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DOMAIN 4 SYNTHESIS AND PROCESSING OF MACROMOLECULES:

DNA Helicases

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Abstract

DNA and RNA helicases are organized into six superfamilies of enzymes on the basis of sequence alignments, biochemical data, and available crystal structures. DNA helicases, members of which are found in each of the superfamilies, are an essential group of motor proteins that unwind DNA duplexes into their component single strands in a process that is coupled to the hydrolysis of nucleoside 5′-triphosphates. The purpose of this DNA unwinding is to provide nascent, single-stranded DNA (ssDNA) for the processes of DNA repair, replication, and recombination. Not surprisingly, DNA helicases share common biochemical properties that include the binding of single- and double-stranded DNA, nucleoside 5′-triphosphate binding and hydrolysis, and nucleoside 5′-triphosphate hydrolysis-coupled, polar unwinding of duplex DNA. These enzymes participate in every aspect of DNA metabolism due to the requirement for transient separation of small regions of the duplex genome into its component strands so that replication, recombination, and repair can occur. In *Escherichia coli*, there are currently twelve DNA helicases that perform a variety of tasks ranging from simple strand separation at the replication fork to more sophisticated processes in DNA repair and genetic recombination. In this chapter, the superfamily classification, role(s) in DNA metabolism, effects of mutations, biochemical analysis, oligomeric nature, and interacting partner proteins of each of the twelve DNA helicases are discussed.

INTRODUCTION

DNA helicases are an essential group of motor proteins that unwind (i.e., denature) DNA duplexes into their component single strands in a process that is coupled to the hydrolysis of nucleoside 5′-triphosphates (1, 2, 3, 4, 5). The purpose of this DNA unwinding is to provide nascent, single-stranded DNA (ssDNA) for the processes of DNA repair, replication, and recombination. In *Escherichia coli* there are currently 12 proteins for which DNA helicase activity has been clearly demonstrated (Table 1). These enzymes perform a variety of tasks ranging from simple strand separation at the replication fork to more sophisticated processes in DNA repair and genetic recombination (6, 7, 8, 9).

All DNA helicases share several common biochemical properties, including the binding of single-and double-stranded DNA (dsDNA), nucleoside 5′-triphosphate (NTP) binding and

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hydrolysis, and NTP hydrolysis-coupled, polar unwinding of duplex DNA into its component single strands (Fig. 1). Although the outcome of the action of DNA helicases is the same (i.e., dsDNA unwinding), the manner in which they achieve this goal is quite different. This is dictated by the in vivo role of the enzyme, its oligomeric structure, and the partner proteins with which it interacts (Fig. 2).

In addition to sharing biochemical properties, the primary amino acid sequences of these enzymes are also similar. Similarity, however, is limited to what is now known as “helicase motifs” (10). These motifs impart the ability to bind and hydrolyze nucleoside 5′-triphosphates (for a review, see reference 11). The changes associated with NTP binding, hydrolysis, and product release are coupled to motion and DNA strand separation (12, 13, 14). Thus, the motifs represent the molecular engine of these motor proteins. Outside of these motifs, the proteins are dissimilar, as reflected in their distinct roles within the cell (11).

Helicases can be organized into families. Initially, organization was based entirely on primary amino acid sequence (10). More recently, a new classification has been put forth combining the previous sequence alignments with the vast amount of biochemical data along with available crystal structures (4). The new classification suggests six SuperFamilies of enzymes. In this chapter, the DNA helicases of E. *coli* are presented in alphabetical order. Their SuperFamily (SF) classification, role(s) in DNA metabolism, effects of mutations, biochemical analysis, oligomeric nature, and interacting partner proteins are discussed.

DinG

The *dinG* (DNA-*damage-in*ducible protein *G*) promoter was first isolated in a genetic screen scoring for damage-inducible loci and was subsequently shown to be under the control of the SOS response (15, 16). Deletion of *dinG* has no significant phenotype, thus it is not essential for cell viability. However, deletion of *dinG* and overexpression of the DinG protein both result in a slight UV sensitivity (17).

The purified, 81-kDa DinG protein is a monomeric, SF2 DNA helicase that translocates and unwinds DNA in the 5′ → 3′ direction (17). The helicase activity of DinG is efficient in the presence of either ATP or dATP and divalent metal cations. It can unwind DNA-RNA hybrids, forked DNA structures, D-loops, and R-loops (18). The substrate specificity is similar to that of RecG, may also play a role in recombinational DNA, like RecG, may also play a role in recombinational DNA repair and the resumption of replication following DNA damage (18, 19).

Intriguingly, DinG contains an iron-sulfur cluster that has been proposed to act as a sensor of the intracellular redox potential (20). The cluster is positioned in the helicase domain of the protein and is sensitive to modification by nitric oxide (NO). Modification by NO inactivates the helicase activity of DinG and this is thought to contribute to NO-mediated genomic instability (20).

DnaB

DnaB was initially identified as a bacteriophage ϕX174 replication factor (21, 22, 23, 24, 25). Genetic analyses demonstrated that *dnaB* is required for DNA replication of the *E. coli* chromosome (26, 27, 28, 29). In fact, DNA replication ceases abruptly upon a shift to the nonpermissive temperature using some $dnaB^{ts}$ alleles, consistent with a role of DnaB in propagation of the replication fork (30). It is now clear that DnaB is the replicative helicase and, as such, is intimately associated with moving DNA replication forks (31, 32, 33). Not surprisingly, inactivation of DnaB leads to collapse and degradation of replication forks (30).

DNA synthesis at replication forks is mediated by a multiprotein assembly called the replisome, which accomplishes concerted DNA synthesis on both the leading and lagging strands (34, 35). DNA replication initiates when the DnaA protein binds to *oriC* (the origin of replication), opens the duplex, and facilitates transfer of a DnaB hexamer from a stoichiometric DnaB:DnaC complex to each of the template strands (36, 37, 38, 39, 40, 41, 42, 43). This results in formation of an active DnaB homohexamer on each strand and ultimately leads to assembly of two replisomes (44). These subsequently move away from one another, bidirectionally around the chromosome, driven by the helicase activity of DnaB, with replication terminating when the two forks meet at *ter* (the terminus of replication) (35). Termination most likely results from the impeding of the helicase action of DnaB by the Tus-*ter* interaction. Tus is a monomeric, site-specific DNA binding protein that binds to 23-bp *ter* sites that are positioned approximately opposite *oriC* (41, 45, 46). The Tus-*ter* block is polar so that forks approaching from one direction pass through unimpeded, while those arriving from the opposite direction are blocked.

Purified DnaB protein is 52,390 Da in mass and, in its active state, DnaB oligomerizes into a homohexameric ring that encircles one strand of the melted duplex and possesses NTPase and DNA helicase activity (47, 48, 49, 50, 51, 52, 53, 54) (Fig. 3). Each subunit of the hexamer contains two domains that are important for function. The N-terminal one-third is an α-helical domain that is required for helicase activity (55, 56, 57, 58). Together with the linker to the C-terminal region, the N-terminal domain of DnaB also mediates the protein's interactions with the primase, DnaG, which is recruited to DNA by DnaB (6, 59, 60). The C-terminal domain of DnaB, which comprises approximately two-thirds of the protein, contains the NTP binding site of the enzyme and is the principal organizing factor for ring formation (55).

DnaB unwinds DNA in the 5′→3′ direction on the strand it encircles, resulting in displacement of the complementary strand. The reaction is fueled by any rNTP, although there is a preference for purine nucleoside triphosphates (22, 23, 47, 48, 61, 62, 63). Both the helicase and ATPase activity are increased by interactions with primase and the DNA polymerase III holoenzyme (Pol III); the latter interaction is mediated by tight binding to the Tau subunit of Pol III that essentially cements the replisome together (6, 32). In the absence of enhancing factors, DNA unwinding by DnaB occurs at a rate of 35 bp/s (32). Once DnaB interacts with the DNA polymerase, the unwinding rate increases up to 29-fold, to rates approaching ~1,000 bp/s (64).

In contrast, the translesion DNA polymerases Pol II and Pol IV have the opposite effect on DnaB. Here, they bind to the helicase, possibly displacing Pol III from the replisome and then slow the rate of DNA unwinding to 1 bp/s (65). This drastic reduction in unwinding rate is proposed to give either the translesion polymerases time to act or to allow the nucleotide excision repair machinery sufficient time to repair lesions prior to the arrival of the advancing replication fork. Once repair has occurred and interactions with Pol III are restored, rapid unwinding, coupled to DNA synthesis via the DnaB-Tau/Pol III interaction resumes.

HELICASE III

This was the third DNA helicase discovered in *E. coli*, hence its name. Despite being identified as a DNA helicase almost 30 years ago, very little is known about this enzyme. Although the gene has yet to be cloned, the protein has been purified to near homogeneity from cells where it was expressed from its chromosomal promoter (66). The resulting protein is 20 kDa in mass, exists as a dimer in solution, and does not form higher order oligomers (66). Helicase III is an ssDNA-dependent ATPase exhibiting very little activity in the presence of dsDNA suggesting that, like many other DNA helicases, it requires a ssDNA tail on which to load. Once loaded, translocation is in the 5′→3′ direction (67). The role of helicase III is unknown.

HELICASE IV

helD is located at 22 minutes on the chromosome and encodes an 82-kDa protein (68). This enzyme was the fourth DNA helicase discovered in *E. coli* and is similar in sequence to both Rep and UvrD (68, 69). It unwinds short duplexes (<100 bp) in the 5′-to-3′ direction in a reaction coupled to the hydrolysis of ATP (70, 71). Helicase IV was initially suggested to have an in vivo role in the RecE and F recombination pathways as Δ*helD*, Δ*uvrD* strains were defective for both conjugational and transductional recombination in both *recBC sbcB(C)* and *recBC sbcA* backgrounds (72). However, and in contrast to this earlier study, insertion mutations in *helD* and double insertions in *helD* and *uvrD* were unaffected for either conjugational recombination or survival following UV irradiation, effects that were independent of the genetic background used (73). Thus, although HelD's in vivo role is still unclear, it may have antirecombinational properties (73). This follows as loss of the antirecombinational properties of *helD* function to suppress mutations in *recJ* by stabilizing recombination intermediates formed in the absence of RecJ exonuclease function.

PriA

PriA (*pri*mosomal protein A) was originally known as factor Y and as protein n′ and is required for the conversion of single-stranded ϕX174 DNA to the duplex, replicative form in an in vitro-reconstituted system (reiewed in references 74 and 75). Here, PriA binds to an ssDNA hairpin structure in ϕX174 called PAS, for n′-*primosome assembly* site, leading to the subsequent assembly of the primosome, a complex responsible for primer RNA synthesis and duplex DNA unwinding at a replication fork (75, 76). Formation of the primosome occurs in an ordered fashion (75). Following binding of PriA to PAS, the complex is then

recognized and bound by PriB, PriC, and DnaT. Formation of the primosome proceeds with the subsequent actions of DnaB, DnaC, DnaT, and primase (74, 75).

In addition to its role in ϕX174 DNA replication, genetic analyses of *priA* mutants demonstrate that PriA plays crucial roles in cellular responses to replication fork arrest (74, 75, 77, 78). Null mutations in *priA* result in a complex phenotype that includes constitutive induction of the SOS response, defects in the repair of UV-damaged DNA, DNA double-strand break repair, and homologous recombination, and these mutants exhibit defects in both constitutive and induced stable DNA replication (79, 80, 81, 82, 83). Collectively, these data suggest that PriA plays a key role in replisome assembly at sites distinct from *oriC* in a process that facilitates replication restart following fork stalling and/or DNA breakage (7, 74, 84).

The 82-kDa PriA protein consists of two domains (85, 86). The N-terminal 181 aa are associated with DNA binding, while the C-terminal 551 aa contain the ATP binding and DNA helicase motifs that are interrupted by two, C4-type, zinc finger motifs. These Zn-finger motifs are essential for in vitro primosome assembly on PAS, for recombination-dependent DNA replication in vivo, and for interactions with other primosomal proteins (87, 88, 89).

The DNA binding properties of PriA, mediated by the N terminus, are consistent with its activity at stalled replication forks. It binds with high affinity to D-loops and to model fork structures in vitro (90, 91, 92). This binding is mediated through specificity for DNA strands with accessible 3′ ends (93). PriA has been assigned to helicase SuperFamily 2 and has been shown to unwind DNA with a 3′→5′ polarity in vitro (94, 95). DNA unwinding is fueled by the hydrolysis of ATP (dATP) and is site specific (i.e., PAS), structure specific, and ssDNA dependent (96). In addition, DNA unwinding of model fork substrates is stimulated by the single-stranded DNA binding protein (SSB protein). This stimulation involves both a physical and functional interaction between the two proteins (97). As for several other proteins at the replication fork, the physical interaction is mediated via the C terminus of SSB protein (reviewed in reference 98).

Once bound to a stalled replication fork, PriA displays two types of activities. The 3′→5′ helicase activity is responsible for unwinding any lagging-strand DNA present at the fork, thereby generating a single-stranded DNA binding site for DnaB (90). The second activity is loading of DnaB onto the lagging-strand template via a complex series of protein-protein interactions reminiscent of primosome assembly for ϕX174 DNA (74, 75, 78). Here, it facilitates assembly of a multiprotein complex that includes PriB and DnaT and the helicase activity of PriA is not required (78). This leads to loading of the replicative helicase, DnaB, from a DnaB-DnaC complex onto SSB-coated ssDNA. Once DnaB has been loaded a new replisome forms, leading to the resumption of DNA replication (74, 99).

RecBCD

RecBCD enzyme is a multifunctional, multisubunit DNA helicase-nuclease involved in genetic recombination, DNA repair, maintenance of cell viability, and degradation of both foreign and damaged DNA (8, 100, 101, 102). As a result of its nuclease activity, the

enzyme was originally known as Exonuclease V (103). It is composed of three separate, nonidentical polypeptides—RecB (134 kDa), RecC (129 kDa), and RecD (67 kDa)—which assemble into the heterotrimeric holoenzyme, RecBCD. In vitro, the enzyme is both a destructive exo- and endonuclease, and a highly processive DNA helicase (8, 102, 104, 105, 106, 107). The degradation of duplex DNA coincides with the unwinding of dsDNA and occurs as a result of endonucleolytic cleavage of the unwound ssDNA (102, 108).

Although the nucleolytic activities are sequence independent, RecBCD enzyme will also recognize chi sites (chi = χ = *c*rossover *h*otspot *i*nstigator), which are known hot spots for genetic recombination (109, 110, 111, 112). The interaction of the translocating enzyme with a chi-site in vivo stimulates RecBCD enzyme-dependent recombination in its vicinity (109, 110, 113, 114). Stimulation of recombination by the χ sequence occurs primarily to the 5′ side of the χ site, requires a functional RecBCD enzyme, and, as such, plays a central role in the primary recombination pathway of E. coli, the RecBCD pathway. Chi is recognized by the translocating RecBCD enzyme as the single strand of DNA containing the sequence 5′-GCTGGTGG-3′ (115). The recognition of χ is critical to RecBCD because it serves to regulate the nuclease activity and translocation velocity of the enzyme, and to stimulate its ability to direct the loading of the DNA strand exchange protein, RecA, onto the strand of DNA containing χ (116, 117, 118, 119, 120, 121).

The interaction of the translocating enzyme with chi elicits a complex set of responses in the multi-subunit complex (Fig. 4A). Prior to interacting with chi, the endonucleolytic activity of RecBCD cleaves the chi-containing strand more vigorously than the χ-complement strand (116). Upon encountering an appropriately oriented chi sequence, the translocating enzyme is induced to pause for several seconds (120), resulting in cessation of endonucleolytic degradation of the DNA strand containing the χ sequence, 4 to 6 nucleotides to the 3′ side of χ (111, 112). Thus, chi defines the locus for the last cleavage event on the χ-containing strand of DNA. Concurrently, the nuclease activity on the χ-complement strand is stimulated severalfold (116, 122). Continued unwinding by RecBCD enzyme generates a ssDNA molecule downstream from χ, onto which RecA protein is preferentially loaded (123). It is this same strand of DNA that is then utilized in RecA protein-dependent homologous pairing reactions in vitro (124, 125). Thus, the χ sequence is a regulatory element that alters the recombinational properties of RecBCD, converting a destructive endonuclease into a recombinogenic enzyme.

In addition to being a complex nuclease, the enzyme is one of the most rapidly unwinding and processive DNA helicases studied to date (104, 105, 126). It is capable of unwinding dsDNA at rates greater than 1,000 bp/s with a maximum processivity of 43,000 bp (126). The reason for the rapid speed of translocation was revealed through careful biochemistry and the crystal structure (Fig. 4B) (127, 128, 129, 130). These studies revealed that the RecB and RecD subunits are simultaneously active helicases that couple the hydrolysis of ATP to DNA translocation and strand separation by pulling DNA into the holoenzyme, and through RecC, where strand separation occurs (127, 130). For this to occur, RecB and RecD must translocate on opposite strands of the DNA duplex and accordingly, with opposite polarity: RecB in the 3′−5′ direction and RecD in the 3′−5′ direction. In addition, the structure also shows that, although RecC has no demonstrable enzymatic activity, it does have key roles in

RecBCD enzyme function. It acts as a scaffold onto which RecB and RecD assemble, it is intimately involved in strand separation, and it is responsible for χ-recognition (131, 132).

In addition to translocating with opposite polarity, the two helicases are thought to move at different velocities, with RecD being the more rapidly moving motor. Surprisingly, and in addition to altering the nucleolytic activities of RecBCD, the interaction with chi also affects the translocation velocity of RecBCD, causing it to reduce speed by a factor of 2 following the pause at chi (120). The current model for the change in velocity is that prior to chi, both RecB and RecD are operating at their maximum speeds. At chi, RecD is shut down so that the only remaining motor is the more slowly moving RecB subunit. The shutting down of RecD is consistent with both in vivo and in vitro results arguing for a RecD-associated change in the enzyme elicited by the interaction with an appropriately oriented chi sequence (119, 122, 134, 135, 136).

Finally, RecBCD contains a single nuclease active site that resides within the C terminus of the RecB subunit and is positioned approximately opposite the entry point of dsDNA into the holoenzyme (Fig. 4B) (129). To feed this active site, DNA is unwound in a series of events. First, the leading domain of RecB reaches out ~23 bp ahead onto the DNA and pulls the duplex into the enzyme where it is split by RecC (Fig. 4B and C) (129, 137). This is followed by several smaller steps of 4 to 5 bp that allow the back end of the enzyme to catch up to the front (138). The combination of these actions results in what has been called a quantum inchworm mechanism for translocation and DNA unwinding (137), where on average, 3 ATP molecules are utilized per base pair unwound (105). The unwound strands of DNA are the tracks on which RecB and RecD translocate and which are subsequently fed into the nuclease site of the enzyme where they are cleaved asymmetrically (116). The differential rates of cleavage of the two strands are proposed to be controlled by a gating mechanism that determines which strand is fed into the cleavage site (129). Not surprisingly, this gating mechanism is thought to be controlled by the interaction with chi (129).

RecG

RecG protein was identified as a mutation that mildly affected recombination and survival after UV-irradiation (139). Subsequent studies demonstrated that it participates in all three pathways of recombination and that it has an overlapping function with the products of the ruvA and ruvB genes (140, 141). The protein possesses ATPase and DNA helicase activities, consistent with its primary sequence containing a Walker A motif and similar to the DEXH class of DNA and RNA helicases (140, 142). It has been classified as a member of the SF2 DNA helicases and nucleic acid translocases (4).

In vitro analyses showed that RecG is a $3'\rightarrow5'$ polarity DNA helicase with a variety of roles in DNA repair and recombination (143, 144). The 76-kDa enzyme functions as a monomer binding specifically to stalled replication fork substrates (and a variety of structures resembling these such as R-loops, D-loops, and Holliday junctions) and subsequently processes them into structures that can be acted on by additional members of the recombination machinery (145, 146, 147, 148).

Once loaded at a stalled replication fork, RecG is thought to regress these away from the site(s) of DNA damage. Stalled replication fork regression is a process that involves net backward movement of the fork, away from the site of DNA damage, concomitant with the unwinding of nascent heteroduplex arms to form a four-stranded, Holliday junction-like structure or “chicken foot” (Fig. 5B) (149). The rate of fork regression is 240 bp/s with the enzyme hydrolyzing 1 ATP to track a distance of 3 bp (150, 151). The similarity of the resulting regressed DNA structures to Holliday junctions suggests that following the action of RecG, further processing is performed by RuvAB (145, 146, 152).

Analysis of the crystal structure of the enzyme bound to a stalled replication fork DNA substrate revealed that RecG can be divided into two domains (Fig. 5A) (147). The first is the wedge domain that confers the ability to bind to all of the above-mentioned branched DNA structures. Binding via this domain is responsible for clamping the enzyme tightly onto the DNA, splitting the junction and stabilizing the unwound fork (147). The wedge domain is coupled to the helicase domain, via an α-helical linker. The helicase domain contains the canonical “helicase” motifs and, with use of the energy released from ATP hydrolysis, drives the enzyme. An additional and more recently identified motif also present in this domain is the TRG motif; TRG is *t*ranslocation by RecG (Fig. 5A) (153). The TRG motif forms a helical hairpin linked to a loop projecting into the proposed dsDNA binding channel positioned between the helicase and wedge domains (153). Mutations in TRG disrupt unwinding of HJ and forked DNA structures in vitro (154).

In addition to being able to process a variety of branched DNA structures in vitro, RecG exhibits significant ATPase activity on (−)scDNA, ssDNA, and SSB-coated M13 ssDNA (155, 156). This suggests different ways for RecG to access a stalled replication fork, dictated by the types of DNA that might be available at the fork. The strong preference that the enzyme exhibits for (−)scDNA in vitro, suggests that DNA must first be converted from (+)- to (−)scDNA for RecG to function (156). Once the DNA is in this form, RecG catalyzes fork regression efficiently (152).

Activity on SSB-coated M13 ssDNA is intriguing because it involves a species-specific, protein-protein interaction between RecG and SSB (155). This interaction is mediated through the C-terminal tail of SSB, similar to that observed for Exonuclease I, PriA, RecQ, and Topoisomerase III (97, 157, 158, 159, 160). Further, this interaction is key to RecG function at a stalled fork since the enzyme can be directly loaded onto the DNA in single-stranded regions and is consistent with the role of SSB in targeting repair helicases to active forks in vivo (Fig. 5B) (155, 161).

Genetic studies have shown that *recG* mutants are only mildly recombination deficient and exhibit only a mild sensitivity to UV irradiation (139). This has led to proposals suggesting RecG is not critical to fork repair in contrast to many in vitro studies (162, 163, 164, 165). Careful microscopic analysis has shown that the interpretation of in vivo data in the absence of RecG can be misleading because, in *recG* cells, there is a pathological cascade of unregulated replication initiation at D- and R-loops and other DNA structures resulting from multiple fork collisions (166, 167). So while *recG* cells survive UV irradiation and give the appearance of a “mild phenotype,” direct examination of their chromosomes showed that

they exist in a disastrous state. Thus, in addition to its proposed role in fork regression, and as a consequence of its ability to disrupt branched DNA structures, RecG plays a key role in limiting replication initiation at sites distinct from *oriC*.

RecQ

RecQ protein was identified as a mutation that increased resistance to thymineless death (168). The *recQ* gene maps to 86 minutes on the E. coli chromosome and is positioned between two genes, *pldA* and *pldB*, that encode enzymes involved in phospholipid degradation (168, 169). Subsequent studies demonstrated that the recQ gene is under the control of the SOS regulon and that its expression is tightly regulated due to the presence of a noncanonical Shine-Dalgarno sequence and GTG initiation codon (170). Although *recQ* is not required for cell survival, overexpression of the RecQ protein is detrimental to the cell (171).

In a *recBC sbcB* background, the *recQ1* mutation (a null phenotype) exhibits a 20-fold increased sensistivity to UV irradiation and a 20- to 70-fold decrease in conjugal recombination efficiency, indicating a role in the RecF recombination pathway (168). This has been more clearly elucidated in a recent in vitro study reconstituting the early part of the RecF pathway by use of purified proteins (172). RecQ is also involved in the RecE pathway of homologous recombination and, in a *recBC sbcA* background, mutations in the gene impair circular dimer plasmid recombination (173).

The 609-amino-acid RecQ protein is 68,364 Da in mass. The purified protein is an r- and dATPase and a DNA helicase that unwinds duplex DNA in the 3′ to 5′ direction (174). RecQ is classified as an SF2 DNA helicase (4). For DNA unwinding to occur, RecQ forms higher order oligomers with the minimal complex being a trimer (175). SSB protein stimulates DNA unwinding and also physically interacts with RecQ via its C terminus (158, 175). This protein-protein interaction is critical to the role of RecQ in maintaining genomic stability (98, 176).

Initially, RecQ was thought to require a single-stranded DNA tail to initiate DNA unwinding (174). Subsequent work demonstrated that the enzyme is more promiscuous in its substrate requirements and is capable of acting on a variety of branched DNA structures and recombination intermediates (177). These data suggested that RecQ could function as both a recombination initiator and as a disruptor of aberrant recombination events. Further biochemical analyses demonstrated that RecQ, in concert with Topoisomerase III, can fully catenate supercoiled plasmid DNA molecules. Here, RecQ was shown to unwind the duplex, thereby providing a substrate for Topoisomerase III (178). More recently, the RecQ-TopoIII enzyme pair was shown to have a role in resolving converging replication forks, consistent with the role of RecQ in maintaining genomic stability (159). Critically, the interaction between RecQ and SSB, and between TopoIII and SSB, plays a key role in facilitating the actions of RecQ-TopoIII enzyme pair in the resolution of converging forks.

Rep

Rep protein was the first helicase discovered in *E. coli* (179). It was identified by its requirement for the replication of genomes of several small phages such as ϕX174 (180,

181). The enzyme is now classified as a member of helicase SF1. It possesses an intrinsic 3′→5′ DNA helicase activity, unwinding DNA with limited processivity of ≤400 bp (182, 183, 184). Although it is monomeric in solution, it dimerizes on binding to DNA and this oligomerization may be required for its helicase activity (185).

Although Rep is a crucial component in the replication of a number of phage replisomes, it is not required for replication initiating at *oriC* in vitro (186). Cells lacking Rep do not halt DNA synthesis, consistent with Rep not being the replicative DNA helicase, although replication does proceed at a reduced rate and the average number of growing replication forks per cell increases in a *rep* mutant (187, 188). These data suggest that the role of Rep in vivo is somehow related to problems facing an advancing replication fork and may play a role in rescuing stalled forks as well (189).

Here, Rep may perform at least two functions that may be dictated by the binding modes of the helicase to model fork structures. These modes are similar to that of PriA but occur with opposite polarity and enable Rep to recognize stalled replication forks with different positions of nascent DNA (7). In either mode, the limited processivity of Rep may be used to permit enzyme function and to rapidly dissociate the protein from the DNA once its work is complete, thereby permitting the resumption of processive, DnaB-driven DNA replication (7).

The first binding mode of Rep facilitates removal of proteins bound to dsDNA ahead of an advancing fork (190, 191, 192). The enzyme, however, cannot displace RecA filaments bound to ssDNA (193). A second role is in the repair of a stalled replication fork in conjunction with PriC, which functions to target Rep to the fork (7, 99, 194). Here, the enzyme is directed to primarily unwind the nascent lagging strand (195). The interaction with PriC is important because it is involved in a PriA-independent pathway for Rep-mediated, replication fork restart (99, 194). Consistently, Rep binds DnaB, an interaction that is disrupted by DnaC binding to the replicative helicase (189).

RuvB OR (RuvAB)

The RuvB helicase functions as an integral component of the RuvABC hetero-oligomeric enzyme that plays a key role in the late stages of homologous recombination and in DNA double-strand break repair (9, 164). The RuvAB complex is responsible for branch migration of Holliday junctions (HJ), which are central, four-stranded recombination intermediates, while the RuvABC complex is responsible for HJ cleavage (Fig. 6). Similarly, RuvAB is involved in processing regressed stalled replication fork structures and RuvABC may be involved in cleavage of various intermediates generated by stalled fork processing (196, 197).

The RuvAB complex is composed of two nonidentical subunits encoded by the *ruvA* and *ruvB* genes (198). Mutations in either of these genes results in a slight UV sensitivity and a moderate defect in recombination (9). However, when mutations in either gene are coupled with a *recG* mutation, the resulting double mutants are severely defective for recombination and for survival following DNA damage (199). This indicates that RuvAB and RecG catalyze the same or overlapping function. Consistent with this proposal, biochemical

analyses of both RecG and RuvAB demonstrated the capability to process recombination intermediates and synthetic Holliday junctions (146, 200, 201, 202, 203).

The active branch migration complex shown in Fig. 6, consists of at least a symmetric tetramer of RuvA protein (monomer mass, 22 kDa) which binds one face of the Holliday junction (204, 205) and two homohexameric rings of RuvB (monomer mass, 37 kDa) which function as chemomechanical motors to drive branch migration (206, 207, 208). The resolution complex forms when a RuvC dimer (monomer mass, 19 kDa), responsible for HJ cleavage at the crossover point (209, 210, 211), associates with RuvAB. Branch migration and junction cleavage require the coordinated actions of all three proteins (9).

Branch migration by RuvAB occurs in the $5'-3'$ direction and requires a screw motion and lateral pulling or pumping of the dsDNA, which passes through the center of the RuvB hexamers, and over the surface of the RuvA tetramer, which uses four acidic pins (residues Glu55 and Asp56) to direct the path of each DNA strand through the complex (205, 212, 213, 214, 215). How does RuvB facilitate the screw motion? Two models have been proposed. The first involves a static RuvA-RuvB interaction, with a subset of RuvB monomers within each hexamer participating in passage of DNA and ATPase activity (216). The second proposes a rotation of RuvB hexamers around the dsDNA, relative to the RuvA complex (214). Rotation is brought about by ATP hydrolysis and is driven by interactions of RuvB monomers with the DNA and RuvA. Thus, RuvB may function as a rotating DNA motor, analogous to the F_1-ATPase another AAA^+ motor (217, 218).

For branch migration to occur, the RuvAB complex must assemble at a Holliday junction. Here, RuvA (a stable tetramer [202]) binds to a dimer of RuvB and the complex binds to the HJ in a reaction that requires only Mg^{2+} ions (206, 219, 220). Thereafter, the remaining 10 monomers of RuvB bind to complete the formation of the diametrically opposed hexameric rings sandwiching the RuvA-HJ complex. The binding of ATP and its subsequent hydrolysis coupled to branch migration ensues.

RuvA plays an essential role in branch migration by RuvAB (9). (i) It functions to change the configuration of a Holliday junction to an open-square structure that is energetically more favorable for branch migration. (ii) It targets RuvB to the junction and stimulates its DNA helicase activity. (iii) It facilitates binding of RuvC leading to resolution.

Structural analysis of RuvA reveals that the protein consists of three domains. Domains I and II constitute the core of the protein which is capable of tetramer formation and HJ binding (212, 221). Domain III, which is flexible, interacts with RuvB and modulates its ATPase and consequently its branch migration activity as well (221, 222). Because the ATP binding sites in each of the subunits of RuvB are nonequivalent, ATP hydrolysis moves in cyclic fashion around the hexameric ring (223).

The rate of passage of the cyclical motion of ATP hydrolysis is thought to be regulated by domain III of RuvA (222). These cyclical passages of ATP hydrolysis around the hexameric RuvB rings may be directly responsible for the screw motion producing branch migration. Each RuvA monomer also contains acidic pins that are crucial to branch migration. They

facilitate junction targeting by restricting binding to duplex DNA and also constrain branch migration by RuvAB in a manner critical for junction processing (213).

Two types of RuvA-junction DNA complexes have been observed. The first contains one RuvA tetramer bound to the junction, while the second contains two tetramers with the junction sandwiched in between (224, 225, 226). The latter complex is thought to correspond to the active branch migration motor and the former, the resolvase (with a RuvC dimer replacing the missing tetramer). However, this remains to be rigorously demonstrated.

RuvB is the DNA helicase or molecular motor that drives branch migration in a 5′ to 3′ direction (227). It has intrinsic ATPase activity that is synergistically enhanced by RuvA and DNA (223, 228). Structural analysis of RuvB indicates that it contains the core fold of the AAA^+ ATPase SuperFamily (ATPases associated with various cellular activities) (214). It is classified as an SF6 hexameric DNA helicase (4).

The RuvB monomer can be divided into three domains. The *N*-terminal and *M*iddle domains are structurally similar to equivalent domains in other AAA^+ family ATPases, except that a unique β-hairpin protrudes from the N-terminal domain (214, 229, 230). The β-hairpin physically interacts with RuvA and is required for formation of the RuvAB complex (231). Domain C of RuvB contains a winged-helix motif, which is topologically similar to the DNA binding domains of metallothionein repressor SmtB and histone H5 (214, 229, 230). The enzyme is typically hexameric bound to DNA, with one hexamer positioned on each side of RuvA and each encircling the DNA duplex (Fig. 6) (215, 232, 233).

RuvC protein (19 kDa) is functional as a stable dimer that binds to RuvA in the context of RuvAB leading to endonucleolytic cleavage of HJs (9, 234). In vitro studies confirm that RuvC specifically interacts with and resolves Holliday junctions by endonucleolytic cleavage. DNA cleavage occurs via the introduction of symmetrical nicks at the consensus sequence 5′-(A/T)TT↓(G/C), where ↓ represents a cleavage site close to the crossover point (235). Following cleavage, the resolution process is completed by DNA ligase.

TraI (OR HELICASE I)

Helicase I was the first helicase to be identified by its DNA-dependent ATPase activity (236, 237). It was found to map to the *traI* gene on the F plasmid (238). DNA helicase I or TraI is a 192-kDa, bifunctional protein that is essential for transfer of bacterial genes during conjugation (238, 239, 240, 241). It catalyzes two distinct but functionally related reactions. The first is a site-, and DNA strand-specific transesterification or DNA relaxation reaction (242, 243). This produces a nick in the DNA duplex that is required for the initiation of DNA strand transfer (244). The second activity is a DNA helicase activity that is directly responsible for the passage of a single DNA strand from one cell to another (236, 237, 245).

The TraI protein can be divided into three domains: the N-terminal 310 aa contain the transesterase activity, residues 990 to 1450 contain the DNA helicase domain, while residues 1451 to 1702 constitute a C-terminal domain that is thought to be involved in protein-protein interactions with other components of the relaxosome (246).

In vitro, TraI is a ssDNA-dependent NTPase that translocates with a 5′ to 3′ directional bias and requires at least 20 nt of ssDNA for unwinding of dsDNA. Once initiated, the enzyme unwinds at least 850 bp of dsDNA per binding event under steady-state conditions at average rates of 1,100 bp/s (237, 247). Early reports suggested that the enzyme functions in a multimeric state, as evidenced by formation of aggregates at low ionic strength and low ATPase activity at KCl concentrations of 150 mM (236, 248, 249). It is now clear, however, that TraI functions as a monomer (247).

UvrD (HELICASE II)

UvrD protein or Helicase II is a member of helicase SuperFamily I and has important functions in methyl-directed mismatch repair (MMR) and nucleotide excision repair (NER) and may also act to displace proteins such as RecA at replication forks or ssDNA gaps embedded within in dsDNA (250, 251, 252, 253, 254). The enzyme was originally purified as a DNA-dependent ATPase known as ATPase I and was subsequently shown to be a DNA helicase now known as UvrD (255, 256, 257, 258).

The UvrD protein is encoded by the uvrD gene that maps to ~84 min (256, 259). This gene has, at various times, been called *uvrE*, *recL*, and *mutU* (260). Mutations in *uvrD* result in increased mutation frequency, enhanced sensitivity to UV irradiation, and other DNA damaging agents and allele-specific affects on recombination, with some conferring enhanced recombination frequencies and others conferring a reduction (for reviews, see references 8 and 261). These phenotypes have led to the suggestion that UvrD may have both recombinogenic and antirecombinogenic roles (253, 262).

The UvrD helicase is 82 kDa in mass and can initiate DNA unwinding from ssDNA tails and gaps, proceeding in the 3′ to 5′ direction and with limited processivity. It can also initiate unwinding from both nicks and blunt ends, albeit at significantly higher enzyme concentrations (263, 264, 265). DNA unwinding is stoichiometric because it depends on the ratio of DNA to protein. In addition to being able to unwind duplex DNA, UvrD can also separate RNA-DNA hybrids, which it does so more efficiently than DNA-DNA substrates (266, 267). Single-molecule studies have revealed an unusual strand-switching property of the enzyme that may assist UvrD in clearing proteins bound to both strands of the DNA (268). This strand-switching involves DNA unwinding in the 3′ to 5′ direction, followed by a switch to the opposite strand with the resumption of translocation leading to reannealing of the unwound strands.

Although the enzyme can oligomerize and form stable homodimers that are active for DNA unwinding (269, 270), UvrD is fully active in vivo and in vitro as a monomer (12, 271). In addition, UvrD and Rep share 40% sequence homology, have similar crystal structures, and can form heterodimers that are functional DNA helicases (12, 272, 273, 274). The significance of heterodimer formation is unclear, however. Analysis of several crystal structures formed in the presence of DNA and ATP hydrolysis intermediates revealed that the monomeric enzyme unwinds DNA via a two-part power stroke using a combined wrench-and-inchworm mechanism (12).

Its ability to unwind duplex DNA from a discontinuity in the phosphodiester backbone of duplex DNA underpins the role of UvrD in NER and in MMR.

In nucleotide excision repair, sites of damage are recognized by the NER proteins UvrA and UvrB, which recruit UvrC to catalyze dual incisions in the DNA at sites which flank the damaged region (for a review, see reference 254). UvrD then unwinds the DNA to excise the damage-containing oligonucleotide, thereby facilitating release of UvrC (275). Similarly, during MMR, UvrD initiates DNA unwinding at an incision made at an adjacent hemimethylated GATC sequence (251). The resulting excised oligonucleotide containing the site of DNA damage is subsequently degraded by an exonuclease. Repair synthesis, followed by DNA ligation, fully restores the duplex. To perform its function in mismatch repair, UvrD interacts with MutL, which modulates its DNA helicase activity (276). In nucleotide excision repair, UvrD interacts with UvrB and not with UvrAB (277), although the UvrAB complex modulates the DNA helicase activity of UvrD (278).

In addition to its roles in NER and MMR, UvrD can displace proteins bound to duplex DNA, including Lac repressor bound to its operator, topoisomerase IV from a nascent, cleaved DNA substrate, and Tus bound to a ter site (192, 279, 280). However, unlike Rep, UvrD can also displace RecA from ssDNA (193, 250). This displacement does not require DNA strand separation per se but instead takes advantage of the processive ssDNA translocation function of UvrD (281). The distinct actions of these two helicases on RecA filaments have led to the proposal that Rep and UvrD do not share a common, essential activity in vivo as previously suggested by synthetic lethality studies of double mutants (282). Instead, Rep functions in DNA replication while UvrD functions as an antirecombinogenic motor, displacing RecA from DNA.

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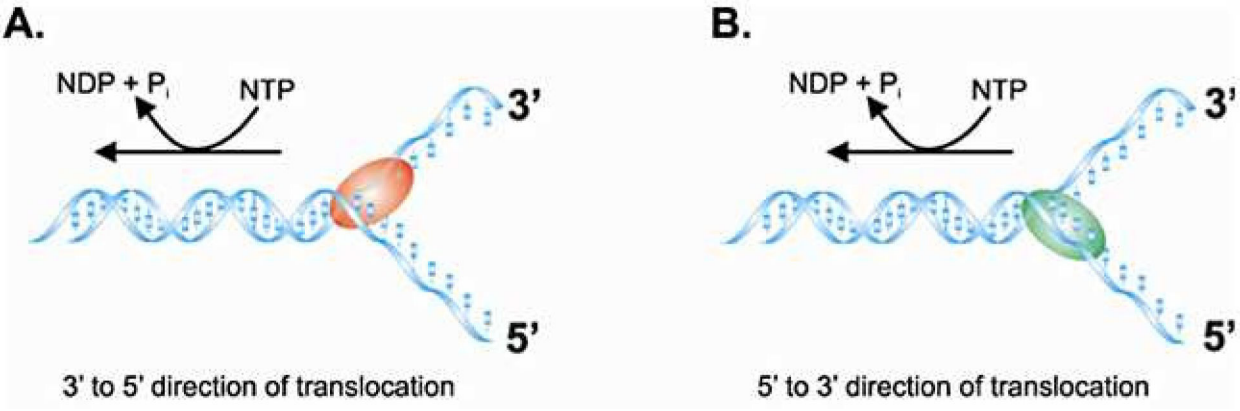

Figure 1. DNA helicases unwind duplex DNA in polar fashion.

Schematics of two hypothetical, monomeric DNA helicases are shown. Each protein is bound to the DNA strand on which it translocates. (A) A 3′→5′ DNA helicase. (B) A 5′→3′ DNA helicase.

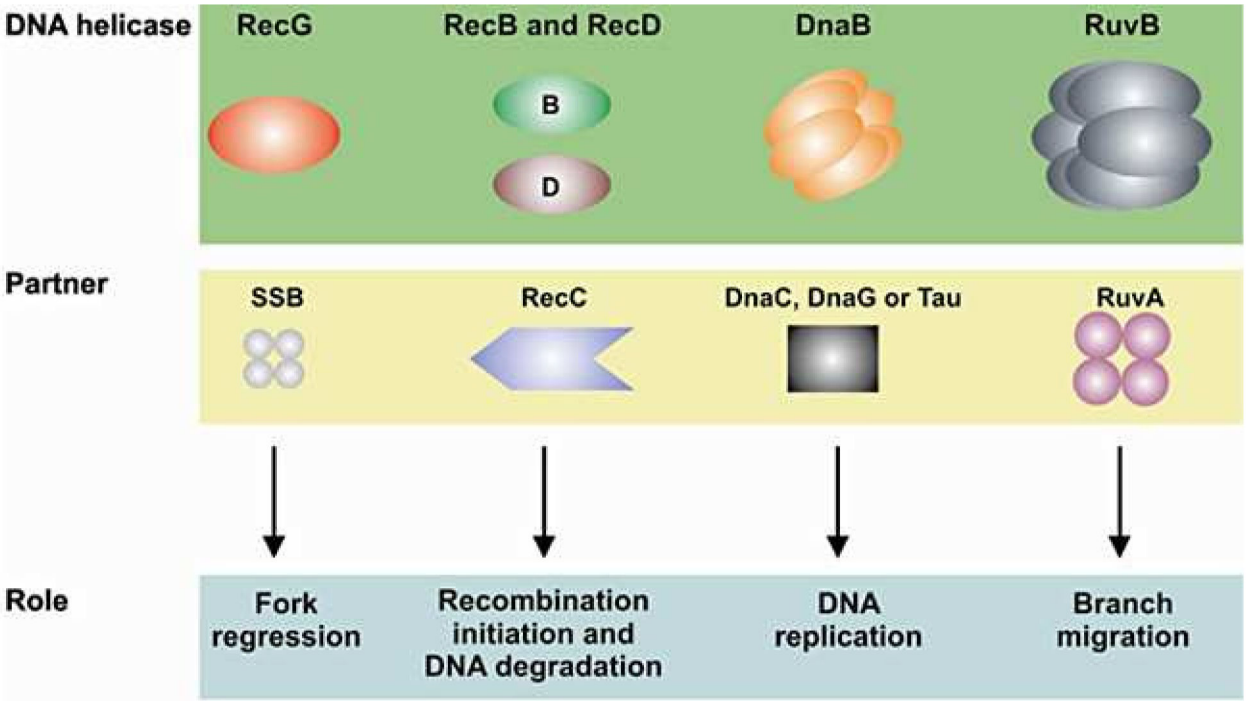

Figure 2. DNA helicases have distinct functional oligomeric states.

(Top) Four DNA helicases are shown. RecG (monomeric), RecB and D (heterotrimeric as RecBCD), DnaB (hexameric), and RuvAB (dodecameric as RuvAB with two diametrically opposed hexameric RuvB rings). (Middle) The partner proteins responsible for either loading the motor onto the DNA (SSB, DnaC, RuvA) or providing scaffolding and structural assistance in DNA unwinding (RecC and RuvA) are indicated. (Bottom) Biological role of each DNA helicase.

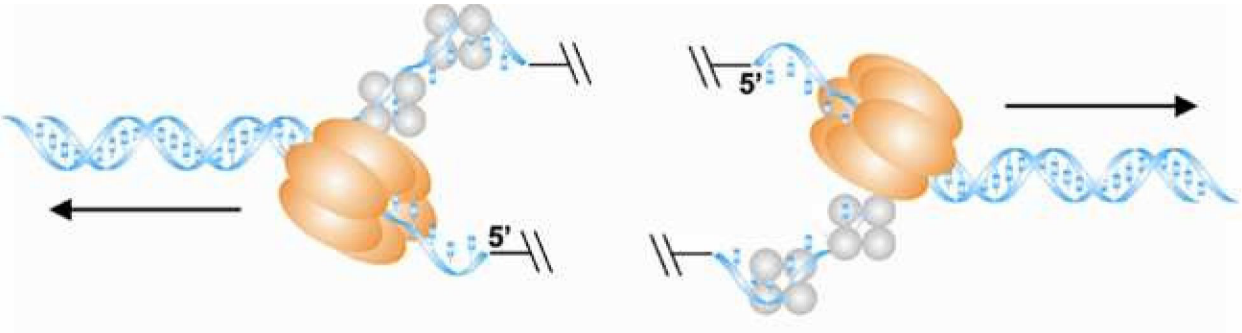

Figure 3. DnaB is the replicative DNA helicase.

Two diametrically opposed DnaB homohexamers are shown translocating and unwinding DNA. Once loaded onto the DNA at oriC, these motor complexes move in opposite directions and are tightly coupled to the replication machinery that follows immediately behind (not shown). To unwind the DNA duplex, one strand of DNA passes through the center of the ring while the other is forced to the outside. Unwound strands of DNA can be bound by SSB protein (gray spheres).

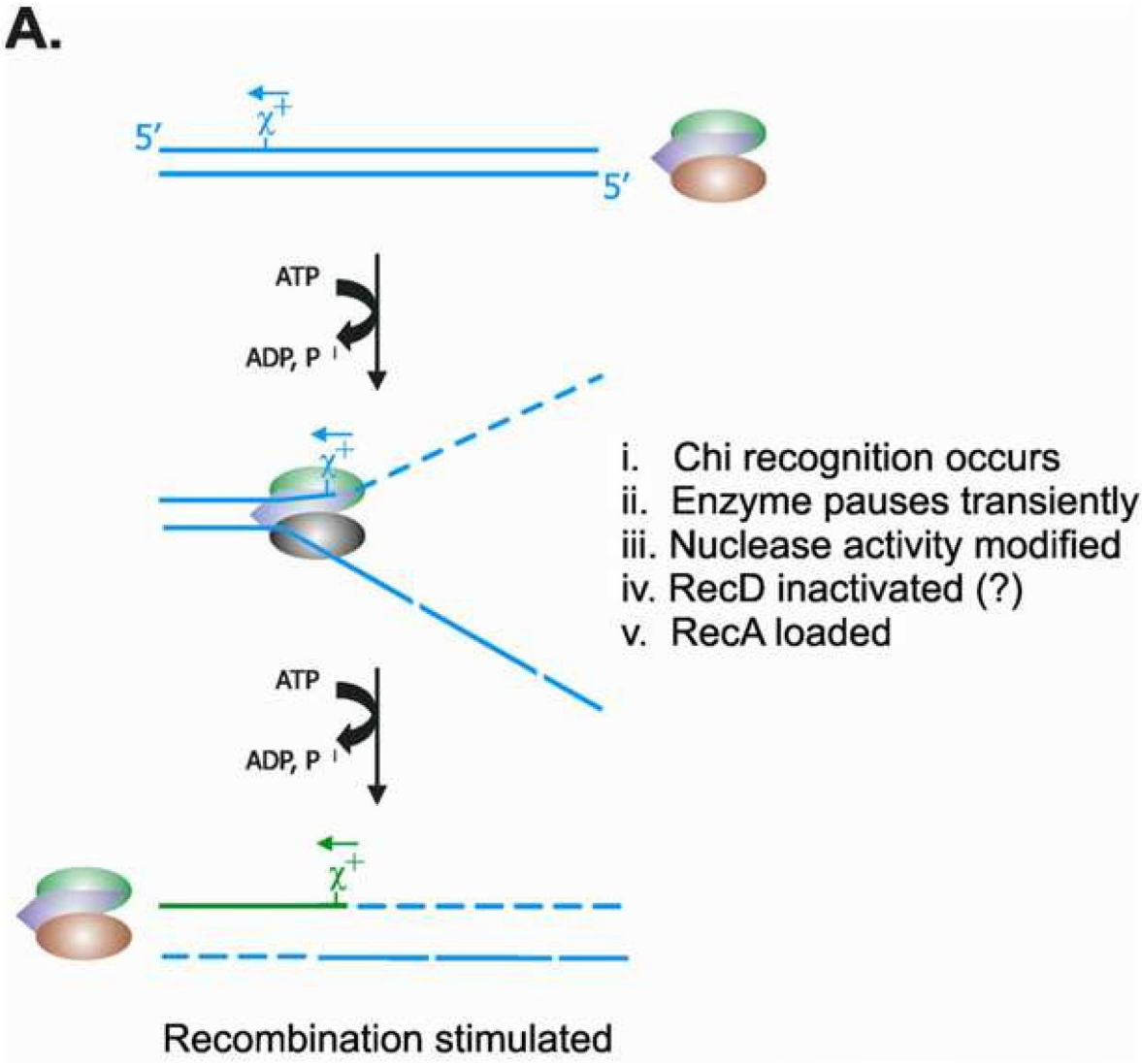

Figure 4A. RecBCD is a multifunctional bipolar DNA helicase.

(A) The interaction of the translocating RecBCD enzyme with chi elicits a complex set of changes in the enzyme. RecBCD binds to DNA ends with high affinity and, in the presence of ATP, translocates, unwinds, and degrades the unwound strands of DNA. Prior to chi, endonucleolytic degradation of DNA is asymmetric as indicated by the dashed lines. Upon encountering chi, the enzyme recognizes the sequence and pauses; the resulting changes include inactivation of the RecD subunit (now in black), alteration of the polarity of endonucleolytic activity, and loading of RecA onto the strand of DNA containing chi to facilitate recombination initiation (not shown).

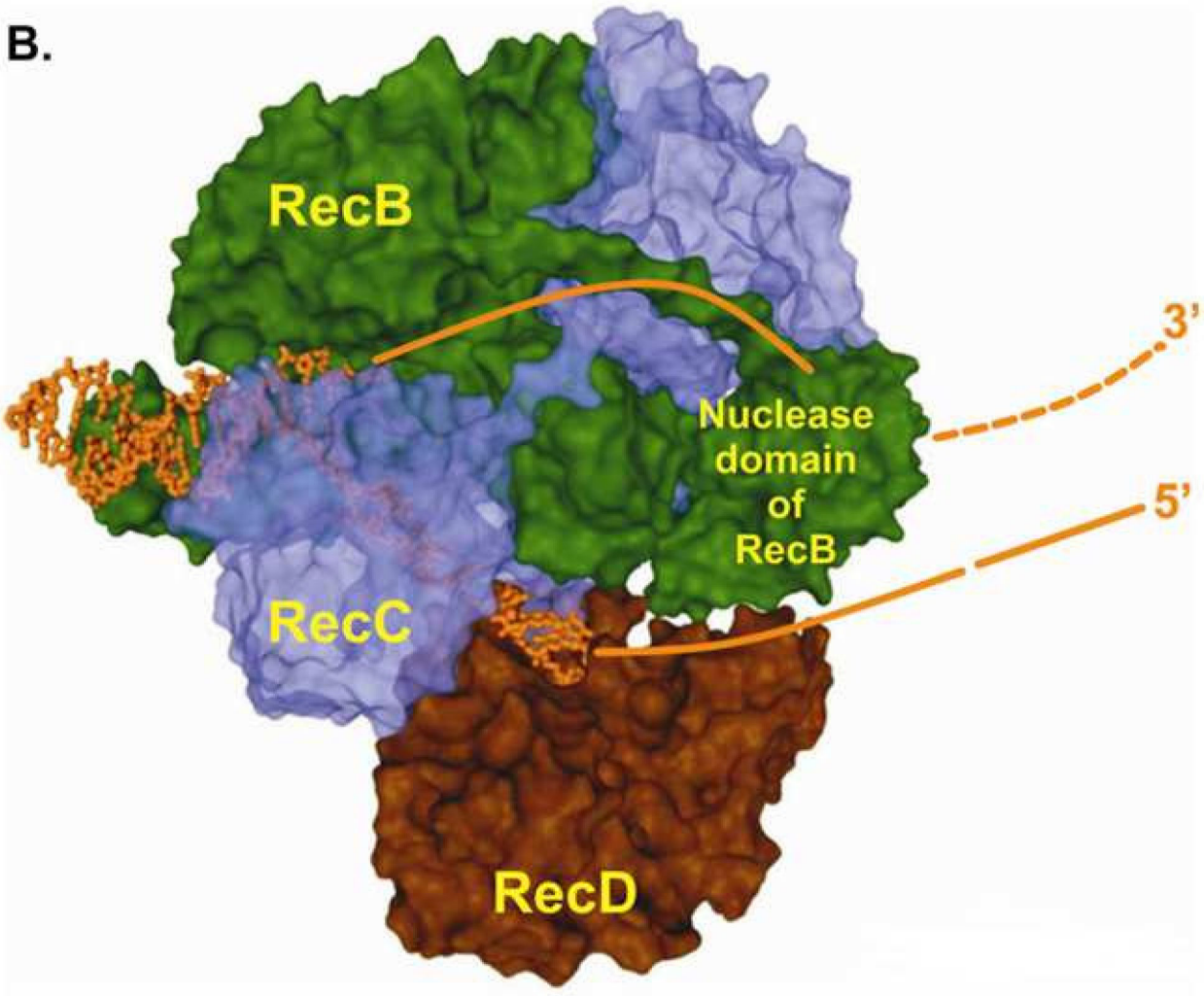

Figure 4B. RecBCD is a multifunctional bipolar DNA helicase.

(B) A side view of the RecBCD heterotrimer is shown bound to the DNA. Each of the subunits is shown in a different color and RecC is transparent so that the path of the DNA through the subunit is apparent. DNA that has been cleaved by the nuclease domain present in RecB is indicated by the dashed lines. This figure is adapted from references 129, 128, and 133.

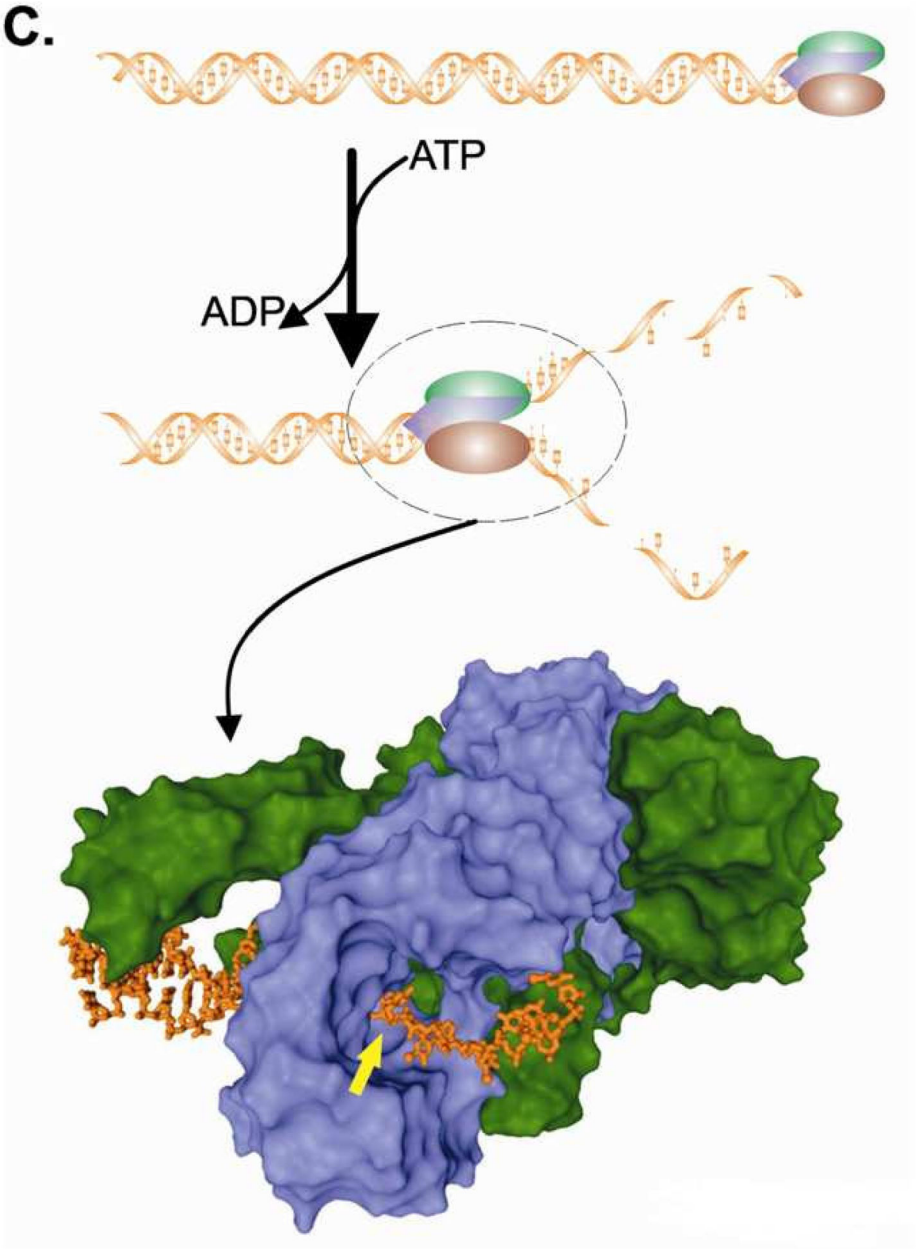

Figure 4C. The unwound single strands of DNA pass through the RecC subunit.
(Top) RecBCD is shown translocating and unwinding dsDNA. (Bottom) The RecBCD enzyme is shown in the same orientation as in panel B, except that the RecD subunit has been removed so that the path of the unwound DNA through the channels in RecC is clearly visible. To facilitate passage of DNA into and through the enzyme, the leading domain of RecB reaches ahead onto the duplex and then pulls the DNA into the enzyme. DNA strands are separated on the surface of RecC and then pass through the channels within RecC (yellow arrow).

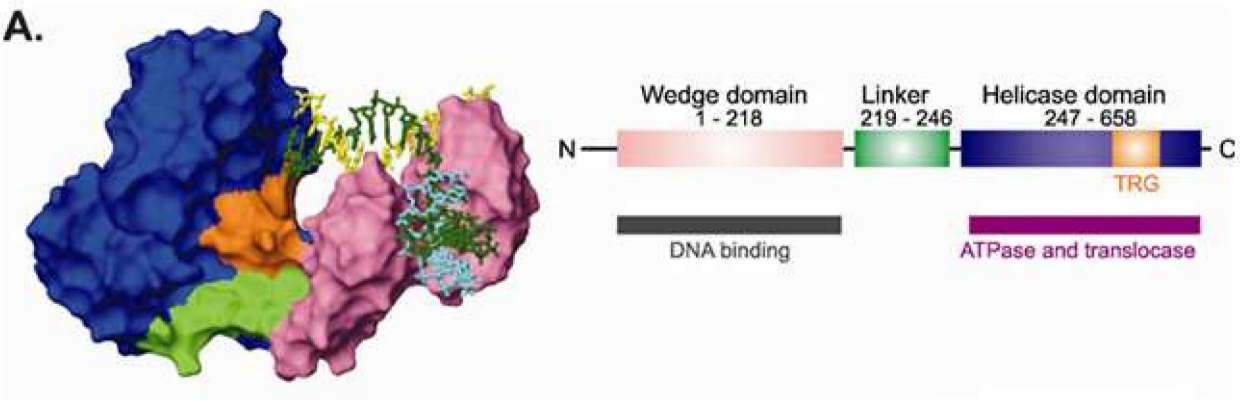

Figure 5A. RecG processes stalled forks.

(A) Architecture of a RecG monomer with the domains identified as follows: pink, wedge domain (AA 1–218); green, linker (AA 219–246); blue, helicase domain (AA 247–658), and orange, TRG motif (147, 153). The color schemes in the left and right panels are the same to enable identification of domains within the structure of RecG. This figure is adapted from reference 153.

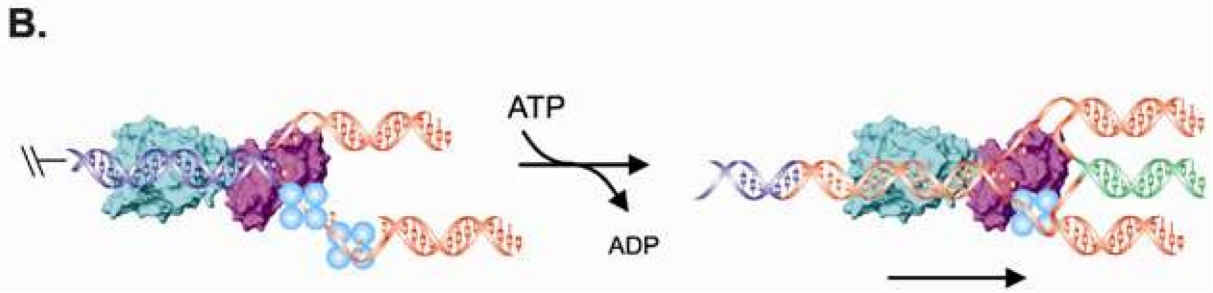

Figure 5B. RecG processes stalled forks.

(B) A surface representation of RecG regressing a stalled fork. Here, the RecG wedge domain is pink and helicase domain is cyan. The arms of the fork are shown in red. Following regression as indicated by the arrow (Right), the DNA at the fork resembles a “chicken foot” with the central, nascent heteroduplex region shown in green. A single SSB tetramer is indicated (it is unclear whether SSB participates in any way in fork regression). Blue spheres, SSB.

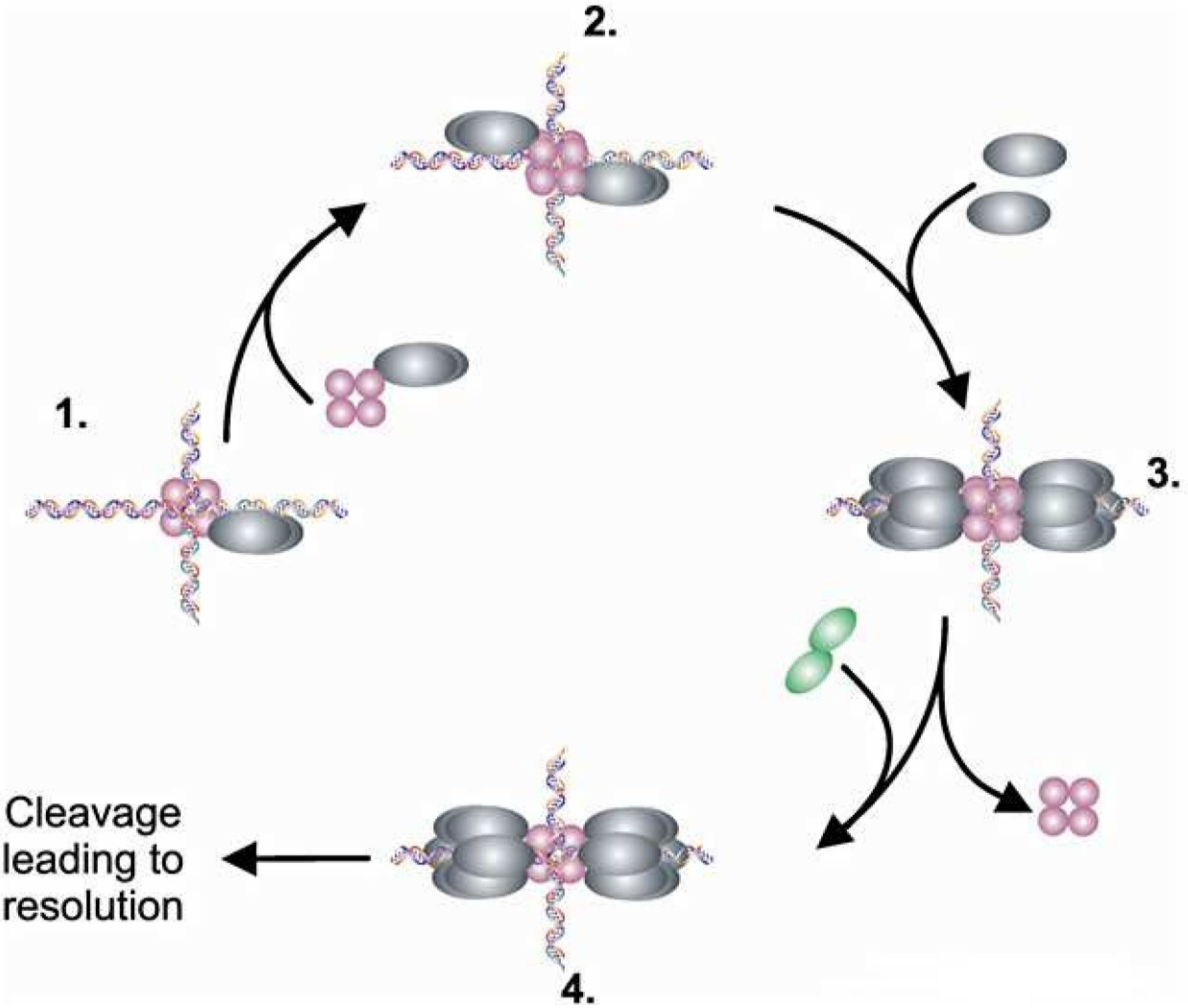

Figure 6. The dynamic, RuvABC heterooligomer catalyzes branch migration and Holliday junction cleavage.

A schematic of the sequential assembly and resulting activity of the enzyme on a Holliday junction. (step 1) A RuvA tetramer (mauve circles) bound to a dimer of RuvB (grey ovals) assembles on a junction. Another RuvA tetramer binds to form a junction sandwich flanked by partially assembled RuvB hexamers. (step 2) Additional RuvB monomers bind leading to formation of the complete branch migration complex. (step 3) Following branch migration, the translocating complex may pause with one RuvA tetramer dissociating, followed by association of the RuvC dimer (green ovals). Cleavage by RuvC ensues, and after RuvABC dissociation and DNA ligation, resolution is completed (step 4).

Table 1

DNA helicases of E. coli

DNA helicase	Mass (kDa)	Gene	Oligomeric form	Polarity of DNA unwinding	Function
DinG	81	*dinG*	Monomer	5′ to 3′	SOS-induced DNA repair
DnaB	52	*dnaB*	Homohexamer	5′ to 3′	Replicative helicase
Helicase III	20	?	Dimer	5′ to 3′	Unknown
Helicase IV	78	*helD*		3′ to 5′	Unknown; possibly in RecF recombination pathway
PriA	82	*priA*	Monomer	3′ to 5′	Primosome assembly at non-oriC sites to facilitate replication fork restart; interacts with SSB
RecBCD	134	*recB*	Heterotrimer	5′ to 3′	Exonuclease V; initiation of recombination; DNA repair
	129	*recC*	Heterotrimer	Not relevant	
	67	*recD*	Heterotrimer	3′ to 5′	
RecG	76	*recG*	Monomer	3′ to 5′	Regression of stalled forks; interacts with SSB
RecQ	80	*recQ*	Multimer	3′ to 5′	Fork stabilization; decatenation; resolution of converging forks; interacts with SSB
Rep	73	*rep*	Monomer - dimer	3′ to 5′	DNA replication to clear proteins ahead of the advancing fork
RuvAB	22	*ruvA*	Homotetramer	Not relevant	Branch migration complex; resolution of Holliday junctions; DNA repair
	37	*ruvB*	Homohexamer	5′ to 3′	
TraI	180	*traI*	Monomer	5′ to 3′	F-plasmid transfer during mating
UvrD	82	*uvrD*	Monomer - dimer	3′ to 5′	NER, MMR, and clearing of proteins bound to dsDNA; removal of RecA from ssDNA