Critical Reviews in Biochemistry and Molecular Biology, 43:289–318, 2008
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ISSN: 1040-9238 print / 1549-7798 online
DOI: 10.1080/10409230802341296

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SSB as an Organizer/Mobilizer of Genome Maintenance Complexes

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When duplex DNA is altered in almost any way (replicated, recombined, or repaired), single strands of DNA are usually intermediates, and single-stranded DNA binding (SSB) proteins are present. These proteins have often been described as inert, protective DNA coatings. Continuing research is demonstrating a far more complex role of SSB that includes the organization and/or mobilization of all aspects of DNA metabolism. *Escherichia coli* SSB is now known to interact with at least 14 other proteins that include key components of the elaborate systems involved in every aspect of DNA metabolism. Most, if not all, of these interactions are mediated by the amphipathic C-terminus of SSB. In this review, we summarize the extent of the eubacterial SSB interaction network, describe the energetics of interactions with SSB, and highlight the roles of SSB in the process of recombination. Similar themes to those highlighted in this review are evident in all biological systems.

Keywords

The genomes of all cellular organisms are organized as double-stranded (ds) DNA, with the information content, in the form of nucleotide bases, sequestered in the interior of the protective double helix (Watson and Crick, 1953a; 1953b). To provide DNA replication, recombination, and repair machinery access to genomic information, dsDNA must be unwound to form single-stranded (ss) intermediates. Such processes are obligatory, but they are not without risks. ssDNA is prone to chemical and nucleolytic attacks that can produce breaks or lesions that are difficult to repair and can self-associate to create impediments to genome maintenance (Hanawalt, 1966, 1967; Hanawalt and Haynes, 1967; Tyrrell *et al*., 1972; Varghese, 1972; Kuzminov, 2001a, 2001b). To help preserve ssDNA intermediates, cells have evolved a specialized class of ssDNA-binding (SSB) proteins that associate with ssDNA with high affinity and in a sequence-independent manner (Sigal *et al*., 1972; Molineux *et al*., 1975; Weiner *et al*., 1975; Chrysogelos and Griffith, 1982; Schneider and Wetmur, 1982; Williams *et al*., 1983; Lohman *et al*., 1986; Greipel *et al*., 1987; Meyer and Laine, 1990; Kowalczykowski *et al*., 1994; Lohman and Ferrari, 1994; Kuzminov, 1999). SSB binding protects ssDNA from degradation (Molineux and Gefter, 1974; Molineux and Gefter, 1975; Mackay and Linn, 1976; Meyer *et al*., 1980; Kowalczykowski *et al*., 1994), and, more globally, defines the nucleoprotein substrates upon which DNA replication, recombination, repair, and

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replication restart processes must act. With these central roles in genome maintenance, it is no surprise that SSB proteins are conserved throughout all kingdoms of life and are indispensable for cell survival (von Hippel and Delagoutte, 2001; Fanning *et al*., 2006; Zou *et al*., 2006).

Beyond their eponymous roles in DNA binding, SSB proteins have a second, less well-appreciated role in which they physically associate with a broad array of cellular genome maintenance proteins. SSB interaction with heterologous proteins targets enzymes to active genome maintenance sites and, in many cases, stimulates the biochemical activities of SSB's partner proteins. In this review, we focus on several aspects of eubacterial SSB interactions with heterologous proteins. First, we summarize the extent of SSB's interaction network by describing what is known about its many partner proteins. In this section, we focus primarily on *Escherichia coli* SSB as a workhorse for understanding SSB structure and function. Second, we consider the thermodynamc mechanisms underlying the binding of heterologous proteins to SSB and the ways in which ssDNA binding by SSB influences its interaction with other proteins. These are important features for defining the specificity of binding to SSB. Finally, we summarize how heterologous proteins have adapted to carry out DNA recombination reactions in the cellular environment where mediator proteins regulate recombinase loading onto ssDNA/SSB nucleoprotein substrates. Although this review focuses on eubacterial SSBs, it is clear that eukaryotic SSB proteins have similarly evolved to interact with numerous genome maintenance enzymes as has been described in excellent reviews (Fanning *et al*., 2006; Wold, 1997). Thus, throughout the kingdoms of life ssDNA/SSB complexes are not merely inert particles but are instead dynamic centers that play a key role in choreographing the processes surrounding DNA replication, recombination, and repair.

SSB PROTEIN OVERVIEW

Eubacterial SSB proteins are linked by two common structural features. The first is the use of oligonucleotide/oligosaccharide-binding (OB) domains to bind ssDNA through a combination of electrostatic and base-stacking interactions with the phosphodiester backbone and nucleotide bases, respectively (Merrill *et al*., 1984; Casas-Finet and Chase, 1987; Khamis *et al*., 1987; Overman *et al*., 1988; Curth *et al*., 1993; Overman and Lohman, 1994; Raghunathan *et al*., 2000; Savvides *et al*., 2004). The second is SSB oligomerization, which brings together four DNA-binding OB folds in the protein's active form (Murzin, 1993; Shamoo *et al*., 1995; Bochkarev *et al*., 1997; Suck, 1997; Matsumoto *et al*., 2000; Raghunathan *et al*., 2000). *E. coli* SSB, which encodes a single OB fold in each monomer and functions as a tetramer, has served as the prototypical SSB protein for decades (Molineux *et al*., 1974; Weiner *et al*., 1975; Lohman and Ferrari, 1994; Matsumoto *et al*., 2000; Raghunathan *et al*., 2000; Savvides *et al*., 2004). Rare exceptions to the *E. coli* SSB-type arrangement exist, including the SSBs from the *Deinococcus-thermus* genera, which contain two OB folds per monomer and assemble as homodimers (Dabrowski *et al*., 2002a; 2002b; Bernstein *et al*., 2004; Eggington *et al*., 2004) (Figure 1). SSB proteins in non-eubacterial systems have distinct quaternary structures, including the heterotrimeric eukaryotic Replication Protein A (RPA) (Wold, 1997), which acts as a heterotrimer, and several bacteriophage and viral SSB proteins that function as monomers (T4 gp32) (Shamoo *et al*., 1995) and dimers (T7 gene 2.5) (Shamoo *et al*., 1995; Suck, D. 1997).

Eubacterial SSB proteins can bind ssDNA in a highly cooperative manner, which leads to clustering of SSB protein tracts to form protein filaments on long ssDNA (Lohman *et al*., 1986; Meyer and Laine, 1990; Lohman and Ferrari, 1994). However, *E. coli* SSB only binds ssDNA with high cooperativity in one of its binding modes (see below). The eukaryotic RPA SSB protein also does not display significant cooperativity in its binding to ssDNA (Wold, M.S. 1997; Kumaran *et al*., 2006). Hence the general role of this cooperativity remains unclear. Due to the presence of four ssDNA binding sites, the *E. coli* SSB tetramer can bind to long stretches of ssDNA in multiple binding modes differing in the number of OB-folds that interact with the ssDNA (Griffith *et al*., 1984; Lohman *et al*., 1985; Bujalowski and Lohman, 1986). The primary ssDNA binding modes are denoted as the $(SSB)_{65}$, $(SSB)_{56}$ and $(SSB)_{35}$ modes, where the subscript reflects the average number of nucleotide residues occluded by each tetramer in the complex. In the $(SSB)_{65}$ mode, ~65 nucleotides of ssDNA wrap around and interact with all four subunits of the tetramer, whereas in the $(SSB)_{35}$ mode, ~35 nucleotides interact with an average of only two subunits (Figure 1). The $(SSB)_{65}$ binding mode is a limited cooperativity mode in which SSB shows little tendency to form protein clusters along ssDNA; the $(SSB)_{35}$ binding mode, on the other hand, is a high, unlimited cooperativity mode in which SSB can form long protein clusters along ssDNA (Chrysogelos and Griffith, 1982; Griffith *et al*., 1984; Lohman *et al*., 1986). The relative stabilities of the different SSB-DNA binding modes is influenced by monovalent salt concentration, Mg^{2+} concentration as well as the polyamines, spermine and spermidine (Lohman and Overman, 1985; Bujalowski and Lohman, 1986; Wei *et al*., 1992), with the $(SSB)_{65}$ mode being favored at monovalent salt concentrations above 200 mM. The $(SSB)_{35}$ mode is also favored at high SSB to ssDNA ratios (Lohman *et al*., 1986; Griffith *et al*., 1984). Whether these different SSB binding modes have specific functions *in vivo* is not clear, although it has been proposed that they may be used selectively in different processes in the cell. For example, under conditions where RecA protein stimulates DNA strand exchange *in vitro*, SSB binds primarily in the low cooperative, fully wrapped $(SSB)_{65}$ binding mode (Bujalowski *et al*., 1988). The $(SSB)_{35}$ mode, which binds with high nearest neighbor cooperativity, has been proposed to function in DNA replication (Overman and Lohman, 1994). The yeast RPA also undergoes a salt-dependent transition from a lower to a higher site size ssDNA binding mode (Kumaran *et al*., 2006).

Eubacterial SSB proteins have been shown to bind more than a dozen different proteins (Figure 2). For all cases tested thus

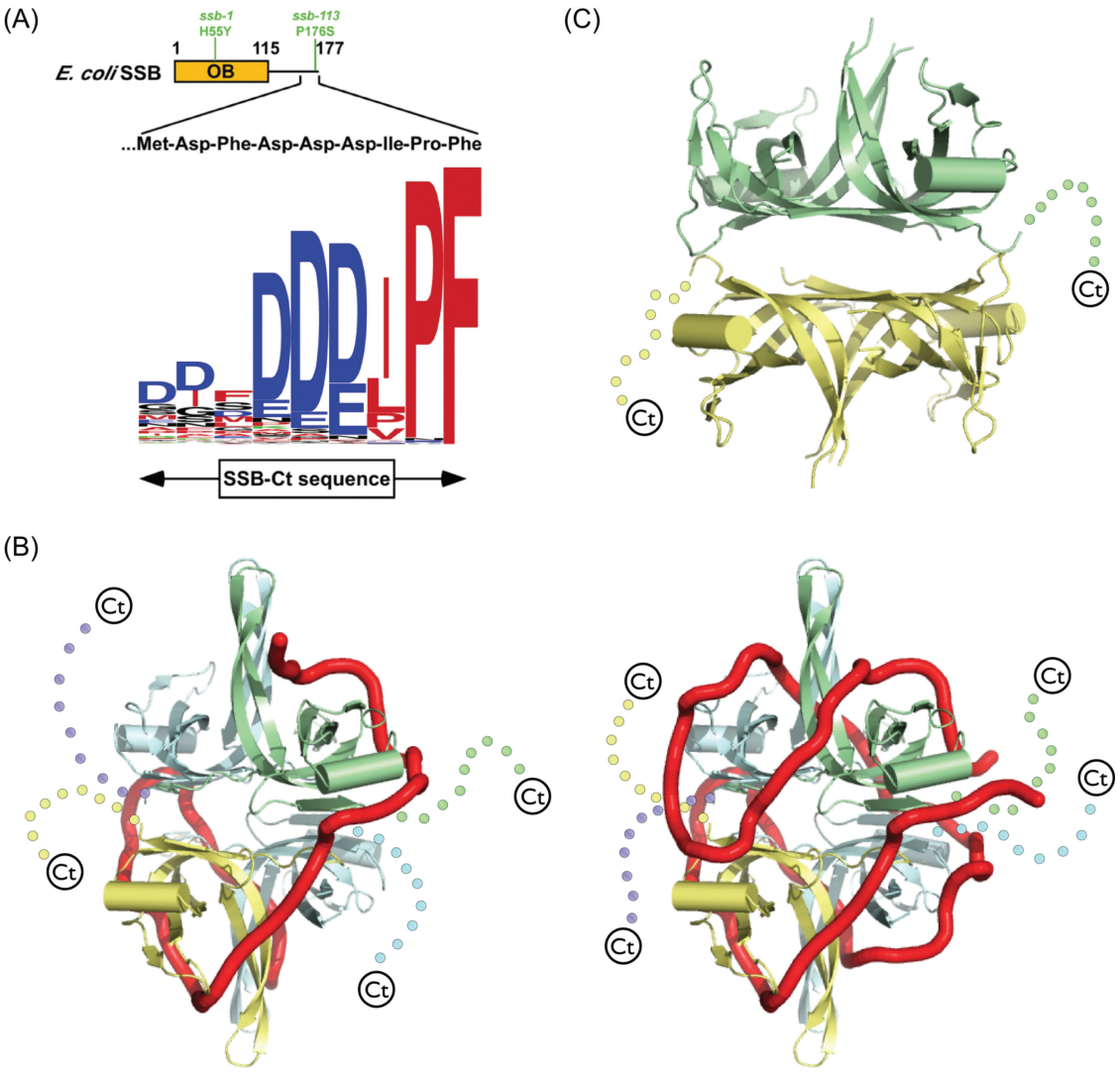
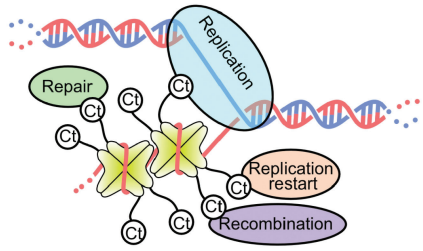


FIG. 1. (A) Schematic representation of SSB. The *E. coli* SSB OB domain (residues 1–115) is shown as a box with its structurally dynamic C-terminal tail (residues 116–177) as a line. The sequence of the *E. coli* SSB-Ct element is displayed with its conservation across 280 eubacterial species represented as a logo (Crooks *et al.*, 2004) in which the height of the residue relates to its frequency at the given position. Logo residues are colored to indicate the hydrophobic (red), electronegative (blue), polar (black), or electropositive (green) nature of their side chains. (B) Ribbon diagram of the proposed structures of the *E. coli* $(SSB)_{35}$ (left) and $(SSB)_{65}$ (right) ssDNA binding models (Raghunathan *et al.*, 2000). Each monomer in the tetramer is separately colored and its C-terminus is shown schematically as a dashed line. ssDNA is shown as a red tube. (C) Ribbon diagram of the crystal structure of *D. radiodurans* SSB (Bernstein *et al.*, 2004) OB folds are colored as for *E. coli* SSB, but with two OB folds in each monomer of the dimer. C-terminal tails are displayed as dots.

far, complex formation requires the C-terminal region of SSB (SSB-Ct), suggesting a conserved mechanism by which proteins can recognize and bind to SSB. Indeed, the C-terminus of eubacterial SSB proteins, which ends in an Asp-Phe-Asp-Asp-Asp-Ile-Pro-Phe sequence in *E. coli* SSB, is very well conserved (Lu and Keck, 2008) (Figure 1). Owing to its high density of Asp residues, this region is often referred to as SSB's "acidic tail," but the hydrophobic tripeptide that forms the extreme C-terminus is well conserved among SSBs and is critical for protein interactions (see below). Thus, the C-terminus of SSB should more accurately be considered as an amphipathic sequence element. In contrast to the well-folded OB domains, the C-termini of bacterial and bacteriophage SSB proteins appear to be structurally dynamic as they are readily removed by proteolysis (Hosoda and Moise, 1978; Burke *et al.*, 1980; Lonberg *et al.*, 1981; Williams *et al.*, 1983). Further, the C-terminus is not visible in the crystal structure of full-length *E. coli* SSB (Savvides *et al.*, 2004). Proteolysis of the SSB-Ct is stimulated by ssDNA binding, and

(A)



(B)

SSB-interacting protein	Require SSB-Ct?
DNA polymerase III, chi	Yes
Primase	Unknown
Topoisomerase III	Yes
RecQ	Yes
RecO	Yes
RecJ	Unknown
RecG	Yes
PriA	Yes
PriB	Unknown
Exonuclease I	Yes
Uracil DNA glycosylase	Yes
DNA polymerase II	Yes
DNA polymerase V	Yes
Exonuclease IX	Unknown
vRNA polymerase	Unknown

(C)

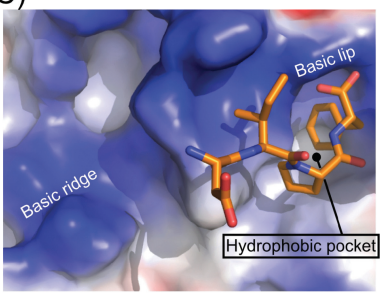


FIG. 2. (A) Schematic representation of SSB interactions. SSB proteins (yellow) are depicted at tetramers with C-termini (Ct) interacting with ovals symbolizing proteins involved the major genome maintenance pathways of DNA replication (teal), recombination (purple), replication restart (orange), and repair (green). (B) List of proteins that are known to physically interact with SSB with their requirement for the SSB-Ct for interaction given. Citations for the interactions are given in the text. Highlighting colors indicate the major genome maintenance activities of the proteins (color coding as in (A)) and the sections in which each is described (except for Topoisomerase III, which is described in the recombination section with RecQ). (C) Binding site for the *E. coli* SSB C-terminus on Exonuclease I (Lu and Keck, 2008). Surface representation of Exonucelase I is stained in blue, red, and white to highlight positive, negative, and hydrophobic electrostatic features, respectively. The final four residues of the SSB C-terminus are shown in ball and stick form. Features shown to be critical for SSB binding by Exonuclease I are labeled.

deletion of the SSB-Ct influences the relative stabilities of the $(SSB)_{35}$ and $(SSB)_{65}$ binding modes (Roy *et al*., 2007). Recent studies have shown that the C-terminal tail of the phage T7 gene 2.5 SSB protein can compete with ssDNA for binding to the OB-fold (Marintcheva *et al*., 2008).

Mutations within the SSB C-terminus have detrimental effects on *E. coli* cell survival. One well-studied mutation (*ssb113*) changes the penultimate Pro of the *E. coli* SSB C-terminus to a Ser (Wang and Smith, 1982; Chase *et al*., 1984). This mutation confers temperature-sensitive lethality by producing an SSB variant that is competent to bind DNA but can no longer support DNA replication at non-permissive temperatures (Chase *et al*., 1984) and is hypersensitive to DNA damage even under permissive conditions (Greenberg and Donch, 1974; Greenberg *et al*., 1974; Meyer *et al*., 1980, 1982; Johnson, 1984). A second set of mutations that alter the C-terminal-most *E. coli* SSB residue, Phe177, similarly impair viability (Kelman *et al*., 1998; Yuzhakov *et al*., 1999; Genschel *et al*., 2000). In both cases, mutations that alter the SSB-Ct sequence produce proteins that fail to interact properly with at least some of SSB's binding partners. Deletion of 10 amino acids from the C-terminus of SSB renders the cells expressing that protein inviable (Curth *et al*., 1996). These dramatic phenotypes have greatly illuminated the importance to cellular genome maintenance pathways of the interactions of SSB with heterologous proteins.

I. INTERACTION OF SSB WITH DNA METABOLISM PROTEINS IN EUBACTERIA

In this section, we gauge the extent of SSB's interaction network by reviewing known eubacterial SSB-interacting proteins, with a particular emphasis on *E. coli* proteins. Members of the interaction network are grouped through their involvement in DNA replication, recombination, replication restart, repair, or as "other SSB-binding proteins", but it should be recognized that in many cases these proteins function in several of the listed areas. Rather than provide an extensive background on each protein, we have limited discussion of each to focus primarily on what is known about the protein interactions with SSB and the biochemical and cellular consequences of such interactions.

DNA Replication

DNA Polymerase III – χ Subunit (χ Binds SSB via the SSB-Ct; Disruption of this Binding is Lethal to Cells)

The DNA polymerase III holoenzyme (Pol III HE) is the multi-subunit replicative DNA polymerase in *E. coli* (Kaguni and Kornberg, 1984; Kornberg, 1984; Marians, 1984; Kornberg and Baker, 1992; Baker and Bell, 1998; Davey and O'Donnell, 2000; Johnson and O'Donnell, 2005; O'Donnell, 2006). Within the Pol III HE, the γ clamp loader (comprised of γ, δ, δ', χ and ψ subunits) forms a subcomplex that loads the β processivity factor onto DNA and helps tie the holoenzyme together through a network of protein–protein interactions (Pritchard *et al*., 2000; Jeruzalmi *et al*., 2001; Johnson and O'Donnell, 2005). Although χ and ψ are not required for clamp loading onto DNA (Onrust, 1995), they do form a complex that facilitates the assembly of the clamp loader itself (Olson *et al*., 1995). Moreover, $\chi\psi$ binds SSB directly via the χ subunit (Glover and McHenry, 1998; Kelman *et al*., 1998; Yuzhakov *et al*., 1999; Witte *et al*., 2003), which allows the Pol III HE to clear potentially inhibitory SSB proteins from lagging-strand DNA during DNA replication (Greenberg *et al*., 1974; Glover and McHenry, 1998; Kelman *et al*., 1998). SSB113 and an SSB truncation variant lacking the C-terminal 26 amino acids of the protein fail to bind χ, establishing the SSB C-terminus as the site of the protein–protein interaction (Kelman

et al., 1998; Yuzhakov *et al*., 1999; Witte *et al*., 2003). The χ/SSB interaction plays a crucial role in Pol III HE function by driving detachment of primase from RNA primers, which stimulates primer hand-off to the Pol III HE (Yuzhakov *et al*., 1999). This activity appears to be essential for cell viability in *E. coli* and accounts for the conditional-lethal *ssb113* phenotype (Quinones and Neumann, 1997; Kelman *et al*., 1998).

Primase (Primase Binds SSB, Possibly at the SSB-Ct)

E. coli Pol III HE cannot initiate DNA synthesis but instead extends preformed nucleic acid primers. RNA primers in bacteria are generated by a specialized RNA polymerase called primase (the product of the *dnaG* gene) (Brutlag *et al*., 1971; Rowen and Kornberg, 1978; Kaguni and Kornberg, 1984; Kornberg and Baker, 1992; Griep, 1995; Benkovic *et al*., 2001). Primase constitutes the lone priming protein in *E. coli* (Rowen and Kornberg, 1978; Kitani *et al*., 1985; van der Ende *et al*., 1985), functioning in both leading- and lagging-strand synthesis in *oriC*-dependent replication and in replication restart processes (Kaguni and Kornberg, 1984; Ogawa *et al*., 1985; van der Ende *et al*., 1985; Zechner *et al*., 1992; Griep, 1995).

E. coli primase interacts with the replicative helicase, DnaB, through its C-terminal protein interaction domain (Zechner *et al*., 1992; Sun *et al*., 1994; Tougu *et al*., 1994; Lu *et al*., 1996; Tougu and Marians, 1996a; 1996b; Keck *et al*., 2000; Podobnik *et al*., 2000; Oakley *et al*., 2005; Bailey *et al*., 2007). DnaB/primase complex formation recruits primase to the replication fork, helps coordinate leading and lagging strand synthesis by Pol III by regulating Okazaki fragment synthesis, and initiates bi-directional replication at *oriC* (Wu *et al*., 1992; Zechner *et al*., 1992; Tougu *et al*., 1994; Lu *et al*., 1996; Hiasa and Marians, 1999; Bhattacharyya and Griep, 2000; Johnson *et al*., 2000).

In addition to its association with DnaB, primase also interacts with SSB. Primase/SSB interaction strengthens the association between primase and the RNA primers it synthesizes (Yuzhakov *et al*., 1999) and is disrupted by the χ subunit, forming the basis of an involved handoff mechanism in which primase dissociates from the RNA-DNA duplex, allowing clamp-loader assembly to occur (Yuzhakov *et al*., 1999). The domains of primase and SSB that are required for complex assembly have not been identified, but apparent competition between primase and χ for SSB suggests that primase might bind to the C-terminus of SSB.

DNA Recombination

RecQ DNA Helicase (RecQ Binds SSB via the SSB-Ct; Interaction Stimulates RecQ Helicase Activity)

E. coli RecQ functions as the DNA helicase in the RecF-recombination pathway (Horii and Clark, 1973; Nakayama *et al*., 1984; Nakayama *et al*., 1985; Wang and Smith, 1985; Tseng *et al*., 1994), which helps repair gapped and UV-damaged DNA and can repair dsDNA breaks in *recBC*-deficient cells (Hegde *et al*., 1996; Courcelle *et al*., 1999; 2003; 2006; Morimatsu and Kowalczykowski, 2003; Ivancic-Bace *et al*., 2005; Centore and Sandler, 2007; Chow and Courcelle, 2007) Notably, many RecF-recombination pathway proteins interact with SSB, as will be described below and in section III. *E. coli* RecQ also plays roles in the SOS DNA damage response (Hishida *et al*., 2004) and in the suppression of illegitimate recombination (Hanada *et al*., 1997). RecQ promotes cell death in *ruv recA(ts) uvrD E. coli* cells, apparently by driving the accumulation of excessive recombination intermediates (Magner *et al*., 2007). RecQ-mediated recombination initiation (Harmon and Kowalczykowski, 1998), plasmid DNA catenation and supercoiling reactions (Harmon *et al*., 1999; 2003), and converging replication fork resolution (Suski and Marians, 2008) have been reconstituted *in vitro*. The latter two activities required the addition of Topoisomerase III, a type-Ia topoisomerase that appears to have coordinated activities with RecQ proteins in eukaryotes and bacteria (Bachrati and Hickson, 2003; Bennett *et al*., 2006; Brosh and Bohr, 2007; Hanada and Hickson, 2007). Interestingly each of RecQ's reconstituted reactions is stimulated by or requires SSB to proceed.

SSB has been shown to physically associate with RecQ and to stimulate RecQ DNA helicase activity (Umezu and Nakayama, 1993; Lecointe *et al*., 2007; Shereda *et al*., 2007) SSB interaction with RecQ is mediated by the nine C-terminal-most residues of the SSB-Ct (Shereda *et al*., 2007). SSB increases the efficiency of RecQ-mediated unwinding of a 71-basepair duplex formed between an oligonucleotide and M13 circular ssDNA; gp32 from bacteriophage T4 also stimulates this unwinding (Umezu and Nakayama, 1993). SSB stimulates unwinding of a 30-basepair duplex DNA with a 70-base single-stranded 3′ overhang; in this case, gp32 and RPA inhibit unwinding, as does an *E. coli* SSB variant that lacks its SSB-Ct (Shereda *et al*., 2007). These studies indicate that in some contexts interaction between RecQ and SSB is required for SSB stimulation. Moreover, *E. coli* Topoisomerase III has recently been shown to interact with SSB (Butland *et al*., 2005; Suski and Marians, 2008), which could indicate that it acts with RecQ in a complex that is nucleated by SSB. Deletion analysis has shown that the RecQ winged-helix subdomain is the site of interaction with SSB (Shereda *et al*., 2007). This subdomain appears to be utilized as a platform for protein interactions in eukaryotic RecQ helicases as well (Doherty *et al*., 2005; Hu *et al*., 2005; Sun *et al*., 2005).

RecJ Exonuclease (RecJ DNA Binding and Exonuclease Activities are Stimulated by SSB In Vitro)

E. coli RecJ is an exonuclease that degrades ssDNA in a 5′ to 3′ direction (Lovett and Kolodner, 1989). It functions as a member of the RecF-recombination pathway (Lovett and Clark, 1984; Lloyd *et al*., 1988; Asai and Kogoma, 1994; Kowalczykowski *et al*., 1994; Kuzminov, 1999) and, in conjunction with RecQ, RecJ acts at stalled replication forks to degrade nascent lagging strand DNA prior to resumption of replication (Courcelle *et al*., 1997; 1999; 2006; Courcelle and Hanawalt, 1999). Additional roles for RecJ in base excision repair (Dianov and Lindahl, 1994;

Dianov *et al*., 1994) and in the excision step of methyl-directed mismatch repair (Burdett *et al*., 2001; Viswanathan *et al*., 2001) have been reported.

In vitro, RecJ binds to the 5′ end of ssDNA and requires a 5′ overhang for cleavage (Han *et al*., 2006). Unlike most nucleases, RecJ DNA binding and degradation are stimulated by SSB (Han *et al*., 2006). Because T4 gp32 does not provide similar enhancement and RecJ is able to supershift SSB-bound DNA; this enhancement is likely to be due to a specific physical interaction between *E. coli* SSB and RecJ (Han *et al*., 2006). Strengthening this view, RecJ has been observed in complex with SSB in affinity purification studies (Butland *et al*., 2005; Shereda *et al*., 2007). The domains of RecJ and SSB that mediate their interaction have not been identified.

RecG DNA Helicase (RecG Binds SSB, Likely via the SSB-Ct; RecG DNA Binding and ATPase Activities are Stimulated by SSB In Vitro)

RecG is a monomeric DNA helicase (Fukuoh *et al*., 1997; McGlynn *et al*., 2000; Singleton *et al*., 2001; Mahdi *et al*., 2003) that binds forked DNA structures (Briggs *et al*., 2005) and promotes regression of stalled replication forks (Gregg *et al*., 2002; McGlynn and Lloyd, 2002; Briggs *et al*., 2004). RecG has been implicated in a multitude of genome maintenance activities, including ssDNA gap repair and recombinational repair of dsDNA breaks (Kowalczykowski *et al*., 1994; Meddows *et al*., 2004), chromosome segregation (Ishioka *et al*., 1997), stabilization of stalled replication forks (Tanaka and Masai, 2006), and resolution of Holliday junctions (Lloyd, 1991; Whitby and Lloyd, 1998; Kuzminov, 1999; McGlynn and Lloyd, 1999; Sharples *et al*., 1999). RecG binds and remodels numerous nucleic acid structures, including 3-way and 4-way DNA junctions (Whitby and Lloyd, 1998; McGlynn and Lloyd, 1999), D-loops (McGlynn *et al*., 1997), and R-loops (Vincent *et al*., 1996; Fukuoh *et al*., 1997). RecG can promote rapid, ATP-dependent regression of replication forks *in vitro* with low processivity (Robu *et al*., 2004) and can inhibit RecA-mediated strand exchange under conditions that are suboptimal for RecA (Whitby *et al*., 1993; Whitby and Lloyd, 1995a; Robu *et al*., 2004).

SSB stabilizes *E. coli* RecG binding to negatively supercoiled DNA, the substrate upon which its ATPase activity is most highly stimulated (Slocum *et al*., 2007). Maximal ATP hydrolysis also greatly increases when SSB is included in RecG reactions (Slocum *et al*., 2007). In *B. subtilis*, RecG colocalizes with SSB at foci that are thought to be stalled replication forks (Lecointe *et al*., 2007). This colocalization is ablated in cells where SSB lacks its 35 C-terminal most amino acids, suggesting that RecG binds the SSB-Ct and requires SSB to associate with the replisome.

RecO (RecO Binds SSB (Likely via SSB-Ct), which Stimulates RecOR RecA Loading)

RecO is a mediator protein in the RecF recombination pathway (Horii and Clark, 1973; Kolodner *et al*., 1985; Clark and Sandler, 1994). Strains harboring mutations in *recO* exhibit numerous defects in DNA replication, recombination, and repair (Luisi-DeLuca *et al*., 1989; Ryder *et al*., 1994; Tseng *et al*., 1994; Rangarajan *et al*., 2002; Ivancic-Bace *et al*., 2003; 2005; Belle *et al*., 2004; Grompone *et al*., 2004a; Fujii *et al*., 2006; Casey *et al*., 2007) and in the SOS response (Hegde *et al*., 1995; Whitby and Lloyd, 1995b), but *recO* mutations can also suppress illegitimate recombination caused by an excess of RecET (Shiraishi *et al*., 2002; Ikeda *et al*., 2004). Disruption of *recO* confers resistance to thymineless death (Nakayama *et al*., 1988) and sensitivity to UV irradiation (Kolodner *et al*., 1985; Morrison *et al*., 1989; Mendonca and Matson, 1995; Veaute *et al*., 2005; Centore and Sandler, 2007). UV sensitivity in strains with mutations in *recF* Horii and Clark, 1973 and *recR* (Mahdi and Lloyd, 1989a) (also RecF-pathway genes) can be suppressed by over-expression of RecO and RecR (Sandler and Clark, 1994a) as well as by certain RecA mutants (Wang *et al*., 1993), suggesting that these proteins function in a common pathway. RecO binds ssDNA and dsDNA and possesses a DNA-annealing activity (Luisi-DeLuca and Kolodner, 1994; Luisi-DeLuca, 1995). This annealing activity is stimulated by SSB and inhibited by RecR (Kantake *et al*., 2002). Together with RecF and RecR, RecO functions as a modulator of RecA activity (Madiraju and Clark, 1990; Madiraju *et al*., 1992; Umezu *et al*., 1993; Kowalczykowski *et al*., 1994; Cox, 2007; Hobbs *et al*., 2007. RecO and RecR facilitate RecA loading onto SSB-coated ssDNA (Umezu and Kolodner, 1994; Shan *et al*., 1997; Bork *et al*., 2001a). RecO and RecR produce an apparent stabilization of RecA filaments that is likely related to the continued association of RecR with the RecA filament after it forms (Shan *et al*., 1997; Bork *et al*., 2001a). The putative stabilization may reflect an actual suppression of RecA filament disassembly or an enhanced re-loading of any RecA protein that dissociates. Roles for RecO in DNA recombination are described in greater detail in section III of this review.

SSB directly binds RecO (Umezu and Kolodner, 1994) and limits the formation of RecOR complexes on ssDNA (Hobbs *et al*., 2007). The ability of RecOR to load RecA is greatly reduced when RPA or an SSB variant lacking the C-terminal eight amino acids are substituted for wild-type protein (Hobbs *et al*., 2007), suggesting that direct physical interaction between SSB and RecO is necessary for maximal efficiency of the RecOR-stimulated reaction. A similar effect has been observed in *Thermus thermophilus*: RecO-assisted loading of RecA is achieved by means of the direct protein–protein interaction between RecO and SSB (Inoue *et al*., 2008). In this case, RecO binds both SSB and ssDNA and in doing so displaces SSB from the DNA.

DNA Replication Restart

PriA DNA Helicase (PriA Binds SSB via the SSB-Ct; Association with SSB Stimulates PriA Helicase Activity)

The primosome was originally identified as a collection of *E. coli* proteins required for the conversion of the phage ϕX174 genome from its single-stranded form to its double-stranded

(replicative) form (Wickner and Hurwitz, 1975). In total, the primosome consists of seven proteins: DnaB, DnaC, DnaG, PriA, PriB, PriC, and DnaT (Marians, 1984, 1992). Of these, DnaB, DnaC, and DnaG (primase) are necessary for initiation of replication of the *E. coli* genome at *oriC* (Kaguni and Kornberg, 1984), whereas the remaining proteins drive origin-independent initiation (replication restart) at the sites of collapsed replication forks (Ng and Marians, 1996; Heller and Marians, 2005a; 2005b). PriA initiates assembly of the PriA/PriB/DnaT primosome by binding DNA structures that result from replication failure and attracting PriB and DnaT (Shlomai and Kornberg, 1980; Lee and Kornberg, 1991; Zavitz and Marians, 1992; Ng and Marians, 1996; McGlynn *et al*., 1997; Jones and Nakai, 1999; Nurse *et al*., 1999; Marians, 1999; 2000; Nurse *et al*., 1999; Sandler and Marians, 2000; Xu and Marians, 2003; Lopper *et al*., 2007). PriA also appears to be an important anti-recombinase by binding stalled replication forks and preventing RecA binding and activity (Mahdi *et al*., 2006). In *B. subtilis* cells, PriA continuously colocalizes with the replication machinery (Lecointe *et al*., 2007). *E. coli* cells with deleterious *priA* mutations harbor numerous defects including UV sensitivity and defects in DNA repair, the SOS response, and chromosomal segregation (Lee and Kornberg, 1991; Zavitz and Marians,1991; Masai *et al*., 1994; Kogoma *et al*., 1996; Sandler *et al*., 1996; Cox, 1999; Sandler and Marians, 2000; Grompone *et al*., 2004b; 2004c).

PriA is a helicase that unwinds DNA with a 3′-to-5′ polarity (Lee and Marians, 1987; Lasken and Kornberg, 1988; Heller and Marians, 2007). PriA can unwind DNA duplexes of up to 40 bp on its own but requires SSB to process longer duplexes (Lasken and Kornberg, 1988). PriA can bind SSB-coated DNA (Allen and Kornberg, 1993) and can displace SSB from DNA (Arai *et al*., 1981). Its helicase activity is stimulated by SSB on branched DNA substrates resembling replication fork lagging strands but is inhibited by SSB on partial duplex DNA (Jones and Nakai, 1999; Cadman and McGlynn, 2004). SSB is able to weakly stimulate PriA-mediated unwinding of forked substrates that have no exposed ssDNA, suggesting that part of the enhancement effect is due to SSB sequestering DNA that PriA has already unwound (Cadman and McGlynn, 2004).

SSB stimulation of PriA appears to be a consequence of the two proteins physically interacting via the SSB-Ct (Cadman and McGlynn, 2004). Neither archaeal nor viral SSB are capable of stimulating PriA activity, and *E. coli* SSB variants with the *ssb113* point mutation or the C-terminal 10 amino acids truncated fail to stimulate PriA activity (Chase *et al*., 1984; Cadman and McGlynn, 2004).

PriB (PriB Binds SSB in an Undefined Manner)

PriB is the second member of the PriA-primosome to assemble (Allen and Kornberg, 1993; Liu *et al*., 1996). It acts to stabilize PriA binding to ssDNA and assists in primosome assembly by facilitating PriA binding to DnaT (Liu *et al*., 1996). Mutations in *priB* do not exhibit the UV sensitivity, recombination deficiency, or constitutive activation of the SOS response seen in *priA* mutants, but contribute to a very slow growth phenotype when combined with *priC* mutations (Sandler *et al*., 1999) and can influence plasmid copy number (Berges *et al*., 1997). PriB is a 12 kDa protein that exists as a dimer in solution (Low *et al*., 1982; Lopper *et al*., 2004) and shares extensive sequence and structural homology with SSB (Liu *et al*., 2004; Lopper *et al*., 2004; Shioi *et al*., 2005). Indeed, the similarities between SSB and PriB are of such a degree that it has been hypothesized that PriB arose due to a duplication of the *ssb* gene (Ponomarev *et al*., 2003). Consistent with this hypothesis, PriB binds to ssDNA (Low *et al*., 1982; Lopper *et al*., 2004), although in an unexpected fashion: while SSB binding of ssDNA is reliant upon base-stacking with the side chains of aromatic residues as well as electrostatic interactions (Bujalowski and Lohman, 1989; Raghunathan *et al*., 2000), PriB appears to utilize a mainly charge-based interaction made possible by multiple lysine residues (Lopper *et al*., 2007), and is still able to strongly bind an oligonucleotide even when its lone surface-exposed tryptophan is mutated (Huang *et al*., 2006).

PriB is also able to bind SSB-coated DNA, suggesting a protein–protein interaction (Low *et al*., 1982). Like SSB, PriB stimulates PriA helicase activity on forked DNA substrates and this stimulation is further increased when SSB is present (Cadman *et al*., 2005). Consistent with previous observations, SSB inhibits PriA helicase activity on partial duplex DNA even when PriB is present (Cadman and McGlynn, 2004; Cadman *et al*., 2005). PriB physically interacts with the helicase domain of PriA and bridges a ternary complex between PriA and DnaT (Lopper *et al*., 2007). What role an interaction between PriB and SSB might play remains unclear.

DNA Repair

Exonuclease I (Exonuclease I Binds SSB via the SSB-Ct; Interaction Stimulates Exonuclease Activity; the Structure of Exonuclease I in Complex with SSB-Ct is Known)

Exonuclease I (ExoI) is a DnaQ-family exonuclease that processively degrades ssDNA in a 3′-to-5′ direction (Lehman, 1960; Lehman and Nussbaum, 1964; Thomas and Olivera, 1978; Brody *et al*., 1986; Phillips *et al*., 1988; Brody, 1991). The gene that encodes ExoI in *E. coli* is known both as *xonA* and *sbcB* owing to the two distinct phenotypes that stem from different ExoI variants (Kushner *et al*., 1972; 1974; Phillips *et al*., 1988). *sbcB* (suppressors of *recBC*) mutations restore cellular recombination activity and reduce sensitivity to DNA damage from UV light in *recBC*- cells (Sunshine and Kelly, 1971; Kushner *et al*., 1974; Phillips *et al*., 1988). The strong reduction of ExoI activity in these cells appears to allow 3′ ssDNA ends to remain intact and available as RecF pathway recombination substrates (Horii and Clark, 1973; Wang and Smith, 1985). Ordinarily, ExoI would degrade the ssDNA ends, leaving DNA structures that cannot be efficiently recombined (Lehman and Nussbaum, 1964; .Horii and Clark, 1973; Wang and Smith, 1985; Phillips *et al*., 1988).

xonA mutants also acquire UV-resistance but are deficient in recombination activity compared to *recBC- sbcB E. coli* cells (Kushner *et al*., 1972; .Phillips *et al*., 1988; Allgood and Silhavy, 1991). The nucleolytic activity of ExoI is important for degradation of incorrectly base-paired DNA in mismatch repair (Lahue *et al*., 1989; Burdett *et al*., 2001; .Viswanathan *et al*., 2001). SSB also plays a central role in mismatch repair, which indicates that ExoI has adapted to act on SSB/ssDNA complexes (Lahue *et al*., 1989). Like RecJ, ExoI activity is stimulated by the presence of SSB. This distinguishes both RecJ and ExoI from several other nucleases that are inhibited by SSB (Molineux and Gefter, 1975). ExoI also plays roles in the preservation of genome integrity by acting as a deoxyribophosphodiesterase at apurinic and apyrimidinic sites (Sandigursky and Franklin, 1992; Sandigursky *et al*., 1992) and by suppressing frameshift mutations (Viswanathan and Lovett, 1998; Bzymek *et al*., 1999). The former activity is stimulated by SSB *in vitro* (Sandigursky *et al*., 1996).

Several experiments have demonstrated a direct physical interaction between *E. coli* ExoI and SSB, and have shown that this interaction is mediated by the SSB-Ct (Molineux and Gefter, 1975; Molineux *et al*., 1975; Kowalczykowski *et al*., 1994; Sandigursky *et al*., 1996; Genschel *et al*., 2000; Lu and Keck, 2008). This interaction is relatively strong ($K_a \sim 7.1 \times 10^6\ M^{-1}$; see .Lu and Keck, 2008) and, consistent with an ExoI/SSB-Ct interaction, SSB113 and C-terminal deletion variants fail to interact with ExoI (Genschel *et al*., 2000; Lu and Keck, 2008). Recently, the structure of ExoI bound to a peptide composed of the nine C-terminal residues of SSB was determined (Lu and Keck, 2008) (Figure 2C). In this structure, the C-terminal-most phenylalanine of the SSB peptide packs into a hydrophobic pocket that is flanked by a basic surface that is thought to contact acidic SSB-Ct residues that lie N-terminal to the phenylalanine (Lu and Keck, 2008). Significantly, mutations that alter residues on the surface of ExoI that disrupt SSB binding also abolish SSB stimulation of ExoI activity. Similar results are seen when the SSB tail is altered or removed, suggesting that SSB acts to recruit ExoI to ssDNA (Lu and Keck, 2008).

Uracil DNA Glycosylase (Uracil DNA Glycosylase Binds SSB via the SSB-Ct; Interaction Impacts Uracil Excision Activity in a DNA-dependent Manner)

Uracil DNA glycosylase (UDG) catalyzes the first step in a base excision repair pathway by creating an abasic site through removal of uracil from DNA (Lindahl, 1974; Lindahl *et al*., 1977; Lindahl, 1982; Sakumi and Sekiguchi, 1990; Dianov and Lindahl, 1994; Mosbaugh and Bennett, 1994; Savva *et al*., 1995). The DNA harboring the abasic site is then degraded and resynthesized (Dianov and Lindahl, 1994; Dianov *et al*., 1994; Mosbaugh and Bennett, 1994). UDG has also been implicated as a generator of dsDNA breaks when two uracils, located on opposite strands of a DNA duplex and separated by seven or fewer bases, are recognized and targeted for repair in rapid succession (D'Souza and Harrison, 2003).

SSB affects uracil excision activity by *E. coli* UDG in different ways depending on substrate structure. On a ssDNA substrate that lacks secondary structure, SSB decreases excision up to three-fold, but in a ssDNA molecule containing a tetraloop, SSB enhances UDG activity 7- to 140-fold depending on the position of the uracil (Kumar and Varshney, 1997). SSB proteins from other bacterial species are also able to stimulate UDG uracil excision in a species-specific manner, but activity is decreased when a UDG from any of the tested species is mixed with a heterologous SSB (Purnapatre *et al*., 1999; Acharya and Varshney, 2002). Surface plasmon resonance experiments suggested that these changes in activity depend upon a physical interaction between UDG and SSB (Purnapatre *et al*., 1999).

Handa and colleagues investigated UDG/SSB interactions in an exhaustive study (Handa *et al*., 2001). Interaction between *E. coli* and *M. tuberculosis* UDG and SSB proteins was demonstrated by yeast two-hybrid screens. *In vitro*, direct interaction between the proteins was demonstrated by far Western blot analysis and interaction on ssDNA was shown using electrophoretic mobility supershift assay (Handa *et al*., 2001). Surface plasmon resonance experiments yielded an association constant (K_a) for *E. coli* UDG and SSB of $5.9 \times 10^6\ M^{-1}$, which is similar to the K_a for ExoI/SSB complexes (Genschel *et al*., 2000; Handa *et al*., 2001; Lu and Keck, 2008).

E. coli UDG can bind a chimeric SSB consisting of the C-terminal 47 amino acids from *E. coli* SSB appended to the N-terminal 130 amino acids of *M. tuberculosis* SSB. It binds this chimera, designated *MtuEco*SSB, with lower affinity than wild type, but it does not bind the reciprocal chimera at all (*EcoMtu*SSB, in which the C-terminus of *M. tuberculosis* SSB is present). *MtuEco*SSB is capable of stimulating *E. coli* UDG activity, but *EcoMtu*SSB has an inhibitory effect (Handa *et al*., 2001). Therefore, the C-terminus of SSB appears to be required for UDG binding and the attendant biochemical stimulation.

DNA Polymerase II (DNA Polymerase II Binds SSB; Interaction Enhances Processivity and Replication Beyond Abasic Sites)

DNA polymerase II (Pol II) is a DNA repair polymerase (Chen *et al*., 1989; Iwasaki *et al*., 1990; Lewis *et al*., 1992; Qiu and Goodman, 1997). It is induced early in the SOS response up to 8-fold over basal levels (Bonner *et al*., 1988; 1990; Iwasaki *et al*., 1990; Schnarr *et al*., 1991; Lewis *et al*., 1992; 1994; Qiu and Goodman, 1997; Napolitano *et al*., 2000; Pham *et al*., 2001). Pol II participates in repair of and synthesis across various lesions (Escarceller *et al*., 1994; Berardini *et al*., 1999; Becherel and Fuchs, 2001; Fuchs *et al*., 2001; Pages *et al*., 2005; Al Mamun and Humayun, 2006) including thymine dimers (Sedliakova *et al*., 2001) and as such is especially important in replication and repair of UV-damaged DNA (Rangarajan *et al*., 1999; Sedliakova *et al*., 2001; Rangarajan *et al*., 2002). Pol II plays a role in maintaining the fidelity of replication (Escarceller *et al*., 1994; Foster *et al*., 1995; Becherel and Fuchs, 2001; Nowosielska *et al*., 2004), which is severely

compromised when its proofreading exonuclease activity is removed (Foster *et al*., 1995; Rangarajan *et al*., 1997; Banach-Orlowska *et al*., 2005).

Pol II was the first SSB interacting partner to be identified; indeed, in the manuscript announcing the isolation of SSB, Sigal and colleagues noted that the "DNA unwinding protein" that they purified to homogeneity had a strong stimulatory effect on DNA synthesis by Pol II (Sigal *et al*., 1972; Meyer and Laine, 1990). Soon after, SSB was found to facilitate binding of Pol II to ssDNA, to stimulate the Pol II-associated nuclease activity, and to form a complex with Pol II in the absence of nucleic acid (Molineux and Gefter, 1974; Weiner *et al*., 1975).

When functioning alone, Pol II is poorly processive, synthesizing approximately five nucleotides before dissociating from the template strand; however, Pol III HE processivity factors (the β subunit and the clamp-loader complex) increase Pol II processivity to about 1600 nucleotides in an SSB-dependent manner (Bonner *et al*., 1992; Dalrymple *et al*., 2001). The processivity factors and SSB are required for by-pass of abasic sites (Bonner *et al*., 1992). β may play a role in determining when Pol II is activated in SOS-induced cells (Becherel *et al*., 2002), as deactivation of Pol II in a strain with a mutant β restored viability to cells that would otherwise have been inviable (Sutton *et al*., 2005).

DNA Polymerase V (DNA Polymerase V Binds SSB via the SSB-Ct; Interaction with SSB is Critical for Translesion Synthesis Activity In Vitro)

DNA polymerase V (Pol V) carries out translesion synthesis on damaged DNA (Goodman, 2000; Livneh, 2001). Pol V is encoded by the genes *umuD* and *umuC* and forms when two molecules of UmuD undergo RecA-mediated cleavage to their active UmuD' form (Nohmi *et al*., 1988; Peat *et al*., 1996; McDonald *et al*., 1998) and assemble with one molecule of UmuC (Bruck *et al*., 1996; Reuven *et al*., 1999; Tang *et al*., 1999; Schlacher *et al*., 2006a). *In vitro*, Pol V translesion synthesis activity requires RecA and SSB (Rehrauer *et al*., 1998; Tang *et al*., 1998; 1999; Reuven *et al*., 1999; Maor-Shoshani and Livneh, 2002; Schlacher *et al*., 2005; Schlacher *et al*., 2006b). Increasing concentrations of SSB increases initiation of Pol V bypass synthesis (Maor-Shoshani and Livneh, 2002). This stimulation has recently been demonstrated to arise, in part, from a physical interaction between SSB and Pol V (Arad *et al*., 2008).

SSB increases Pol V access to the 3′ end of a DNA gap that is flanked by RecA filaments (Arad *et al*., 2008). The SSB113 protein and viral SSB proteins can substitute for *E. coli* SSB in this respect. However, when SSB113 is included in a translesion synthesis assay, little synthesis is observed, whereas the reaction is substantially more efficient in the presence of wild-type SSB (Arad *et al*., 2008). Interestingly, viral SSB proteins (gp32 from T4 phage and ICP8 from herpes simplex virus 1) allowed for attenuated activity in which DNA synthesis proceeds up to, but not beyond, the DNA lesion (Arad *et al*., 2008). When Pol III HE subunits β and γ (proteins that have been shown to assist with Pol V activity; see Tang *et al*., 2000; .Maor-Shoshani and Livneh, 2002) were included in reactions containing the viral SSBs, translesion synthesis occurred. Because Pol V coprecipitates with SSB but not SSB113, a physical interaction between the SSB C-terminus and Pol V is likely to play a crucial role in maximizing Pol V translesion synthesis activity (Arad *et al*., 2008). This conclusion is strengthened in light of the physical interaction between SSB and MucB, a plasmid-encoded UmuC homolog (Sarov-Blat and Livneh, 1998).

Other SSB-Binding Proteins

Exonuclease IX (Exonuclease IX Binds SSB in an Undefined Manner)

E. coli Exonuclease IX (ExoIX) was initially identified as a putative exonuclease since it shares 60% identity with the DNA polymerase I 5′-to-3′ exonuclease domain (Sayers, 1994). Indeed, partially purified preparations of ExoIX appeared to possess exonuclease activity (Shafritz *et al*., 1998); however it has since been shown that this activity is most likely due to an Exonuclease III contamination in ExoIX preparations, and that ExoIX itself is devoid of exonuclease activity (Hodskinson *et al*., 2007). The function of ExoIX in the cell remains unclear, as it has no apparent enzymatic activity and strains harboring ExoIX deletions (*xni*-) are indistinguishable from wild type (Lombardo *et al*., 2003). However, ExoIX does interact directly with SSB as demonstrated by coprecipitation and crosslinking experiments in the absence of nucleic acid (Hodskinson *et al*., 2007).

Bacteriophage N4 Virion RNA Polymerase (N4 RNA Polymerase Binds SSB (Most Likely via the SSB-Ct) and Requires SSB to Stabilize a Promoter Hairpin)

RNA polymerase from bacteriophage N4 (vRNAP) specifically requires *E. coli* SSB for early transcription (Markiewicz *et al*., 1992; Glucksmann-Kuis *et al*., 1996; Davydova and Rothman-Denes, 2003). N4 injects vRNAP into its host along with its genome in the initial stage of infection (Falco *et al*., 1977; Davydova *et al*., 2007). Even though N4 encodes its own SSB protein (Lindberg *et al*., 1989), its binding activity appears to be specialized to destabilize a hairpin structure that functions as a promoter, making the phage reliant on *E. coli* SSB as well (Glucksmann-Kuis *et al*., 1996). Interestingly, the N4 SSB functions as a transcriptional activator late in the phage's replication process, but does so through stimulation of *E. coli* RNA polymerase (Cho *et al*., 1995; Miller *et al*., 1996). *E. coli* SSB not only allows the N4 promoter hairpin structure to remain intact, but also assists in displacing nascent RNA from the ssDNA template, a task vRNAP is unable to accomplish alone (Davydova and Rothman-Denes, 2003). SSB binds both the ssDNA template and the RNA product, preventing the formation of a DNA-RNA hybrid. The result of maintaining both species in their non-duplex form is increased access to ssDNA and template recycling (Davydova and Rothman-Denes, 2003).

The stimulation of transcription by SSB is dependent upon the presence of the SSB-Ct element. Wild type SSB increases vRNAP transcription 20-fold, but variants that lack the C-terminal 10 residues of SSB fail to stimulate, but do not inhibit, transcription (Davydova and Rothman-Denes, 2003). Although a direct protein–protein interaction between vRNAP and SSB has not been explicitly demonstrated, experimental evidence strongly suggests that one exists.

Proteomic Identification of SSB-Binding Proteins

Two large-scale studies that probe networks of interacting *E. coli* proteins have been published to date (Table 1). The first utilized dual affinity-tagged proteins to identify binding partners of essential proteins (Butland *et al*., 2005), whereas the second used hexahistidine affinity-tagged variants of the majority of the *E. coli* proteome to define interaction networks (Arifuzzaman *et al*., 2006). Surprisingly, the His-tagging study detected just two of the known binding partners of SSB (RecG and UDG), which were only found when the partner proteins are the tagged bait (that is, tagged SSB failed to co-purify with either partner) (Arifuzzaman *et al*., 2006). Two other His-tagged proteins (DNA photolyase and YbcN, a hypothetical protein) were also found to co-purify with SSB, but neither interaction has been confirmed outside of the co-purification study. Only two proteins co-purify with His-tagged SSB in the study: Peptidase D and RhlE, a putative helicase. It is possible that the purification conditions for His-tagged proteins are too stringent for most SSB-interacting proteins to remain stably bound to SSB throughout the purification method, which led to the large number of apparently false negative results for SSB-interacting proteins in the study.

In contrast to the His-tagged proteins screen, the dual affinity-tag study identified 52 interactions involving SSB: 37 when SSB was C-terminally tagged, and 15 others in which a partner protein was tagged (Butland *et al*., 2005). This study validated interactions in experiments in which co-purifying partner proteins were tagged and the same interaction was detected reciprocally in a second, separate purification. This reduced SSB interacting proteins to the 13 verified complexes listed in Table 1. It is worth noting that since this study used C-terminal affinity tags to identify protein complexes, many false negatives could arise since the SSB-Ct forms a critical binding site for its partner proteins.

While nearly all of the listed binding partners have a clear role in nucleic acid metabolism, there are some indications that neither study has sampled the complete SSB interaction network. First, between the dual-affinity and His-tag studies, only one common binding partner was detected (RecG). This indicates experimental conditions greatly altered the spectrum of identified interacting proteins. Given that interactions with SSB can be relatively weak and dependent upon solution conditions, this is not surprising. Second, at least one of the "validated"

TABLE 1
SSB-interacting proteins found from proteomic studies

SSB-interacting protein	Found in dual-affinity experiment?	Found in His-tag experiment?
DNA polymerase III α	Yes, as bait	No
DNA polymerase III χ	Yes, as bait	No
PriA DNA helicase	Yes, as prey	No
RecG DNA helicase	Yes, as prey	Yes, as bait
RecQ DNA helicase	Yes, as bait/prey	No
RecJ exonuclease	Yes, as bait/prey	No
Exonuclease I	Yes, as prey	No
RNase H	Yes, as bait	No
DNA photolyase	No	Yes, as bait
Uracil DNA glycosylase	No	Yes, as bait
Topoisomerase I	Yes, as bait	No
Toposimerase III	Yes, as bait/prey	No
HU-α	Yes, as prey	No
SecA translocase	Yes, as prey	No
DnaK chaperone	Yes, as prey	No
Peptidase D	No	Yes, as prey
RhlE putatitve helicase	No	Yes, as prey
YbcN hypothetical protein	No	Yes, as bait

protein interaction partners, Topoisomerase I, is not believed to interact directly with SSB (Sikder *et al*., 2001), consistent with these purification schemes detecting both direct and indirect binding partners. Finally, since validation requires that both protein partners be amenable to similar tagging and purification procedures, some interactions may be lost as false negatives in validation screens. In the dual affinity-tag screen, there were several candidates that one can imagine as interacting with SSB in the list of non-validated partner proteins, such as DNA gyrase and Topoisomerase IV. However, since the reciprocal interaction was not detected, they are considered non-validated. Selected non-validated proteins such as these may warrant further investigation.

II. THERMODYNAMICS OF SSB–PROTEIN INTERACTIONS

The proteins that have been shown to interact directly with *E. coli* SSB protein all appear to contact the unstructured C-terminal region of the SSB protein, in particular the last nine amino acids. One question that arises is whether there is any specificity associated with these different interactions; i.e., is SSB binding to these different proteins determined solely by its unstructured C-terminus or are there other interactions that are specific to the protein partner? A second question is whether the stoichiometry of binding and/or specificity is influenced by SSB binding to DNA (either ssDNA or more complex junction structures) and furthermore whether the mode of SSB binding to ssDNA influences its interactions with these other proteins. Of course, answers to these questions require quantitative thermodynamics studies; however, to date, only a few of the proteins known to interact with SSB protein have been studied using direct quantitative methods (Table 2). Furthermore, even for those that have been studied quantitatively, the solution conditions used for those studies often differ and since solution conditions generally affect these interactions, questions of specificity are currently difficult to answer.

Binding of SSB to the χ subunit of the Pol III HE in the presence and absence of ssDNA was investigated using Surface Plasmon Resonance (SPR) (Glover and McHenry, 1998; Kelman *et al*., 1998; Witte *et al*., 2003), analytical ultracentrifugation (AU) (Witte *et al*., 2003) and gel filtration (Kelman *et al*., 1998). The interactions of PriA helicase with the SSB C-terminal peptide (Cadman and McGlynn, 2004), RecO with SSB (Umezu and Kolodner, 1994), and *E. coli* UDG with SSB (Purnapatre *et al*., 1999) have also been examined using SPR methods, and AU has been used to study the interaction of exoI with SSB and SSB with mutations in its C-terminus (Genschel *et al*., 2000). Isothermal titration calorimetry (ITC) has been used to characterize the interactions of SSB and its C-terminal peptide with RecQ helicase (Shereda *et al*., 2007), PriA helicase, and the χ subunit of the Pol III HE (Kozlov and Lohman, unpublished results).

As discussed above, *E. coli* SSB tetramers can bind to long ssDNA in a number of different binding modes that display distinct ssDNA binding properties, differing in the number of subunits that interact directly with the ssDNA, the inter-tetramer cooperativity, the affinity and the occluded site size (Lohman and Ferrari, 1994; Genschel *et al*., 2000; Raghunathan *et al*., 2000; 2007; Savvides *et al*., 2004). The transitions among these different binding modes can be modulated by the monovalent salt concentration (Lohman and Overman, 1985), divalent and mutivalent cations (Bujalowski and Lohman, 1986; Wei *et al*., 1992), as well as the SSB to ssDNA binding density (Chrysogelos and Griffith, 1982; Griffith *et al*., 1984; Bujalowski *et al*., 1988; Roy *et al*., 2007). It is therefore conceivable that the ability of SSB to recruit other proteins through interactions with its C terminus might be influenced by the particular mode of SSB binding to ssDNA. In addition, due to the acidic nature of the C-terminus of SSB, there is likely to be an electrostatic component to its interaction with other proteins. For these reasons, changes in solution conditions and especially salt concentration and type are likely to affect the binding properties of these proteins to SSB and its complexes with DNA.

Protein Binding to SSB and its C-terminal Peptides at High Salt

Most studies of SSB binding to other proteins have been carried out under high salt conditions (100–300 mM NaCl) (Kelman *et al*., 1998; Witte *et al*., 2003; Shereda *et al*., 2007). These are conditions that at equilibrium *in vitro* favor the fully wrapped high site size, $(SSB)_{65}$ mode of binding to ssDNA. Under these conditions, the affinities of SSB (without DNA) for the χ subunit. (Kelman *et al*., 1998; Witte *et al*., 2003), and for RecQ helicase (Shereda *et al*., 2007) are within the range of 2×10^5 to 4×10^5 M^{-1} (Table 2A and 2C). Similar values have been reported for the interaction of RecQ (Shereda *et al*., 2007) and PriA (Cadman and McGlynn, 2004) with peptides containing the last nine or 15 amino acids of the SSB C-terminus also at similar high salt concentrations (Table 2B and 2C). Importantly, C-terminal deletion mutants of SSB that are missing the last eight (Shereda *et al*., 2007) or 26 amino acids (Witte *et al*., 2003) as well as the SSB-113 mutant (Pro 176 to Ser) do not show any detectable affinity for χ (Kelman *et al*., 1998; Witte *et al*., 2003) or RecQ (Shereda *et al*., 2007). The affinities of C-terminal peptides carrying the Pro to Ser substitution are also reduced dramatically for χ (Kelman *et al*., 1998), RecQ (Shereda *et al*., 2007) and PriA. (Cadman and McGlynn, 2004). On the basis of these data it appears that at high salt concentrations (100–300 mM NaCl) SSB displays little specificity for χ vs. RecQ and interacts weakly ($(2–4) \times 10^5$ M^{-1}) with these proteins using primarily its unstructured C-terminus. The reported stoichiometries of binding (proteins per SSB tetramer) are four for RecQ (Shereda *et al*., 2007), but only 2–3 for χ. (Kelman *et al*., 1998; Witte *et al*., 2003). The lower values for χ might be explained by the fact that they were obtained using SPR (Witte *et al*., 2003), where chemical coupling of SSB to the chip surface could result in some occlusion of potential binding sites.

TABLE 2
Thermodynamic binding data for SSB protein complexes*

[Salt]	Method	SSB-Ct peptide binding data	SSB binding data	SSB/ssDNA binding data
		(A) χ/SSB interaction		
High				
300 mM	AU (Witte *et al*., 2003)	ND	N = 4 K = (2 ± 1) x 10^5	N = 4 K = (2 ± 1) × 10^5
200 mM	ITC [a]	ND	ND	N = 2.8 ± 0.6 K = (4.5 ± 1.1) × 10^5 ΔH = –7.7 ± 1.1
150 mM	SPR (Kelman *et al*., 1998)[b]	ND	N = 2.9 ± 0.1 K = (3.3 ± 0.3) × 10^5	N = 5.1 ± 0.4 K = (4.6 ± 0.1) × 10^5
150 mM	SPR (Witte *et al*., 2003)	ND	N = 2.5 K = (2.7 ± 0.5) × 10^5	N = 4.4 K = (4.2 ± 0.5) × 10^5
100 mM	SPR (Glover and McHenry, 1998)[c]	ND	K = 3.7 × 10^5	K=(1 – 3) × 10^{8d}
Low				
20 mM	ITC [a]	N = 0.9 ± 0.1 K = (1.3 ± 0.6) × 10^6 ΔH = –8.6 ± 1.8	ND	N = 4.2 ± 0.3 K = (6.1 ± 2.1) × 10^6 ΔH = –9.0 ± 0.4
5 mM	AU (Witte *et al*., 2003)	ND	N = 4 K = (4.0 ± 1.0) × 10^5	N = 4 K = (7.4 ± 1.0) × 10^6
None	Gel filtration (Kelman *et al*., 1998)	ND	ND	K = 1.9 × 10^7
		(B) PriA/SSB interaction		
High				
200 mM	ITC [a]	ND	N = 3.7 ± 1.4 K = (1.0 ± 0.8) × 10^6 ΔH = –5.1 ± 0.6	N = 4.6 ± 0.5 K = (1.8 ± 0.5) × 10^6 ΔH = –6.8 ± 0.3
150 mM	SPR (Cadman and McGlynn, 2004)	K = (4.2 ± 0.3) × 10^5	ND	ND
Low				
20 mM	ITC [a]	N = 1.0 ± 0.1 K = (1.8 ± 0.7) x 10^6 ΔH = –6.9 ± 0.6	ND	ND
		(C) RecQ/SSB interaction		
High				
150 mM	ITC (Shereda *et al*., 2007)	N = 0.90 ± 0.02 K = (1.5 ± 0.3) × 10^5 ΔH = –9.3 ± 1.1	N = 3.4 ± 0.6 K = (1.5 ± 0.4) × 10^5 ΔH = –18.0 ± 2	ND
		(D) UDG/SSB interaction		
Intermediate				
50 mM	SPR (Purnapatre *et al*., 1999)	ND	ND	K = 5.9 × 10^6

*binding parameters: N – stoichiometry of protein binding, K (M^{-1}) – association constant, ΔH (kcal/mol) – enthalpy change.
[a]Kozlov and Lohman, unpublished data.
[b]Parameters obtained fitting SPR data presented in Table I of Kelman *et al*. (1998), to the N noninteracting sites model.
[c]Includes ψ protein.
[d]Determined in the presence of $\gamma\delta\delta$' or $\tau\delta\delta$' subunits of pol III HE.

Protein Binding to ssDNA/SSB Complexes at High Salt

Under high salt conditions no differences in affinities were reported for the binding of χ to a pre-formed ssDNA/SSB complex compared to SSB alone (Table 2A). The equilibrium constants reported for χ in the presence of poly(dT) using AU (Witte *et al*., 2003) and for SSB bound to $(dT)_{65}$ using SPR (Kelman *et al*., 1998; Witte *et al*., 2003), are within the same range as reported for SSB alone with stoichiometries of ~4 χ proteins bound per SSB tetramer. This also seems to be the case for PriA binding to SSB even in the presence of $(dT)_{70}$. Therefore, it appears that the presence of ssDNA at high salt conditions has little effect on χ-SSB interactions, although PriA does display a higher affinity for SSB than does χ.

Interestingly, the presence of the ψ subunit, which is also a component of the Pol III HE and interacts with the χ subunit, does not affect the affinity of χ for SSB alone (3.7×10^5 M^{-1}). (Glover and McHenry, 1998), whereas on a DNA template coated with SSB the affinity increases to 3×10^8 M^{-1} when the $\gamma\delta\delta'$ subunits (clamp loader assembly) are also present. Hence, the presence of ssDNA and auxiliary proteins appears to increase the affinity between SSB and χ considerably (~1000 fold).

Protein Binding to ssDNA/SSB Complexes and SSB at Lower Salt

In contrast to the results obtained at high NaCl concentrations, the binding of ssDNA to SSB has a more pronounced effect on SSB-χ binding affinity at lower salt concentrations. The equilibrium constant for χ binding to SSB determined by AU at 5 mM NaCl ($(4.0 \pm 1.0) \times 10^5$ M^{-1}) increases ~20 fold (7.4×10^6 M^{-1}) when SSB is complexed with poly(dT) (Witte *et al*., 2003) (Table 2A).

With increasing salt concentration, the affinity of χ for ssDNA/SSB complexes decrease (Table 2A). However, essentially no change in affinity is observed for the interaction of χ with SSB alone as the salt concentration increases from 5 mM to 300 mM NaCl (Witte *et al*., 2003). This is somewhat surprising, especially since a ~3–5 fold increase in affinity is observed for just the C-terminal peptide (nine or 15 amino acids long) binding to χ at low salt (20 mM NaCl) as determined by ITC (Table 2A). A significant decrease in affinity upon increasing salt concentration was also reported for SSB binding to Exonuclease I (Genschel *et al*., 2000).

In summary, for χ and RecQ, the interaction with SSB at high salt concentrations (100–300 mM NaCl) is characterized by moderate affinities ($(2–4) \times 10^5$ M^{-1}), which are unaffected by ssDNA (although this is shown only for χ) and are similar to the affinities determined for the interaction of these proteins with the C-terminal SSB peptide. Presently there are not enough data to estimate quantitatively the effect of low salt conditions on the equilibrium constants for SSB-protein binding, although strengthening of the interaction is expected (Genschel *et al*., 2000). On the other hand it is evident that at low salt χ (Kelman *et al*., 1998; Witte *et al*., 2003) interact with ssDNA/SSB complexes with much higher affinities than with SSB alone. The affinity of this protein for ssDNA/SSB complex also decrease with increasing salt concentrations. This latter effect may simply reflect an effect on the electrostatic component of the interaction or it could suggest that SSB bound in different binding modes (e.g. $(SSB)_{35}$ at low salt or $(SSB)_{65}$ at high salt) possesses different binding properties for these proteins.

III. ROLE OF SSB IN BACTERIAL RECOMBINATION PROCESSES

Recombination is a process focused on the repair of DNA strand breaks, primarily double strand breaks and single strand gaps. Both types of DNA damage are found most commonly at the sites of stalled or collapsed replication forks (Kuzminov, 1996; 1999; 2001a; Cox *et al*., 2000; Michel, 2000; Cox, 2001; Michel *et al*., 2001; 2004). The single strand gaps at stalled replication forks can be quite extensive (Cordeiro-Stone *et al*., 1999; Higuchi *et al*., 2003; Heller and Marians, 2005b; .McInerney and O'Donnell, 2007). Inevitably, SSB protein binds to the ssDNA in these gaps. Its role is not simply protective. As already described, SSB is a facilitator of ssDNA metabolism, and its interactions with the proteins of recombinational DNA repair are critical to the course of that repair. In this section, we consider the roles played by SSB in recombination both as a facilitator and an impediment to the overall process.

The late 1970s and early 1980s witnessed a renaissance in the understanding of bacterial recombination, centered on the functional characterization of the RecA protein, both *in vivo* and *in vitro*. The primary roles of RecA protein, in recombination (McEntee, 1977; McEntee *et al*., 1979; Shibata *et al*., 1979a; 1979b), in the induction of the SOS response (Roberts *et al*., 1978; Roberts *et al*., 1979), and in SOS mutagenesis (Witkin *et al*., 1982; Witkin and Kogoma, 1984; Witkin, 1991), were established. In recombination, RecA protein promotes a series of DNA strand exchange reactions that lie at the heart of all recombinational processes (Cox and Lehman, 1981; Cunningham *et al*., 1981; West *et al*., 1981). In the induction of the SOS response, RecA protein acts as a coprotease – facilitating the autocatalytic degradation of the LexA repressor of SOS genes (Little, 1984; 1991). In the mutagenesis that accompanies the SOS response, RecA protein acts as an essential activator and probable subunit of the error-prone translesion DNA polymerase V (Schlacher *et al*., 2005; 2006b).

Just out of the limelight, it became apparent at about the same time that SSB played a significant role in just about everything RecA protein did (McEntee *et al*., 1980; Cox and Lehman, 1981; Lieberman and Witkin, 1981; 1983; West *et al*., 1982; Cox *et al*., 1983; Kowalczykowski *et al*., 1987). The RecA and SSB proteins were linked in their functions by three other proteins: RecF, RecO, and RecR (Kolodner *et al*., 1985; Moreau, 1988; Madiraju and Clark, 1990; Dri and Moreau, 1991; Madiraju *et al*., 1992; Umezu *et al*., 1993; Umezu and Kolodner, 1994). Notably, as was described above, RecO protein interacts with the

SSB (Umezu *et al*., 1993; Umezu and Kolodner, 1994; Kantake *et al*., 2002), and in particular the SSB C-terminus (Hobbs *et al*., 2007).

Two SSB mutations played key roles in elucidating the function of SSB in recombinational DNA repair. The first is *ssb113*, which was described above as producing a SSB-Ct variant mutation (Pro176Ser) that diminishes heterologous protein interactions with the SSB C-terminus (Chase *et al*., 1984). The *ssb113* alteration results in a temperature-sensitive conditional lethality at 30°C that is not suppressed by overexpression of the mutant protein (Chase *et al*., 1984). The second is the *ssb1* mutation, which codes for an SSB with a mutation in the OB fold (His55Tyr) and confers a temperature-sensitive phenotype, with much SSB function abrogated at 42°C (Williams *et al*., 1984). The *ssb1* mutation is known to destabilize the SSB tetramer (Williams *et al*., 1984; Bujalowski and Lohman, 1991a; 1991b). Overproduction of the SSB1 protein suppresses the temperature-sensitive phenotype (Williams *et al*., 1984). Both mutant proteins confer a variety of defects in DNA metabolism in the strains expressing them, including sensitivity to UV irradiation, growth defects, and recombination defects (Tessman and Peterson, 1982; Wang and Smith, 1982; Chase *et al*., 1984; Williams *et al*., 1984). Studies of SSB113 led to some of the first suggestions that SSB interacted directly with multiple other proteins (Chase *et al*., 1984). The *ssb113* mutation produced severe defects in DNA synthesis and an increase in double strand breaks that led to chromosome degradation, while the *ssb1* mutation produced more modest effects (Wang and Smith, 1982). Wang and Smith suggested that SSB played a key role in protecting exposed ssDNA during recombinational DNA repair (Wang and Smith, 1982). Lieberman and Witkin (1983) noted that the DNA degradation and UV sensitivity seen at 42°C in an *ssb1* mutant cell was not rescued by the inactivation of *recBCD* (exonuclease V), or by overexpression of the wild type *recA* gene. This indicated that multiple nucleases were involved in the chromosomal degradation, and RecA did not function properly in recombinational DNA repair unless normal SSB was present. The *ssb113* mutation blocks the induction of SOS at 30°C (its restrictive temperature). The increase in UV sensitivity and decline of SOS-associated functions such as mutagenesis seen in the *ssb113* strains was suppressed by the introduction of a *recA* allele (*recA*730 = *recA* E38K) that promotes constitutive SOS induction (Lieberman and Witkin 1983). The results implied that SSB played some direct role in the activation of RecA protein for SOS induction and SOS mutagenesis.

Although many proteins interact with the C-terminus of SSB, the details of the interaction are likely to vary from one protein to the next. A deletion of 10 C-terminal amino acids of SSB renders *E. coli* cells inviable (Curth *et al*., 1996). This implies that key interactions required for basic processes such as DNA replication occur at the SSB C-terminus. However, the alteration of the proline at position 176 in *ssb113* allows cell growth while rendering the cell UV sensitive (Chase *et al*., 1984). This indicates that interactions required for DNA repair are disrupted by the Pro176Ser change in *ssb113*, but the interactions required in replication remain intact.

Effects of SSB on RecA Protein Function

SSB plays a complicated role in RecA reactions. RecA binding to ssDNA generally occurs in two phases, nucleation and filament extension. Nucleation must involve one or a few RecA monomers, and recent work suggests the number is about 4–5 (Galletto *et al*., 2006; Joo *et al*., 2006). Under most conditions, RecA filament extension is relatively fast, allowing single filaments to coat long ssDNA molecules contiguously. Filament extension on ssDNA occurs in the 5′ to 3′ direction (Register and Griffith, 1985; Shan *et al*., 1997), with little addition of subunits to the 5′-proximal end detectable (Arenson *et al*., 1999). RecA disassembles from the 5′-proximal end (Bork *et al*., 2001b), in a reaction that requires ATP hydrolysis (Arenson *et al*., 1999). Disassembly from filaments bound to ssDNA occurs at a rate of about 70 subunits min^{-1} at 37°C (Arenson *et al*., 1999). This is substantially slower than filament extension, so that the growing ends of RecA filaments nucleated on a circular ssDNA soon encounter the disassembling end of the same or other filaments on the same DNA. Filament extension is blocked or impeded by secondary structure in the ssDNA substrate (Kowalczykowski *et al*., 1987).

SSB has different effects on the two phases of RecA filament formation. RecA filament nucleation is inhibited, and under some conditions blocked entirely, if SSB is allowed to coat the DNA prior to RecA addition (Cox and Lehman, 1981; Kowalczykowski *et al*., 1987; Lavery and Kowalczykowski, 1990; Umezu and Kolodner, 1994; Shan *et al*., 1997; Bork *et al*., 2001b). This inhibition is relieved in some RecA mutant proteins. These include RecA E38K (RecA 730; see Wang *et al*., 1993; Ennis *et al*., 1995), RecA V37M (RecA 803; see Madiraju *et al*., 1988), RecA T121I (RecA 2020; see Wang and Smith, 1986; Wang *et al*., 1991), RecA E38K, I298V (RecA 441; see Thomas and Lloyd, 1983; Knight *et al*., 1984; Volkert *et al*., 1984), and a truncation of the RecA C-terminus of 17 amino acid residues (RecA ΔC17; E.A. Wood and M.M. Cox, unpublished results). The involvement of the RecA C-terminus (also highly negatively charged) in the suppression of RecA loading has some possible mechanistic implications. The RecA C-terminus (the last 25 amino acid residues) is a kind of autoregulatory flap, removal of which enhances a range of RecA functions (Yu and Egelman, 1991; Kurumizaka *et al*., 1996; Eggler *et al*., 2003; Lusetti *et al*., 2003a; 2003b; Drees *et al*., 2004a; 2004b; Schlacher *et al*., 2005; 2006b). A plausible scheme is that the RecA C-terminus buries a surface on RecA protein that is required for a RecA interaction with SSB or the ssDNA bound to SSB, an interaction that is in turn necessary for SSB displacement and RecA nucleation. One or more of the other amino acid residues (E38, V37, T121) whose mutation also creates a protein more adept at bypassing the SSB block to nucleation may also be involved in interactions needed to cover the SSB displacement surface on RecA. For wild-type RecA protein, mediator

proteins alleviate the slow nucleation imposed by pre-bound SSB, as described below. These mediators may interact with the RecA C-terminus as part of their function.

When SSB is added to the ssDNA after, rather than before, RecA protein in an experiment that also includes ATP, the subsequent RecA reactions are enhanced rather than inhibited (Morrical *et al*., 1986; Cox and Lehman, 1987). The early addition of RecA provides an opportunity to get past the slow nucleation step. In contrast to nucleation, the extension phase of RecA filament formation is facilitated by SSB. The wild-type *E. coli* RecA protein is unable to disrupt secondary structure in ssDNA that is encountered during filament extension, leading to the formation of abbreviated filaments that do not uniformly coat the DNA. The SSB protein binds to and disrupts the ssDNA secondary structure. Extending RecA filaments readily displace SSB, allowing RecA to form a contiguous filament on the DNA. This general scheme, first proposed in the mid-1980s (Flory *et al*., 1984; Muniyappa *et al*., 1984; .Kowalczykowski *et al*., 1987), is now seamlessly consistent with more than two decades of work on the reactions promoted by RecA and SSB (Lusetti *et al*., 2002; Cox *et al*., 2006).

RecA protein promotes DNA strand exchange *in* vitro optimally under conditions that include relatively high concentrations of free Mg^{2+} ion ($\sim$10 mM). The SSB binding mode under these conditions may play a major role in the course of the reactions. Under these conditions, SSB binds primarily in the low cooperative, fully wrapped $(SSB)_{65}$ binding mode (Griffith *et al*., 1984; Bujalowski and Lohman, 1986; Lohman *et al*., 1986). The $(SSB)_{35}$ mode, which binds with high nearest neighbor cooperativity, has been proposed to function in DNA replication (Lohman *et al*., 1988).

There is some evidence for a persistent association of SSB with RecA protein filaments after contiguous RecA filaments are formed on ssDNA (Morrical *et al*., 1986; Muniyappa *et al*., 1990). A similar interaction has been detected between the eukaryotic RecA-homologue Rad51 protein and the eukaryotic RPA protein (Golub *et al*., 1998). However, the positive effects of SSB on RecA filament formation (and of RPA on Rad51 filament formation in eukaryotes) are not limited to species-cognate SSBs (Namsaraev and Berg, 2000; Egner *et al*., 1987), and no indication of a persistent *E. coli* RecA-SSB complex has been evident in studies employing electron microscopy. If an association exists, it is relatively weak, does not occur between RecA and SSB when neither is bound to DNA (Umezu and Kolodner, 1994), and does not play a role that is essential (or even stimulatory) to the RecA-mediated DNA strand exchange reactions commonly carried out *in vitro*. In those DNA strand exchange reactions, the RecA filaments form on ssDNA, and the bound DNA is then aligned with a homologous duplex DNA. A strand switch ensues, in which one strand of the duplex DNA is transferred to the original ssDNA to create a new duplex, and one strand of the original duplex is displaced. The SSB involved in facilitating the RecA filament formation prior to strand exchange is bound to the displaced ssDNA once strand exchange is complete (Lavery and Kowalczykowski, 1992). The RecA protein remains bound to the product duplex DNA, or dissociates, depending on solution conditions (Pugh and Cox, 1987; Lee and Cox, 1990; Cox *et al*., 2005). *In vivo*, a persistent association of SSB with the RecA filaments could help choreograph the efficient transfer of the SSB to the displaced strand, and the transferred SSB could serve as a target for the binding of multiple other proteins involved in post-recombinational processes. In fact, direct transfer of SSB between two DNA strands has been documented and is facilitated when SSB is bound in the $(SSB)_{35}$ binding mode such that two SSB OB-folds are unoccupied by ssDNA (Kozlov and Lohman, 2002). A persistent association of SSB with a RecA nucleoprotein filament, one that leaves ssDNA binding surfaces on the SSB unoccupied, might serve a similar function. Such a role might not translate into a measurable advantage of a RecA filament-SSB interaction during *in vitro* reactions, but may merit further experimental investigation. Notably, the SSB protein of *Mycobacterium smegmatis* interacts directly and in a species-specific manner with *M. smegmatis* RecA nucleoprotein filaments (Reddy *et al*., 2001). This interaction relies on the C-terminus of *M. smegmatis* SSB (Reddy *et al*., 2001).

The *E. coli* mediators, RecF, RecO, and RecR proteins

The SSB barrier to RecA nucleation gives rise to a need for protein mediators – proteins that bypass the barrier and facilitate the nucleation process. The same problem exists in the loading of RecA-class recombinases in all organisms, and mediators and their critical loading functions are now recognized as common in bacteria, archaeans, and eukaryotes (Sung, 1997; Beernink and Morrical, 1999; Song and Sung, 2000; Gasior *et al*., 2001). There is potential for damaging genomic rearrangements inherent in recombination. Mediators provide a critical opportunity for every cell to regulate recombinase function at a point prior to the initiation of any recombinational process. The *E. coli* RecF, RecO, and RecR proteins are considered the prototypes of this class of proteins. However, considerable mechanistic variation may exist in different species and classes of organisms, as well as phages and viruses encoding recombination systems.

The genes coding for the RecF (40.5 kDa; see Horii and Clark, 1973), RecO (27 kDa; see Morrison *et al*., 1989), and RecR (22 kDa; see Mahdi and Lloyd, 1989a; 1989b) proteins were discovered independently as functions that had modest effects on recombination and UV resistance in *E. coli*. The phenotypes of mutations in the three genes are very similar, and the effects of mutations in two or three of the genes are in many cases equivalent to the effects of any one of them, defining them as an epistatic group (Mahdi and Lloyd, 1989a; Clark and Sandler, 1994). Several additional lines of evidence indicate that these three proteins function together early in recombinational processes, and tie them to a role in facilitating RecA filament assembly on SSB-coated ssDNA. Mutations in all three genes are suppressed by the *recA* E38K (Wang *et al*., 1993; Ennis *et al*., 1995), *recA* V37M (Madiraju *et al*., 1988), *recA* T121I (Wang and Smith, 1986; Wang *et al*., 1991), *recA* E38K, I298V (Thomas

and Lloyd, 1983; Knight *et al*., 1984; Volkert *et al*., 1984), and a truncation of the *recA* gene that removes 17 codons at the end encoding the C-terminus (E.A. Wood and M.M. Cox, unpublished results). As already noted, the mutant RecA proteins produced by these same genes generally exhibit an enhanced capacity to displace SSB and bind ssDNA. In addition, a gene in bacteriophage λ called *ninB* or *orf* can replace the functions of all three *recFOR* genes in lambda recombination (Sawitzke and Stahl, 1992; 1994). Overexpression of SSB in *E. coli* produces a *recFOR*-like phenotype (Moreau, 1988), providing another link between RecFOR and the SSB barrier to recombinase nucleation. Mutant bacteria missing any of the *recFOR* functions exhibit a delayed activation of the SOS response, most easily interpreted as a block to the formation of the RecA filaments required to facilitate the autocatalytic cleavage of the LexA repressor (Madiraju *et al*., 1988; Whitby and Lloyd, 1995b).

Some results indicate that the *recF, recO, and recR* genes possess some functional distinctions. The three genes are not ubiquitous in bacteria, nor are they reliably coincident. A survey of recombination functions in 117 bacterial species demonstrates that bacteria tend to have all three genes, only the *recO* and *recR* genes, *recR* alone, or none (Rocha *et al*., 2005). The*recF* gene is absent from 29 species in the survey, while *recR* is absent from only 10. There are only two cases where a *recF* gene is not accompanied by both *recO* and *recR*, and in both cases it is *recO* that appears to be missing (Rocha *et al*., 2005). This may reflect a high substitution rate that seems to exist for *recO*, and an accompanying difficulty in identifying some *recO* homologues by classical search algorithms. A *recO* gene was subsequently identified in one of the two species in question (*T. thermophilus*), and its protein product has been studied at some length (Honda *et al*., 2006; Inoue *et al*., 2008). Taking the potential for discovery of a few more *recO* genes into account, the standard (or at least most common) complement of mediator functions in bacteria is either *recFOR* or *recOR* (Rocha *et al*., 2005).

Even where all three genes are present, some results indicate that they do not always function together. In a strain lacking the function of PriA protein, the additional loss of *recO* produces different results than the loss of *recF* (Sandler, S.J. 1996; Grompone *et al*., 2004a). Mutation of *recR* or *recF* suppresses the strong effects of *recO* mutation, suggesting that RecF and RecR are deleterious to the cell in the absence of RecO (Grompone *et al*., 2004a). The RecF protein, but not RecO or RecR, is needed for the activation of DNA polymerase V and mutagenic translesion DNA synthesis (TLS) (Rangarajan *et al*., 2002), providing one instance in which RecF may function without the other two proteins. SOS induction, UV resistance, and viability at 42°C are all reduced if RecF protein is overexpressed *in vivo* (Sandler and Clark, 1993). Overexpression of the RecOR proteins suppresses many of the effects of either RecF overexpression (Sandler and Clark, 1994b) or a *recF* null mutation (Sandler and Clark, 1994a). These varied results indicate that RecOR may function on its own, or as part of a larger RecFOR system, and RecF may have a few independent functions.

This evidently complex situation is mirrored *in vitro*. Structural information about these proteins is becoming available, and this should promote mechanistic insight as it is coupled to ongoing biochemical analysis. All of the structures made available to date are from the RecFOR homologues of *D. radiodurans*. The *D. radiodurans* RecF protein exhibits an unexpected structural similarity with the head domain of the eukaryotic Rad50 protein (Koroleva *et al*., 2007). However, it lacks the long coiled-coil domain of Rad50 (Koroleva *et al*., 2007). RecF is a member of the ATP-binding cassette (ABC) ATPase family of proteins, and possesses a weak ATPase activity (Webb *et al*., 1995; 1997; 1999). RecF binds to DNA, with increased affinity for dsDNA (Griffin and Kolodner, 1990; Webb *et al*., 1995; 1997). ATP binding triggers RecF dimerization (Koroleva *et al*., 2007). ATP hydrolysis triggers dissociation from DNA (Webb *et al*., 1999). RecR protein forms a complex with RecF and improves the stability of RecF-DNA complexes (Webb *et al*., 1995, 1997).

The *D. radiodurans* RecO protein contains an N-terminal domain that adopts an OB-fold, a novel α-helical domain, and a zinc-binding C-terminal domain (Makharashvili *et al*., 2004; Leiros *et al*., 2005). RecO catalyzes complementary DNA strand annealing and invasion of duplex DNA by a complementary ssDNA (Luisi-DeLuca and Kolodner, 1994; Luisi-DeLuca 1995; Kantake *et al*., 2002). The RecO binds directly to ssDNA, a property established for the RecO proteins derived from *E. coli*, *T. thermophilus*, and *D. radiodurans* (Umezu *et al*., 1993; Luisi-DeLuca and Kolodner, 1994; Luisi-DeLuca 1995; Kantake *et al*., 2002; Makharashvili *et al*., 2004; Leiros *et al*., 2005; Inoue *et al*., 2008). Notably, it is the RecO protein that interacts with SSB (Umezu *et al*., 1993; Umezu and Kolodner, 1994; Kantake *et al*., 2002; Hobbs *et al*., 2007).

The RecR homologs in *D. radiodurans* and *B. subtilis* both bind DNA (Alonso *et al*., 1993; Lee *et al*., 2004a; 2004b), although the *E. coli* RecR protein has no known intrinsic enzymatic or DNA binding activities. The *D. radiodurans* RecR structure is a tetrameric ring, with each monomer featuring a helix-hairpin-helix motif, a zinc finger motif, a Toprim domain, and a Walker B motif (Lee *et al*., 2004a, 2004b).

In vitro, the *E. coli* and *T. thermophilus* RecR proteins bind to their cognate RecF and RecO proteins (Umezu *et al*., 1993; Umezu and Kolodner, 1994; Webb *et al*., 1995; 1997; Bork *et al*., 2001a; Honda *et al*., 2006; Inoue *et al*., 2008). Both *T. thermophilus* RecF and RecO proteins interact with the C-terminal TOPRIM domain of *T. thermophilus* RecR (Honda *et al*., 2006), providing a plausible explanation for an apparent competition between RecF a*nd* RecO for RecR binding that has been observed for the *E. coli* proteins (Bork *et al*., 2001a). The structure of a *D. radiodurans* RecOR complex has also been elucidated (Timmins *et al*., 2007). The proteins form a heterohexamer, with two RecO subunits on opposite faces of the RecR tetramer ring, and the OB domains of the RecO subunits proximal to the RecR ring (Timmins *et al*., 2007). No structures of thse proteins with ssDNA or SSB are yet available.

The RecOR proteins clearly function together, and under many conditions these two proteins are necessary and sufficient to load RecA protein onto SSB-coated ssDNA (Umezu *et al*., 1993; Umezu and Kolodner, 1994; Bork *et al*., 2001a; Hobbs *et al*., 2007; Inoue *et al*., 2008). No conditions have yet been found in which one protein or the other alone can mediate the RecA loading process. As already noted, the RecO protein interacts directly with SSB (Umezu and Kolodner, 1994; Hobbs *et al*., 2007; Inoue *et al*., 2008). Significantly, removal of the eight C-terminal residues of SSB eliminates most RecO function in the loading reaction (Hobbs *et al*., 2007), indicating that a RecO interaction with the SSB C-terminus is critical to the loading pathway. Early models indicated that RecOR does not displace SSB, but instead binds to it to form a RecO-RecR-SSB complex that facilitates RecA nucleation (Umezu and Kolodner, 1994; Shan *et al*., 1997). A recent examination of the loading process with the *T. thermophilus* proteins provided evidence for SSB displacement (Inoue *et al*., 2008). The rate-limiting step in

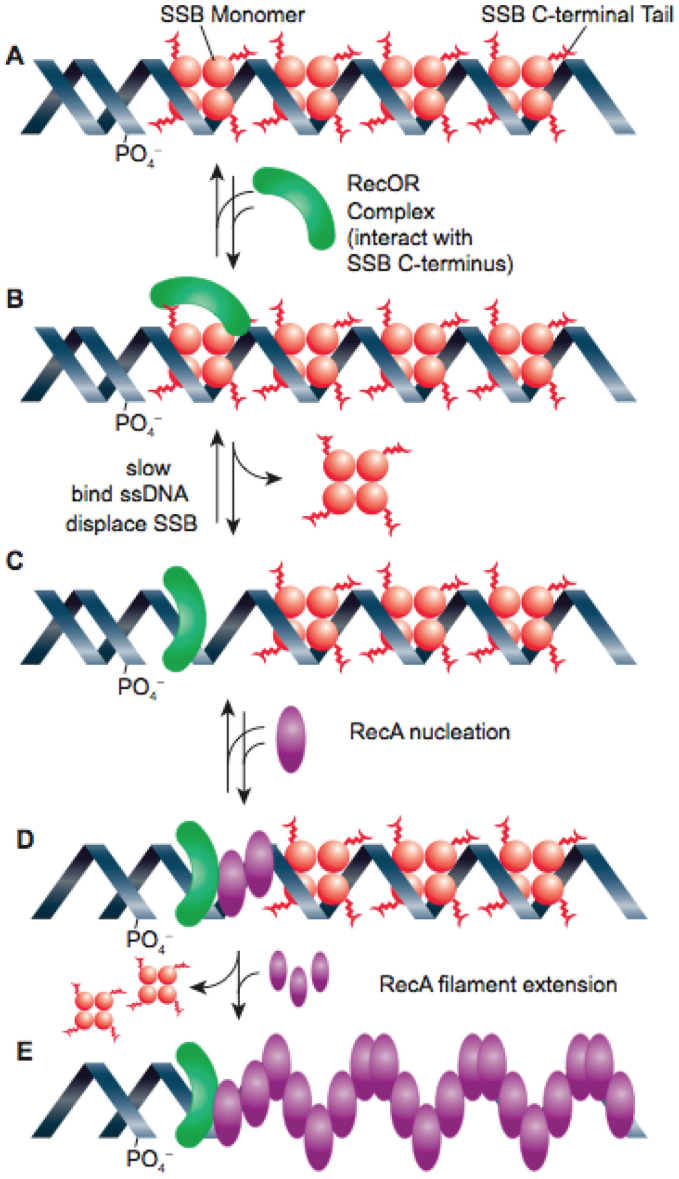


FIG. 3. Loading of RecA protein onto SSB-coated ssDNA by the RecOR proteins. The RecO protein, in a complex with RecR, first binds to the C-terminus of SSB. The RecOR complex with SSB is then rearranged to permit direct binding of RecOR to the ssDNA and displacement of an SSB tetramer. Once RecOR is loaded, RecA interacts with RecOR (perhaps in a way that alters the conformation of the RecA C-terminus so as to expose an intrinsic loading surface), and RecA nucleation occurs. This is followed by rapid and unassisted RecA filament extension. This figure is based on recent studies of the loading process (Hobbs *et al*., 2007; Inoue *et al*., 2008).

E. coli RecOR-mediated loading of RecA protein is the binding of RecO to ssDNA (Hobbs *et al*., 2007). This is inhibited by SSB, in spite of the direct interaction of RecO with the SSB C-terminus (Hobbs *et al*., 2007). The only set of conditions in which a small (8–10 min) lag in RecA loading was abolished was one in which the RecO was bound to ssDNA prior to the SSB (Hobbs *et al*., 2007). A model for the RecOR-mediated RecA loading process is presented in Figure 3.

Under most conditions, the RecF protein is either neutral or inhibitory for RecA loading on SSB-coated ssDNA when added to reactions containing RecOR (Umezu *et al*., 1993; Umezu and Kolodner, 1994; Shan *et al*., 1997; Bork *et al*., 2001a; Hobbs *et al*., 2007). The RecF protein has other demonstrable functions on the RecA filament formation process. RecFR complexes bind tightly to dsDNA, and can block the extension of RecA protein filaments initiated in ssDNA gaps into adjacent duplex DNA regions (Webb *et al*., 1997). RecF also interacts directly with the *E. coli* RecX protein, and antagonizes its function (Lusetti *et al*., 2006). The RecX protein blocks RecA filament extension, and the RecF function in this case may facilitate RecA protein extension in some instances. However, neither of these functions appears to fully explain the phenotypes of studied*recF* mutant strains.

When DNA substrates are used that incorporate short duplex regions on the ssDNA (generated by annealing short oligonucleotides to a bacteriophage ssDNA circle), the *E. coli* RecF protein has a positive effect on the RecA loading process in concert with RecR protein (Morimatsu and Kowalczykowski, 2003). This may reflect a special role for RecF protein in augmenting the loading process at the ends of DNA gaps. The positive effect of RecF is seen only when SSB is present at very high concentrations, corresponding to a 6–10-fold excess relative to available ssDNA binding sites (Morimatsu and Kowalczykowski, 2003; M. D. Hobbs and M. M. Cox, unpublished data), a requirement that is not yet explained.

With accumulating structural and biochemical data, this system seems poised for rapid advancement. Although RecF may have a special function in augmenting RecOR at the ends of gaps, there is no evidence that RecF binds specifically to those gap ends (Webb *et al*., 1997). Thus, there is potential for the discovery of additional targeting proteins in this system. A complete understanding of the RecFOR loading mechanism will facilitate studies of this critical function in all organisms. It should also facilitate an improved understanding of the dynamic nature of the SSB interaction with many other proteins.

IV. SUMMARY AND PERSPECTIVE

By binding both ssDNA and proteins central to every aspect of genome maintenance, eubacterial SSB proteins form a prominent interface at which genome maintenance pathways converge. As we have attempted to highlight in this review, the notion that SSB proteins are inert protective factors in bacterial cell biology vastly underestimates the contributions of this central scaffolding protein to genomic information storage and fidelity. From defining the substrates upon which DNA replication, recombination and repair must operate to playing an active role in nucleating complexes of enzymes, SSB proteins are central players in genome biology. Future work is needed to assess whether and how protein complex formation with SSB is regulated *in vivo* to determine which of the many competing interactions will predominate in a particular situation. In addition, the SSB-Ct-dependent nature of SSB/heterologous protein complexes could offer distinguishing features against which novel antibacterial therapies might be developed.

ACKNOWLEDGEMENTS

J.L.K acknowledges financial support from the NIH (GM068061). T.M.L. acknowledges financial support from the NIH (GM030498). M.M.C. acknowledges financial support from the NIH (GM032335 and GM0676085). R.D.S. is a Cremer Scholar. We apologize to any colleagues whose contributions to SSB studies might have been inadvertently overlooked in this review.

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Editor: William S. Reznikoff