protein, the scale of the search problem is much larger: the binding protein is the entire nucleoprotein filament (which can consist of thousands of protein monomers, depending on the ssDNA length). Since the binding of RecA protein to ssDNA is largely nonspecific, specificity in the search process is conferred by the sequence of the ssDNA within the filament. Although the entire nucleoprotein filament is involved in the search

for homology, the minimum length of homology required for recognition is as low as 15 nucleotides *in vitro*, which is somewhat less than that needed *in vivo*, where homologous recombination requires, minimally, about 23–40 bp of homology. **See also**: Protein–DNA complexes: specific

The recognition of homology takes place when the ssDNA within the presynaptic filament hydrogen bonds, presumably via non-Watson–Crick base pairing, to the bound dsDNA, in a mechanism that does not require stable triplex DNA formation (Howard-Flanders *et al*., 1984). How then does RecA protein 'sense' when homology has been located? During the homology search process, the dsDNA is topologically unwound, and is 'tested' for complementarity with the ssDNA within the filament. The recognition of homology between these two DNAs provides the signal to RecA protein that homology has been located, and base switching occurs. This requires a local denaturation of the dsDNA molecule and the coordinate exchange of the identical single strands of DNA. These steps may be simultaneous or separated in time, but the result is the production of an intermediate known as a joint molecule. Immediately after base-pair switching, the heteroduplex dsDNA product occupies the primary site, whereas the displaced ssDNA occupies the secondary site (Mazin and Kowalczykowski, 1998). **See also**: Base pairing in DNA: unusual patterns

Two types of joint molecules may form, depending on the topological constraints of the DNA: either paranemic or plectonemic. A paranemic joint is one in which the individual complementary strands do not intertwine, producing a molecule that is base-paired, but not topologically linked. A plectonemic joint is one in which the incoming single strand is intertwined around its complement, as in native dsDNA. In the reaction displayed in **Figure 4**, paranemic joints form at interior sites of duplex DNA, and plectonemic joints form at the ends of the duplex substrate. Since there are far more internal sites than end sites, paranemic joints are more likely to form and are thus probable intermediates on the reaction pathway to the formation of the more stable, plectonemic joint molecules.

DNA heteroduplex extension

Once a plectonemic joint has been formed, the branch migration phase of DNA strand exchange commences (Cox and Lehman, 1981). During this phase, the DNA heteroduplex in the nascent joint molecule is extended until complete exchange of DNA strands occurs, resulting in a nicked, double-stranded circle. Although kinetically distinct, branch migration may not be a mechanistically separate step, but rather may represent a continuation of plectonemic joint molecule formation. Branch migration proceeds in a 5′→3′ direction relative to the incoming single strand (the same direction as RecA protein polymerization (Register and Griffith, 1985)) at a rate of 2–10 bp s^{-1}, requires ATP hydrolysis and induces torsional stress in the dsDNA.

Noncanonical DNA strand exchange reactions

In addition to the prototypic reaction just described, RecA protein can also promote at least two other types of DNA strand exchange reactions. One is 'inverse DNA strand exchange' (Zaitsev and Kowalczykowski, 2000), so named because the RecA filament is assembled initially on the ds*DNA* and DNA strand exchange is promoted with free ss*DNA*. This is the 'inverse' of the typical reaction. Interestingly, in contrast to conventional DNA strand exchange, the RecA–dsDNA nucleoprotein filament can exchange strands with ssRNA to form an RNA–DNA hybrid. Such an activity may facilitate recombination-dependent replication (Kogoma, 1996) or recombinational DNA repair in the amazingly radiation-resistant organism, *Deinococcus radiodurans* (Kim and Cox, 2002).

A second noncanonical reaction is referred to as a DNA strand exchange '*in trans*' (Mazin and Kowalczykowski, 1999). As the name implies, a RecA protein nucleoprotein filament that is assembled on nonhomologous ssDNA can stimulate DNA strand exchange between dsDNA and free homologous ssDNA that is not within the filament (i.e. *in trans* to the filament). This unusual reaction shows that the RecA nucleoprotein filament can serve as a catalytic surface to activate normally unreactive dsDNA for strand exchange with free ssDNA. Catalysis of this simple collisional reaction suggests that a probable path for the evolution of DNA strand exchange started with the development of a catalytic protein surface (an early RecA protein ancestor) that permitted a heterogeneous surface catalysis. Later, this protein evolved the capacity to assemble, in ATP hydrolysis-controlled processes, into a structure (the filament) that accommodated both homologous DNA molecules within the filament (i.e. *in cis*) to effect a more efficient reaction.

Energetics

RecA protein is a DNA-dependent NTPase with a single active site present in each monomer for the binding and hydrolysis of ATP and other NTPs (Ogawa *et al*., 1978; Roberts *et al*., 1978). However, despite the symmetrical structure of the RecA nucleoprotein filament, many activities display asymmetry at the enzymatic level. The enzyme can hydrolyse ATP with either ss- or dsDNA as cofactor. The active species in ATP hydrolysis is the nucleoprotein filament, with ATP being hydrolysed uniformly throughout the filament and with no detectable enhancement at filament ends. Hydrolysis of ATP to adenosine diphosphate (ADP) results in conformational changes in RecA protein that serve to modulate RecA between the

'high-affinity' and 'low-affinity' DNA-binding states, respectively. **See also**: Adenosine triphosphate

Since ATP hydrolysis coincides with the pairing and exchange of DNA strands, it was initially thought that ATP hydrolysis was a requirement for DNA strand exchange. It is now known, however, that neither the hydrolysis of ATP nor the presence of a high-energy phosphate bond is necessary for DNA strand exchange (Menetski *et al*., 1990). DNA strand exchange requires only that RecA protein assumes the high-affinity ssDNA-binding state brought about by ATP binding. The binding of either the nonhydrolysable analogue of ATP, ATPγS or the noncovalent complex of ADP–AlF_4^-, also induces the high-affinity DNA-binding state of RecA protein and supports DNA strand exchange. Although the hydrolysis of ATP is not required for the exchange of DNA strands, it is needed to dissociate RecA protein from the heteroduplex products of DNA strand exchange once the reaction is complete, to facilitate the bypass of structural barriers such as heterologous sequences and to maintain the polarity of DNA strand exchange.

The Regulatory Role of RecA Protein

The SOS regulon is a group of more than 40 unlinked genes that are controlled by the LexA repressor, and whose expression is induced to high levels following exposure to DNA-damaging agents (Courcelle *et al*., 2001). Proteins with known functions that are encoded by these induced genes (**Table 2**) participate in all aspects of DNA metabolism, acting to excise DNA damage, activate transcription and transport and facilitate the error-prone, recombinational repair of DNA. RecA protein plays a key role as a regulator of the SOS regulon and inducible DNA repair, where it functions as a coprotease, stimulating the autocatalytic cleavage of a number of proteins (Ogawa *et al*., 1978; Roberts *et al*., 1978). **See also**: SOS response

The primary controller of the expression of genes in the SOS regulon is the LexA repressor, which binds to the SOS box of these SOS-inducible genes and limits their transcription. After a DNA-damaging event, such as ultraviolet (UV) irradiation, the coprotease activity of RecA protein becomes 'activated'. Activation occurs due to the generation of ssDNA resulting either from the action of nucleases or from stalled replication forks. The ssDNA is bound by RecA protein in the presence of an NTP cofactor, promoting nucleoprotein filament formation that leads to cleavage of the LexA repressor and induction of SOS genes, including *recA*. Genes with operators that bind LexA protein weakly are the first to be expressed fully (e.g. *recA*). If the damage persists or if sufficiently high quantities of the damaging agent are used, the concentration of activated RecA protein increases, leading to further

Table 2 Genes of the SOS regulon whose function is known

Gene	Gene product function
dinB	Error-prone DNA polymerase IV
dinG	DNA helicase
dinI	Inhibitor of RecA coprotease activity
dinS	Transposase (IS150)
dnaN	DNA synthesis as part of DNA polymerase III
dnaQ	DNA synthesis as part of DNA polymerase III
fis	DNA inversion factor, transcription factor
glvB	PTS system; arbutin-like IIB component
grxA	Glutaredoxin coenzyme for ribonucleotide reductase
ibpB	Heat-shock protein
intE	Prophage e14 integrase
lexA	Represses transcription of ~20 genes by binding to operators
ogrK	Prophage P2 protein
oraA	Regulator, OraA protein
polB	DNA polymerase II
potB	Spermidine/putrescine transport system permease
recA	DNA strand exchange; induces SOS; activates UmuD; SOS mutagenesis
recN	Recombination
recQ	DNA-dependent ATPase and helicase; can both promote homologous recombination and disrupt illegitimate recombination
ruvA	Forms a complex with RuvB; recognizes Holliday junctions
ruvB	Forms a complex with RuvA; branch migration helicase
smpA	Small membrane protein A
smpB	Small membrane protein B
ssb	Binds to ssDNA
sulA (sfiA)	Inhibits cell division
sunB	Enhances synthesis of sigma-32
umuC	Forms a complex with $Umu(D')_2$; subunit of error-prone DNA polymerase V
umuD	Forms complex with UmuC; subunit of error-prone DNA polymerase V
uvrA	Excision-repair nuclease subunit A; part of the UvrABC endonuclease that initiates excision repair
uvrB	Helicase and ATPase; excision-repair nuclease subunit B; part of the UvrABC endonuclease that initiates excision repair
uvrC	Excision-repair nuclease subunit C; part of the UvrABC endonuclease that initiates excision repair
uvrD	Helicase II; required for excision repair

(See Courcelle *et al*. (2001) for additional genes that are induced, but whose function is currently unknown.)

cleavage of LexA protein, and derepression of even those genes whose operators bind LexA tightly (e.g. *sulA*).

Under normal cellular conditions, *recA* expression is repressed and the basal level of RecA protein is maintained at ~1000 molecules per cell. Following LexA repressor cleavage, the level of RecA protein in the cell increases by as much as 20-fold. The increase in the level of RecA protein is rapid, occurring at a rate of 10 molecules s^{-1}, and reaches a maximum within 1 h of a DNA-damaging event. RecA protein levels return to the basal level within 4–6 h following the initial damage event. This reduction is presumably due to removal of the inducing signal via repair of the DNA damage eliminating the agent that activated RecA protein. As a result, the intracellular concentration of LexA repressor increases, since RecA protein is no longer able to induce its cleavage. This reestablishes repression of the SOS system and returns the cell to its uninduced state. **See also**: DNA damage

The Role of RecA Protein in Mutagenic Bypass

When an unrepairable DNA lesion is encountered by DNA polymerase III, replication is stalled until an error-prone lesion bypass can occur. Bypass requires a special error-prone DNA polymerase to insert an incorrect nucleotide opposite the lesion (producing a mutation) and then allowing normal DNA synthesis. This process is referred to as SOS-induced mutagenesis or error-prone repair, and is the last recourse to ensure cell survival when all other error-free processes have acted (Tang *et al*., 1999). **See also**: Mutagenesis

SOS mutagenesis requires high levels of the *umuC* and *umuD* gene products. In exponentially growing *E. coli*, these proteins are expressed at a low, basal level (due to LexA repressor binding to the SOS box of the *umuDC* operon) with approximately 180 UmuD proteins per cell and an undetectable amount of UmuC protein. Following DNA damage, the level of RecA protein increases and this results in (1) the cleavage of the LexA repressor, causing derepression of the *umuDC* operon, leading to an increase in the level of UmuC protein to 200 molecules per cell and of UmuD protein to 2400 copies per cell and (2) the proteolytic processing of UmuD to UmuD′ by the activated RecA protein (Nohmi *et al*., 1988). The *C*-terminal fragment is referred to as UmuD′, and it is the active species in UV-induced mutagenesis (Nohmi *et al*., 1988). Two UmuD′ monomers associate with UmuC to form the $Umu(D')_2C$ complex, which comprises the novel error-prone DNA polymerase V (Tang *et al*., 1999). DNA polymerase V binds to and is targeted by the RecA nucleoprotein filament to a DNA lesion where catalyses is efficient, but error-prone, DNA synthesis across the lesion. This bypass is only the first step of a complex series of biochemical events that permit the mutagenic repair of DNA and the restart of DNA replication; DNA polymerases II, III, IV, V, PriA, RecA, RecFOR and SSB proteins are required minimally.

Summary

RecA protein is an essential component of homologous recombination and DNA repair in *E. coli*. The key, universally conserved, structure in each of these processes is the RecA nucleoprotein filament. It is a ternary complex consisting of RecA protein, ssDNA and an NTP cofactor. This structure has the capacity to bind, in a mutually exclusive manner, dsDNA, LexA repressor and DNA polymerase V. Binding of dsDNA to the filament allows RecA protein to function as a DNA strand exchange protein. Binding of LexA repressor to the filament induces an autocatalytic cleavage that inactivates the repressor, which, in turn, results in derepression of the SOS regulon. Finally, binding of the processed $Umu(D')_2C$ complex, DNA polymerase V, to the filament enables DNA synthesis, although mutagenic, past unrepaired DNA lesions. The *in vitro* capabilities of this specialized nucleoprotein filament are consistent with the roles of RecA protein *in vivo*, and explain the pleiotropic effects of mutations in the *recA* gene. **See also**: Recombinational DNA repair in bacteria: postreplication

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