The SeqA protein, which prevents overinitiation of chromosome replication, has been suggested to also participate in the segregation of chromosomes in Escherichia coli. Using a bacterial two-hybrid system, we found that SeqA interacts with the ParC subunit of topoisomerase IV (topo IV), a type II topoisomerase involved in decatenation of daughter chromosomes and relief of topological constraints generated by replication and transcription. We demonstrated that purified SeqA protein stimulates the activities of topo IV, both in relaxing supercoiled plasmid DNA and converting catenanes to monomers. The same moderate levels of SeqA protein did not affect the activities of DNA gyrase or topoisomerase I. At higher levels of SeqA, topo IV favored the formation of catenanes, caused by intermolecular strand exchange among plasmid DNA aggregates formed by SeqA. Excess SeqA inhibited the activity of all topoisomerases. We also found that stimulation of topo IV was dependent upon the affinity of SeqA for DNA. Our results suggest that this stimulation is mediated by the specific interaction of topo IV with SeqA. Some of the known phenotypes of mutant cells lacking SeqA, such as deficient chromosome segregation and increased negative superhelicity, suggest that the SeqA protein is required for topo IV-mediated relaxation and decatenation of chromosomes and plasmids, during and after their replication.

Escherichia coli SeqA protein, which is a homotetramer of 21-kDa polypeptides, preferentially binds to DNA containing hemi-methylated GATC sequences (1–3, 48). Sequential binding of tetrameric SeqA to pairs of hemi-methylated GATC sequences mediates formation of higher order complexes (6). SeqA will also bind, with lesser affinity, to long, fully methylated DNA containing multiple GATC sequences (1, 4, 7). The seqA gene was identified in a screen for factors that prevent initiation of hemi-methylated origins (8, 9). The binding of SeqA to newly replicated, hemi-methylated GATC sequences mediates formation of higher order complexes (6). The binding of tetrameric SeqA to pairs of hemi-methylated GATC sequences preferentially binds to DNA containing multiple GATC sequences (1, 4, 7). The binding of tetrameric SeqA to pairs of hemi-methylated GATC sequences mediates formation of higher order complexes (6). The binding of tetrameric SeqA to pairs of hemi-methylated GATC sequences mediates formation of higher order complexes (6).

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**EXPERIMENTAL PROCEDURES**

**Reagents**—Sources were as follows: kDNA, TopGEN; [γ-32P]ATP (5000 C/mmol) and poly[dI–dC], Amersham Biosciences; T4 polynucleotide kinase, New England Biolabs; restriction and cloning enzymes, Promega; calf thymus topoisomerase I, Invitrogen; Pyrobest DNA polymerase and T4 DNA ligase, Takara; QIAEX II gel extraction kit, Qiagen; and deoxyxynucleotide sequencing kit, USB. Unless otherwise indicated, all other reagents were purchased from Sigma.

**Bacterial Strains and Plasmid DNAs**—The *E. coli* strains DH5α (34) and GM3819 (dam Δ(16Km)) were used for isolating plasmid DNA (DH5α for fully methylated and GM3819 for unmethylated plasmid DNA). *E. coli* MC1061 (37) was used in all assays. E. coli strain GM3819 was constructed by inserting the SmaI/BclI fragment of the *mcrA mcrB* plasmids pT18- or pT18-ΔseqA into the multiple cloning site of pBAD18 (35) and pBluescript II SK(+) (Stratagene) to carry out topoisomerase assays. The Dam assay solution (0.1 M Tris-HCl at pH 8.0, 10 mM EDTA, 2.5 mM dithiothreitol, 1.6 mM S-adenosylmethionine) containing 0.5 μg/mL of Dam DNA was used to generate hemi-methylated DNA. The unmethylated DNAs, which were used as controls, were generated by treating the DNA with Dam methylase (4 μg) then adding the mixture was incubated at 37 °C for 5 min. The DNA was recovered by phenol/chloroform extraction and ethanol precipitation. Fully methylated plasmids were obtained by omitting *seqA* from the Dam assay solution and extending the reaction and ethanol precipitation. Fully methylated plasmids were observed in all assays (unless otherwise indicated) are as follows: *SeqA*, 1.4 μg/mL; DNA gyrase, 0.6 μg/mL; topo I, 0.24 μg/mL; topo IV, 0.5 μg/mL. 

**Bacterial Two-hybrid Screening**—Bacterial two-hybrid screening with the adenylate cyclase protein of *Bordetella pertussis* has been previously described (5, 38). The DHP1 strain (derivative of DH1, cya) was used for detecting protein-protein interactions. The coding region of *seqA* was inserted into the KpnI/HindIII sites of the pT18 plasmid and used as bait for screening. For constructing a prey library, 0.5- to 3-kb fragments of Sau3AI partial digests of *E. coli* genomic DNA were ligated into the BamHI site of the pT25 plasmid; the library diversity was determined to be over 106. The pT25 genomic DNA library was electro- 

**Results**

**Interaction of SeqA with the C-terminal Domain of the ParC Subunit of Topo IV**—Interaction between proteins can be detected with a bacterial two-hybrid system by using the functional complementation of the N (T25)- and C (T18)-terminal regions of *Bordetella pertussis* adenylate cyclase (5, 38). SeqA proteins cooperatively bind to DNA and form aggregates (5, 7). When the SeqA protein is fused to both T25 and T18, SeqA-SeqA interaction allows the reconstitution of active adenylate cyclase and results in reporter (β-galactosidase) activity 4-fold higher than the activity of the control (pT18-SeqA/pT25) (Table I) (5). To identify the one or more proteins that interact with the SeqA protein, we used SeqA-T18 expressed from the pT18-SeqA plasmid as bait. After screening an *E. coli* genomic library cloned into the pT25 plasmid, we identified two independent SeqA-interacting clones expressing the C-terminal regions of the ParC subunit of topo IV that interacted with SeqA (Table I). These two clones exhibited 2.5- and 2.5-fold higher β-galactosidase activities than the activity of SeqA alone (pT25).

**SeqA Stimulates the Relaxation Activity of Topo IV**—Topo IV relaxes supercoils in DNA (18–20, 40). To determine the effect of SeqA on the relaxation activity of topo IV, we examined the relaxation activity by using hemi-methylated, negatively supercoiled pBS (Fig. 1A). The unmethylated DNAs, which were used to generate hemi- and fully methylated DNAs in vitro (see “Experimental Procedures”), were isolated from dam mutant cells and therefore contained higher amounts of multimerized DNAs than DNAs obtained from wild-type cells. The relaxation reaction mixtures containing topo IV and hemi-methylated pBS were incubated for the times indicated and were then quenched with stop solution containing EDTA and SDS. The resulting topoisomerases were separated by agarose gel electrophoresis and detected by Southern blot hybridization (Fig. 1A). In the absence of SeqA, the presence of SeqA facilitated the relaxation of supercoiled DNA to relaxed plasmid DNA. The amount of SeqA required to facilitate topo IV activity was determined by titrating SeqA into a topo IV reaction (Fig. 1B). With increasing amounts of SeqA (up to 10 nM tetramer, or the equivalent to 8 ng), the formation of relaxed DNAs was enhanced. Addition of excess SeqA (equal to or greater than 20 nM) inhibited this stimulation. In the absence of topo IV, SeqA did not alter supercoiled or relaxed DNAs (Fig. 1C). These results show that moderate levels of SeqA stimulate the relaxation activity of topo IV.

**SeqA Does Not Stimulate the Activity of Topo I or DNA Gyrase**—To determine whether SeqA activates all topoisomerases or topo IV exclusively, we examined the effects of SeqA on

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**Table I**

| pT25 | pT25-SeqA | pT25-parC(C310-753) | pT25-parC(C321-753) |
|------|-----------|---------------------|---------------------|
| 1    | 1.4       | 2.3                 | 2.5                 |

**Agarose Gel-shift Assays**—The SeqA binding mixture (10 μl), which contained the same components as the topoisomerase assay mixture, was incubated at 32 °C for 10 min. After incubation, 2 μl of 6× gel-loading buffer (30% glycerol, 10 mM Tris–HCl at pH 8.0, 1 mM EDTA, 0.25% xylene cyanol, 0.25% bromophenol blue) was added, and samples were separated through 1% agarose for 1.5 h at 50 V. Gels were visualized by ethidium bromide staining.
the other *E. coli* topoisomerases, topo I, and DNA gyrase (Fig. 2). For the topo I assay, the reaction mixtures contained supercoiled, hemi-methylated plasmid DNA. The same procedure was used for the DNA gyrase assay, but relaxed, hemi-methylated plasmid was used instead of supercoiled plasmid. The relaxation activity of topo I (Fig. 2A) and the supercoiling activity of DNA gyrase (Fig. 2B) were not significantly affected with up to 5 nM SeqA. As seen with topo IV, excess SeqA inhibited both DNA gyrase and topo I. This inhibition of topo I agrees with previous studies (41). Thus, stimulation by SeqA is unique to topo IV and does not occur with the other topoisomerases.

**SeqA Allows Topo IV to Interlink Plasmid DNAs**—In the presence of SeqA, topo IV produced slowly migrating DNAs (SMDs), which were observed in the upper part of gels near the wells (Fig. 1). In contrast, addition of SeqA to either topo I or DNA gyrase reactions did not result in the production of SMDs (Fig. 2). The formation of SMDs was confirmed with hemi-methylated pFToriC plasmid DNA, which contains the GATC abundant oriC region cloned into the pBS vector (data not shown). Under the reaction conditions described in Fig. 1, SeqA also stimulated the relaxation of this plasmid by topo IV. As with the relaxation activity of topo IV, the accumulation of SMDs of pFToriC occurred in a SeqA concentration-dependent manner. Topo IV converted negatively supercoiled plasmids to relaxed plasmids at lower concentrations of SeqA and to SMDs at higher concentrations. SMD formation appeared to occur more readily with pFToriC containing the abundant GATC

![Image](https://via.placeholder.com/150)
sequences than with pBS. This preference of pFToriC caused that topo IV produced more SMDs than relaxed DNAs (Fig. 3).

It is reasonable to suppose that SMDs are high molecular weight forms of DNA. Topo IV, a type II topoisomerase, cleaves both strands on duplex DNA, transiently generating 5'-ends that are covalently linked to the tyrosine residue of the enzyme (19, 20, 42). This covalent linkage is required for strand passage during relaxation and decatenation. These properties of topo IV indicate two possible ways in which the SMDs might be formed: 1) topo IV might be covalently cross-linked to DNA, forming a so-called protein-DNA adduct, or 2) Topo IV causes catenation, which is the reverse reaction of decatenation. To examine whether SMDs formed with hemi-methylated pFToriC are protein-DNA adducts of topo IV, SeqA, or both proteins covalently linked to DNA, the reaction mixtures containing SMDs were treated with combinations of SDS, EDTA, proteinase K, and phenol (Fig. 3A). The resistance of SMDs to all of these treatments implies that SMDs are not protein-DNA adducts. Digestion of SMDs with XhoI restriction enzyme, which cleaves one site on pFToriC, produced a unit-length of DNA (Fig. 3B). Incubation with topo IV resolved the SMDs to relaxed DNAs (Fig. 3C). DNA gyrase, which does not effectively decatenate catenanes in vitro (28, 29), did not resolve a significant amount of the SMDs. These results suggest that the SMDs generated by the cooperative action of topo IV and SeqA are interlinked plasmid DNAs, also known as catenanes, which can be resolved by topo IV, but not by DNA gyrase.

Like topo IV, DNA gyrase makes a double-strand break and performs strand passage between adjacent stretches of DNA. If plasmid molecules are aggregated by spermidine, the activity of gyrase leads to intermolecular linking and catenation of the plasmid DNA (43). Electron microscope studies have shown that binding excess SeqA to DNA results in aggregation of DNA molecules (7). This aggregation of DNA by SeqA might explain the catenation of plasmid DNAs found in the presence of topo IV. At a certain level of SeqA, plasmid DNAs form aggregates, allowing topo IV, which in addition might be stimulated by SeqA, to carry out intermolecular strand passages between adjacent plasmids in the aggregates. This intermolecular linking catenates the aggregated plasmid DNAs.

**Topo IV Stimulation Is Dependent upon SeqA Affinity for DNA**—Next we determined if SeqA binding to DNA is involved in the stimulation of topo IV activity (Fig. 4). Binding of SeqA to un-, hemi-, and fully methylated plasmid DNA was compared in agarose gel-shift assays (Fig. 4, A and B). Each type of plasmid bound SeqA with a different affinity. The hemi-methylated plasmid bound SeqA with the highest affinity, followed by fully methylated and then unmethylated DNA. These differences in affinity are in agreement with previous studies (4). As shown in Fig. 1, SeqA facilitated the topo IV-mediated conversion of negatively supercoiled hemi-methylated DNA to the relaxed state or to catenanes (Fig. 4C). Hemi-methylated substrate DNA was converted to relaxed DNA most efficiently, and unmethylated DNA was converted least efficiently. Catenate formation was most pronounced in the presence of hemi-methylated DNA, followed by fully methylated DNA. These differences in the relaxation and the formation of catenanes are comparable to the respective binding affinities of SeqA to DNAs of the three categories methylation. These results suggest that the stimulation of relaxation...
activity and formation of catenanes are dependent on binding of SeqA to DNA.

The Decatenation of Topo IV Is Stimulated by SeqA—Topo IV possesses decatenation activity that resolves interlinked DNAs to monomers. To examine the effect of SeqA on the decatenation activity of topo IV, we treated the catenated pFToriC of Fig. 3 with topo IV and SeqA (Fig. 5A). The catenated DNAs were inefficiently detected by Southern blot analysis, because their transfer to nitrocellulose membranes is inefficient; however, decatenation could be detected by increasing the amount of the monomer plasmids. Addition of 1.25 and 2.5 nM SeqA stimulated the conversion to monomers by topo IV. With increasing levels of SeqA, the conversion to monomers was inhibited. At more than 10 nM SeqA, further catenane formation, rather than monomerization, seemed to be favored.

Kinetoplast DNA (kDNA), highly interlinked catenanes of 2.5-kb minicircles, of the insect trypanosome Crithidia fasciculata can be used as a substrate for analyzing the decatenating activity of topoisomerases (26, 44). Incubation of topo IV with kDNA resolved much of the interlinked DNA to monomers (Fig. 5B). Because the highly interlinked kDNA was not transferable to nitrocellulose membranes, only the decatened DNA was detected in Southern blot analysis. In the presence of topo IV, SeqA increased the amount of resolved monomers. Without topo IV, SeqA was unable to produce monomers. SeqA seemed to stimulate the rate of decatenation as well as the total amount of monomers produced (Fig. 5C). The optimal amount of SeqA was 10 nM for decatenating 10 ng of kDNA (Fig. 5B) but 2.5 nM for decatenating 10 ng of hemi-methylated pFToriC (Fig. 5A). The insect trypanosome does not contain Dam methylase, therefore kDNA is not methylated at GATC sequences. The reason for the requirement of a greater amount of SeqA for kDNA decatenation might be the reduced affinity of SeqA for unmethylated DNA (Fig. 4, A and B). These results indicate that the process of decatenation is also dependent on the binding of the SeqA protein to DNA.
We demonstrate here that both the relaxation and decatenation activities of topo IV are stimulated by the SeqA protein. Moderate levels of SeqA stimulated topo IV to convert negatively supercoiled DNA to its relaxed state (Figs. 1 and 4) and catenanes to monomers (Fig. 5). Whereas moderate levels of SeqA stimulate topo IV, DNA gyrase and topo I were not affected by similar SeqA levels, implying that the stimulation is specific to topo IV. Dependence of the stimulation upon SeqA affinity to DNA suggests that the stimulation of topo IV is mediated by the binding of SeqA to DNA. Because higher levels of SeqA cause substrate DNA to aggregate, topo IV might be able to carry out the formation of catenanes by intermolecular strand exchange between adjacent plasmid DNAs simply by virtue of aggregation. Therefore, the stimulation of the catenation activity of topo IV by SeqA might be of a passive character and due to aggregation of the DNA by SeqA.

Topo IV is the principal enzyme for decatenation of replicated DNA and mutations in parC or parE, and therefore, the cause of defects in the segregation of daughter chromosomes (23, 24, 45). Lack of topo IV activity also leads to an increase in the steady-state level of negative supercoiling because of a shift in the balance of topoisomerase activities in the cell (27, 28, 30, 32). SeqA-deficient strains exhibit aberrant nucleoid formation, abnormal segregation of chromosomal DNA, and an increased steady-state level of negative superhelicity (11–14, 17). These until now unexplained parC- and parE-like phenotypes of seqA mutants might be explained by the results we are reporting here, namely that the SeqA protein is required for proper activity of the topo IV enzyme.

During replication, positive supercoils accumulate ahead of the replication fork. Relief of overwinding is necessary for progression of the replication fork, and DNA gyrase releases the increased positive superhelicity by introducing negative supercoils. Studies using topo IV-inhibiting drugs show that topo IV also participates in relieving the positive supercoils accumulated in front of replication forks. It has been proposed that part of the positive supercoils diffuses over to the replicated daughter strands behind the fork and forms positive precatenanes (21, 33, 46). If the precatenanes are not effectively removed, the daughter strands are suggested to become interwound and cause barriers for progression of the replication fork and segregation of the replicated chromosomes. Topo IV activity seems to be responsible for resolving the precatenanes (20, 21, 33). In an experiment in which topo IV, but not gyrase, was inhibited by norfloxacin, chromosome replication rapidly stopped in cells lacking SeqA, but did not stop in cells harboring SeqA (30). In this experiment, fork arrest was caused by the formation of topo IV-DNA adducts by the drug. This result therefore indicates that topo IV might be ahead of the forks in the absence of SeqA, but behind the forks in the presence of SeqA. ParC co-localized with the replication factory containing DNA polymerase III (47). The hemi-methylated daughter strands behind the fork are normally bound by the SeqA protein (4). SeqA bound here might contribute to localizing ParC to the area behind the fork. This option suggests that SeqA stimulates decatenation of the positive precatenanes diffused from the front of replication fork in two ways, both by stimulating the activity and affecting the localization of topo IV.

Our results suggest that the SeqA protein is involved in maintaining the integrity of replication forks throughout the replication cycle. At initiation, SeqA is involved in preventing the launch of an excessive number of forks (8, 10). During replication, SeqA stimulates topo IV-mediated removal of precatenanes diffused from ahead of replication forks and, at the
end of replication, stimulates topo IV-mediated decatenation of newly replicated daughter chromosomes.

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SeqA Protein Stimulates the Relaxing and Decatenating Activities of Topoisomerase IV
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