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The SOS Regulatory Network

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Abstract

All organisms possess a diverse set of genetic programs that are used to alter cellular physiology in response to environmental cues. The gram-negative bacterium, *Escherichia coli*, mounts what is known as the "*SOS response*" following DNA damage, replication fork arrest, and a myriad of other environmental stresses. For over 50 years, *E. coli* has served as the paradigm for our understanding of the transcriptional, and physiological changes that occur following DNA damage (400). In this chapter, we summarize the current view of the SOS response and discuss how this genetic circuit is regulated. In addition to examining the *E. coli* SOS response, we also include a discussion of the SOS regulatory networks in other bacteria to provide a broader perspective on how prokaryotes respond to DNA damage.

OVERVIEW OF THE SOS RESPONSE

In *E. coli*, DNA damage and replication perturbations results in the SOS response, a genetic program that transcriptionally up-regulates over 50 unlinked genes (Table 1). The term "SOS" was coined by Miroslav Radman in 1974 when he postulated the existence of the pathway on the basis of a set of physiological responses induced by DNA damage whose regulation was controlled by the *lexA*$^+$ and *recA*$^+$ gene products (300). Radman defined "SOS" as a distress signal used to sense DNA damage or replication fork blockages.

Since the original hypothesis, the distress signal has been shown to be the accumulation of single stranded DNA (ssDNA). As described in greater detail below, LexA protein is a negative regulator of the SOS response by acting as a transcriptional repressor. RecA is a positive regulator of this response, and the interaction between LexA and RecA polymerized on ssDNA is required to relieve LexA-dependent transcriptional repression of SOS genes. Of the >50 unlinked genes that comprise the SOS response, several are directly involved DNA repair, DNA damage tolerance or inducing a DNA damage checkpoint by blocking cell division.

The SOS response is wired to allow for high fidelity repair to take place before giving way to a more mutagenic mode that allows for cell survival. When the SOS response is induced the first set of genes to be expressed are gene products involved in high fidelity DNA repair. Further into SOS induction, *sulA* gene expression is induced and this protein causes a DNA damage checkpoint by inhibiting cell division. The SulA-dependent checkpoint allows cells

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time to repair their DNA before damaged chromosomes are segregated into daughter cells. Late in the SOS response, *umuC* and *umuD* genes are expressed and these gene products assemble into a translesion polymerase that has mutagenic potential, as high fidelity repair gives way to lower fidelity damage toleraence. This lower fidelity DNA damage tolerance pathway, is so named because the damage is not removed, but instead tolerated.

Below, we review and discuss the experiments leading toward our current understanding of the SOS response. We also provide a comprehensive summary (Table 1) of all the genes known to be LexA regulated bringing the total number 57. Moreover, we include a table of genes that are potentially LexA regulated, but have yet to be verified (Table 2).

THE GENETICS OF SOS REGULATION

The SOS response is a genetic circuit that is regulated by the LexA and RecA proteins (4, 46, 47, 56, 91, 194, 211–214) (Fig. 1). LexA is a transcriptional repressor that occupies its cognate operator binding site (SOS box) as a homodimer thereby blocking RNA polymerase (RNAP) binding and transcription (1, 33, 34, 161, 218). LexA has a cryptic autocleavage activity that is activated when LexA interacts with a RecA/ssDNA nucleoprotein filament. Expression of $recA^+$ and $lexA^+$ gene products are regulated in an SOS dependent fashion, and RecA is rather abundant in the non-induced state (331). Considerable *in vitro* and *in vivo* evidence has shown that when bacterial DNA is damaged, ssDNA is generated (See Section: Mechanisms Generating ssDNA). RecA binds ssDNA forming a nucleoprotein filament (104, 147, 347, 419). Interaction between the RecA/ssDNA nucleoprotein filament and LexA activates LexA auto-digestion, thereby inactivating LexA as a repressor and leading to the transcription of LexA repressed genes (46, 47, 91, 162, 215). Below, we review the sophisticated network of proteins that influence the magnitude and timing of SOS induction.

The $recA^+$ gene product

RecA, a key player in DNA repair, is required for homologous recombination, SOS induction, and translesion synthesis (TLS). Many of the original *recA* mutant allele studies suggested that RecA is a positive regulator of SOS because these alleles were defective in recombination and SOS induction (257, 408). It is now known that RecA is required to facilitate LexA autocleavage and thus is a coprotease. The role of RecA in SOS induction was genetically defined when alleles of *recA* were isolated that result in constitutive SOS induction in the absence of exogenous DNA damage (192, 409). These coprotease constitutive *recA* alleles [$recA(Cpt^c)$] induced SOS during normal growth conditions, or in the case of *recA441* a temperature shift to 42°C to induce SOS (61, 409). Biochemical examination of the proteins encoded by *recA441* and *recA730* showed that these proteins displayed an exceptionally high affinity for ssDNA and are able to displace single-strand binding protein (SSB), an activity that is not observed with wild-type RecA protein (192, 201). It is hypothesized that *recA* coprotease constitutive mutants are able to compete with SSB for the low levels of ssDNA present at the replication fork during normal replication. It should be noted that RecA803 is capable of SSB displacment under specific *in vitro* conditions, but does not result in consitutive SOS *in vivo* (201, 229, 230). These results can be explained by the idea that more than ssDNA binding is important for SOS induction or by

the observation that RecA803 displaces SSB *in vitro* only under certain conditions that are not mimicked *in vivo* (201, 229, 230). Taken together, RecA binding to ssDNA is a critical step towards SOS induction, but more than ssDNA binding is involved including proper protein-protein interaction between RecA/ssDNA and LexA.

Other classes of *recA* point mutants that interfere with the ability of RecA to regulate SOS have also been described (90). For example, RecA430 is proficient for homologous recombination, but inefficient as a LexA coprotease (90, 244). To date several hundred *recA* alleles have been isolated and examined for repair and SOS defects [for review (239)].

The *lexA*$^+$ gene product

Alleles of the *lexA* gene have been identified that are defective in SOS induction [*lexA*(Ind$^-$)] (146, 210, 258), as well as alleles that encode variants of the LexA protein that fail to act as a repressor thereby resulting in constitutive SOS induction [*lexA*(Def)] (55). The *lexA*(Ind$^-$) class are dominant alleles so named for their lack of SOS induction. These alleles encode mutations that prevent autocleavage by altering the LexA cleavage site, or by altering the interaction between LexA and the RecA/ssDNA nucleoprotein filament. *lexA*(Def) alleles are lethal in an otherwise wild-type *E. coli* genetic background, a factor that complicated their original isolation (259). LexA protein represses *sulA*$^+$ (also called *sfiA*$^+$) (70), which inhibits cell division by blocking FtsZ ring assembly (35) . Therefore, *lexA*(Def) mutations must be propagated in a *sulA* deficient background to prevent a SulA-dependent block to cell division. The *lexA*(Def) mutation alone results in excessive SulA-dependent filamentation and cell death. SulA homologs are not as wide-spread as LexA homologs. For example, in *Bacillus subtilis*, SOS dependent cell filamentation is mediated by YneA a protein that interferes with FtsZ ring polymerization, but does not share sequence similarity to *E. coli* SulA (179).

These genetic studies established that RecA/ssDNA nucleoprotein filament formation activates the cryptic protease activity of LexA resulting in cleavage, and derepression of LexA-regulated genes. Although *recA*$^+$ and *lexA*$^+$ are the two key regulatory elements of the SOS regulon, a growing list of other proteins are involved in modulating SOS induction through positive or negative regulation of RecA/ssDNA nucleoprotein filament formation, LexA cleavage or both (for an overview of the SOS response see Fig. 1).

LexA binds to SOS boxes and inhibits transcription

In addition to genetic studies, which indicated that LexA is a negative regulator of SOS, *in vitro* studies have demonstrated that purified LexA protein can bind to operator sites resulting in inhibition of transcription (45, 47, 120, 218, 325, 326, 335). Comparisons of these sequences led to the discovery of a LexA binding site known as an SOS box, with a consensus sequence of TACTGTATATATATACAGTA in *E. coli* (120). All known SOS operators contain a 5′ CTGT consensus sequence with some preference for alternating $(AT)_4$ sequence. Within the 5′ CTGT consensus sequence, the central T and G bases are absolutely required for LexA binding. Mutations that lead to an operator-constitutive phenotype have also been isolated, resulting in increased expression of the affected LexA controlled gene (69, 241, 402, 403). Diversity within SOS boxes contributes to temporal

activation of gene expression as well as final induced levels. Induction ranges from about 100 fold in the case of *sulA*$^+$, one of the most tightly repressed SOS genes, to 4–5 fold in the case of *uvrA*$^+$, *uvrB*$^+$ and *uvrD*$^+$, *ruvAB*$^+$, and *lexA*$^+$ (335). Many parameters may be attributed to the differences in expression besides operator strength, such as location of operator relative to the promoter, promoter strength, and existence of additional, constitutive promoters. SOS boxes have been mapped to many locations, including overlapping with the −35 promoter region (*uvrA*$^+$), between the −10 and −35 regions (*recA*$^+$, *uvrB*$^+$), overlapping with the −10 region (*sulA*$^+$, *umuDC*$^+$) as well as downstream of the transcriptional start site (*uvrD*$^+$, *cea*$^+$, and *caa*$^+$) (120, 335) thus, allowing for a multivariable coordination of expression throughout the SOS response (for SOS box locations throughout the genome see Tables 1 and 2).

In vitro studies have shown that LexA binds to DNA as a dimer. Dimerization has proven critical for the repression of the SOS response. LexA consists of two structurally defined domains joined by a relatively flexible hinge region (227). The N-terminal domain, amino acids 1–84, specifically recognizes SOS boxes, although at a lower affinity than the intact protein (34, 161, 162, 186). The C-terminal domain is necessary for dimerization, with both intact and C-terminal fragments forming dimers in solution, with a dissociation constant <20 pM (253, 334). LexA cleavage of the Ala^{84}-Gly^{85} bond located within the hinge region during SOS induction separates the two domains, inactivating LexA as a transcriptional repressor. This cleavage not only regulates LexA activity, lowering LexA's affinity for DNA, but also LexA's stability by exposing residues that target LexA for degradation by ClpXP protease (268) (see below: Post-Translational Regulation of SOS Induced Proteins).

VARIOUS MECHANISMS OF SOS INDUCTION

Extensive analyses have shown that several seemingly unrelated stresses result in DNA lesions that impede replication, ultimately resulting in SOS induction. Experimental evidence suggests that these lesions are processed to ssDNA leading to SOS induction through RecA/ssDNA nucleoprotein filament-mediated cleavage of the transcriptional repressor LexA. The mechanisms ultimately leading to the formation of ssDNA is not well understood for all the SOS inducing stresses. Furthermore, it is becoming more apparent that many bacterial species utilize the SOS response to promote cell survival in a variety of stressful environmental conditions.

DNA damaging agents

A myriad of DNA altering or damaging agents have been shown to induce the SOS response in *E. coli* including: nalidixic acid, 3'-azido-3'-deoxythymidine (AZT), nitrofurazone, mitomycin C, benzo[a]pyrene diol epoxide, hydrogen peroxide, and 4-nitroquinoline among many others (20, 131, 140, 141, 164, 270, 295, 339, 361). The lesions created by these agents (altered nucleotides, ssDNA nicks, gaps, dsDNA breaks etc.) can impede DNA replication and must be removed by DNA repair mechanisms or tolerated by using DNA damage tolerance pathways, which are integrated into the SOS circuit. However, over 1000 *E. coli* genes are regulated in response to mitomycin C exposure suggesting that SOS induced genes may not be sufficient for recovery after treatment (184).

High Pressure

Hydrostatic pressure was recently shown to induce a *recA*$^+$, *recB*$^+$, and *lexA*$^+$-dependent SOS response in *E. coli* (3). The requirements for RecB suggests that ssDNA is formed through the processing of a double-strand break intermediate. Subsequent experiments revealed that an endogenous restriction endonuclease Mrr generates a double strand break after high pressure stress (2). The mechanism responsible for high pressure stress activation of Mrr is unknown, but represents an example of self targeted DNA restriction, a rather unusual method to manage stress. Although *E. coli* is not naturally subjected to high pressure environments, foods are often subjected to a combination of bacterial stresses, such as high pressure, to inactivate food-borne pathogens such as *E. coli* O157:H7, *Salmonella*, and *Listeria monocytogenes* (7, 66, 129, 261, 282, 412).

Antibiotics

Cell wall stress induced by treatment with β-lactam antibiotics or by compromising penicillin-binding protein 3 (*ftsI*$^+$) activity induces the DpiBA two component signal transduction system in *E. coli* (246, 247). DpiA binds A+T rich sequences thereby preventing DnaA and DnaB activity at the origin of replication resulting in SOS induction (246). Induction of SOS leads to the transcriptional up regulation of the *sulA*$^+$ gene. SulA binds to FtsZ thereby blocking FtsZ ring formation which temporarily prevents cell division and provides protection against cell death (260, 369, 401). Many recent studies suggest that the pathogens *Staphylococcus aureus* and *Pseudomonas aeruginosa* utilize the SOS response as a mechanism to promote antibiotic resistance (37, 67, 68, 232). For example, SOS induction by antibiotics not only results in increased TLS-dependent mutagenesis, but can also lead to transfer of pathogenicity islands (232, 374).

Starvation

Under starvation conditions in late stationary phase, the mechanistically controversial phenomenon known as adaptive mutagenesis is observed. An increase in-1-bp frameshift of *lacZ* revertants is used to measure adaptive mutagenesis. This is measured when cells are starved for lactose using a genetic system harboring F′ plasmids with an inactive lactose gene (*lac*) that can revert to *lac*$^+$ by a specific mutation (116, 117, 315, 316, 318). The −1 frameshift reversion is dependent on DNA Pol IV encoded by the *dinB* gene. Several studies suggest that the SOS response is required for the increase in point mutations by DinB (54, 240). It is possible that DinB maybe induced by the production of ssDNA during F′ amplification segregation (318). However, it has also been shown that the stress regulator RpoS may result in DinB induction (226). In addition to carbon limitation, amino acid starvation also triggers the SOS response upon resumption of growth on glycerol (167).

Intracellular pH

E. coli cells regulate their intracellular pH through redox and proton pumps (276, 277). However, improper regulation can lead to SOS induction (336). The mechanism for pH induced expression of SOS regulated genes might be explained by the result that pH alters the structure of the transcriptional repressor LexA (100, 355). It has been proposed that the

structurally altered LexA leads to aggregates, degradation, and ultimately a derepression of LexA regulated genes (355).

MECHANISMS GENERATING ssDNA

The major SOS inducing signal is the accumulation of ssDNA which is generated by a number of different mechanisms that ultimately result in SOS induction. During normal growth, the limited amount of ssDNA generated during DNA replication is tolerated *in vivo*. However, an increase in the amount of ssDNA provides a sensitive signal that requires a very low threshold for SOS induction. The most common situation that results in an increase in ssDNA occurs when the cell attempts to replicate damaged DNA (see below). However, generation of the SOS response by conversion of dsDNA to ssDNA can occur by a number of other mechanisms.

Replication of damaged DNA

Replication is required to induce the SOS response following UV irradiation. Evidence that DNA lesions were not sufficient to induce the SOS response was obtained in experiments in which a *dnaC28*^{TS} derivative in a nucleotide excision repair defective genetic background was exposed to UV light (324). The *dnaC28*^{TS} strain has impaired DNA replication at 42° due to its temperature sensitive helicase loader allele. When shifted to 42° after UV exposure, the *uvrB dnaC28*^{TS} double mutant fails to induce SOS, implying a role for DNA replication in the induction of the SOS response (324). Furthermore, following a 70 minute shift to 42°, UV irradiated *dnaC28*^{TS} cells fail to cleave LexA protein, in comparison to 70% cleavage of LexA in a wild-type strain within 10 minutes at the permissive temperature of 30° (331). These results indicate that the presence of UV lesions is not sufficient to induce SOS in cells lacking nucleotide excision repair, and that an active replication fork must attempt to replicate over DNA lesions for SOS induction to occur. A slight SOS induction does occur in *dnaC28*^{TS} strains at high UV doses at the restrictive temperature, implying either that removal of lesions results in gaps that are sufficient for SOS induction (324) or that a low level of replication is supported by the *dnaC28*^{TS} allele at the restrictive temperature.

Double-strand breaks are processed by RecBCD

The rate of formation of double-strand breaks under normal growth conditions is very low with 0.01 breaks detected per genome for *E. coli* (285). Several stresses, however, including nalidixic acid, high pressure, and gamma irradiation, result in SOS induction as the result of a dsDNA break intermediate processed to ssDNA (101, 131, 353, 361). Experimental evidence suggests that the RecBCD helicase/exonuclease degrades and unwinds dsDNA creating a 3′ ssDNA tail that induces SOS (Fig. 1) (149, 177). A crystal structure of the RecBCD enzyme suggests that, once the enzyme complex binds blunt-ended DNA, unwinding is initiated by the two helicases RecB and RecD and splits the two strands around the pin of RecC (350). RecB, a helicase and nuclease, initially degrades the 5′ tail less efficiently than the 3′ tail, which is channeled into the nuclease active site. As the 3′ tail is moved toward the nuclease active site, RecC scans the DNA and binds when it recognizes a chi (5′ – GCTGGTGG) sequence. Binding to a chi sequence prevents further degradation of

the 3′ tail and allows the 5′ tail to be degraded, thus creating a 3′ ssDNA tail for RecA binding. An *in vitro* reconstitution assay consisting of RecA, RecBCD, SSB, and LexA recapitulated the LexA derepression of an SOS promoter in the presence of a double-stranded break on DNA containing a chi site (10).

RecFOR-mediated processing of arrested replication forks generates ssDNA

Replication forks frequently stall because of physical blocks. The formation of an activated RecA/ssDNA nucleoprotein filament in response to a replication fork encountering a physical block, such as a UV photoproduct, requires processing by the RecFOR complex (Fig.1)(described in detail below). *recF*, *recO*, and *recR* are sensitive to DNA damaging agents, and exhibit delayed SOS induction (73, 305, 372). Several studies suggest that these proteins form a complex that enhance and stabilize RecA binding to ssDNA, in part through clearing SSB from ssDNA to nucleate RecA/ssDNA binding (43, 73, 256)

Furthermore, RecFOR function is required to prevent inappropriate RecQ and RecJ dependent degradation of the nascent strand at stalled replication forks. However, some RecQ and RecJ dependent processing of nascent DNA is required for replication restart following UV irradiation (73, 74). A current model, based on *in vitro* data, for nascent strand processing suggests that RecQ, a 3′ to 5′ helicase, unwinds template dsDNA ahead of the fork to remove impeding structures. RecQ then switches to the lagging strand and begins to unwind creating a ssDNA substrate for RecJ. Limited RecJ degradation of nascent DNA provides an area of ssDNA for RecA filament formation (154) which in turn prevents extensive DNA degradation (73).

Foreign DNA

Indirect SOS induction occurs when UV irradiated foreign DNA such as F or F′plasmids, P1, M13, bacteriophage λ, and Hfr DNA is introduced into cells (41, 42, 80, 89, 133, 317). The kinetics of SOS induction by plasmid P1 and λ are similar as measured by *sulA*::*lac* fusion expression. However, induction of SOS is markedly reduced without bacteriophage λ DNA replication, suggesting that replication of damaged DNA and subsequent processing of the lesion are necessary at least for bacteriophage λ (80).

DNA metabolism mutants

Mutations in genes encoding proteins that participate in DNA metabolism can result in SOS induction; these include *dam* (223, 287), *dnaQ* (208, 351), *polA* (23), *priA* (271, 329), and *uvrD* (275). Point mutants in essential genes encoding components of the replicative polymerase DNA Pol III and those necessary for chromosome segregation can also induce the SOS response. Mutants of Pol III subunits, including *dnaN159* (the β processivity clamp), display a partial chronic induction of SOS due to an impaired ability to interact with the catalytic subunit (363). *xerCD*, *div*, and *ftsK* mutants suffer from a more acute induction after the dividing septum shears chromosomes that fail to properly segregate (152, 219). Single cell studies of mutants expressing SulA::GFP suggests that in the case of DNA metabolism mutants, SOS induction only occurs in a subpopulation. In contrast, SOS induction in *lexA*(Def) mutants occurs uniformly in all cells within the culture (238), an issue that is discussed below in more detail (please see Single Cell Analysis of the SOS

Response). It was suggested that SOS induction occurs in a subpopulation of the DNA metabolism mutants because the cell has several pathways to process DNA intermediates. The non-induced cells may not have experienced enough DNA damage or the cell utilized a pathway that does not require the mutated gene product for repair (238).

Decreased nucleotide pools result in SOS induction

Exposing *E. coli* cells to hydroxyurea, a specific inhibitor of ribonucleotide reductase, decreases the intracellular concentration of dNTPs resulting in replication fork pausing and SOS induction (20). RecA, SulA, and λ prophage induction as a result of hydroxyurea exposure is RecBC-independent. Although RecA requires ATP for LexA cleavage, intracellular ATP pools are not a limiting factor for SOS induction (20, 213, 383). Survival during nucleotide starvation is enhanced by the SOS regulated Y-family polymerases UmuC and DinB (138), possibly due to their higher affinity for dNTPs as compared with Pol III. Interestingly, in the opportunistic pathogen *Serratia marcescens*, hydroxyurea treatment results in the LexA-dependent induction of an exocellular nuclease scavenging pathway (166).

STRUCTURAL INSIGHTS INTO RECA/DNA NUCLEOPROTEIN FILAMENT

Structural data is available for both the *E. coli* (Fig. 2) and an inactive compact *M. smegmatis* complex with a bound nucleotide between RecA monomers (84–86, 358–360) showing 6 RecA monomers per turn (Fig. 2). Furthermore, conserved residues in all bacterial RecA proteins lie along the RecA monomer interface, highlighting their importance for filament formation. The recent advances in optical techniques have allowed for the real time visualization of RecA or Rad51 polymerization on ssDNA and suggest that nucleation is the rate limiting step (127, 170, 292). A reconstruction of electron micrographs with RecA bound to dsDNA in the presence of LexA has also been generated (418). These results show that LexA is bound to a deep groove of the RecA/dsDNA (418). LexA contacts two adjacent RecA monomers within the 6_1 helical structure composed of 6 RecA monomers. These studies have collectively provided a picture of how RecA and RecA-like proteins form filaments on DNA *in vivo*.

RecA MODULATING PROTEINS

Proteins RecX, DinI, PsiB, RdgC, RecFOR, SSB, RecBCD, HU and UvrD affect the formation or disassembly of RecA/ssDNA nucleoprotein filaments, thereby modulating the magnitude of the SOS response (Fig. 1). In this section we will discuss the current view of how these proteins affect SOS and direct readers to reviews that provide an in-depth view of how these proteins regulate RecA-mediated repair.

Antagonistic functions of RecX and DinI modulate the stability of RecA filaments

RecX prevents RecA/ssDNA nucleoprotein filament extension, thereby decreasing SOS induction (357). In contrast, DinI stabilizes the filament, increasing SOS induction (413–415). RecX is an SOS induced gene product that caps the RecA filament, preventing polymerization (98, 99, 379). *In vivo*, RecX overexpression decreases SOS induction in some bacteria (362, 381) and in *Mycobacterium smegmatis*, overexpression of MsRecA is

toxic in the absence of Ms*RecX* (279, 280). However, *recX E. coli* strains fail to show an observable phenotype, suggesting that any RecX effect in *E. coli* is subtle (278, 357). It should be noted here that RecF has an inhibitory affect on RecX (228). RecF interacts with RecX and prevents RecX from exerting a negative affect on RecA (228).

The SOS-regulated DinI protein binds to and stabilizes RecA/ssDNA nucleoprotein filaments (206, 413, 414). In addition to this function, DinI interferes with UmuD cleavage to UmuD´ (269, 366, 367, 386). As discussed previously, the differential affinity of LexA for SOS boxes allows for genes to be turned on early or late in the SOS response. DinI is expressed early in SOS to stabilize RecA/ssDNA nucleoprotein filaments and may thus inhibit UmuD cleavage, thereby delaying mutagenic TLS and allowing for higher fidelity repair to take place prior to lower fidelity TLS (182, 413, 415). The affect of DinI on RecA and UmuD is an excellent example of how many different layers of regulation help make the *E. coli* SOS response a sophisticated physiological response to genotoxic stress.

Recently, RecA has been fused to green fluorescent protein (GFP) to visualize localization during normal growth and following challenge with DNA damaging agents. These experiments have revealed that the appearance and longevity of RecA-GFP foci (185, 307, 348) are altered by the absence of both *dinI* and *recX* (308). These experiments show that although the phenotype of *dinI* and *recX* strains is subtle, the absence of these proteins affects RecA-GFP focus formation *in vivo*.

PsiB limits SOS induction during plasmid conjugation

PsiB protein, expressed from conjugative plasmids including F and IncN, is a potent inhibitor of the SOS response (15, 16, 18, 103, 142). During conjugation the *psiB* gene is located in the leading region of DNA that is transferred allowing for early expression in the recipient cell (15). The transferred ssDNA in principle could be considered “excess” and results in RecA binding and SOS induction. The early expression of PsiB protein prevents induction of the SOS response. Although the mechanistic details of this inhibition remain to be elucidated, the current model postulates that PsiB interferes with RecA function [for review (76)].

RdgC competes with RecA for binding and inhibits LexA cleavage *in vitro*

Recombination-dependent growth (RdgC) is a DNA binding protein that binds both single and double stranded DNA, prevents RecA function by competing for binding sites on DNA (97, 323). The crystal structure of the RdgC dimer suggests dsDNA binding takes place in the central hole of the ring-shaped dimer (50). Binding of RdgC has been shown *in vitro* to inhibit RecA-dependent cleavage of LexA (97). Genetic experiments have demonstrated that the *rdgC*$^{+}$ gene product is required for viability in *priA* mutant strains, which are deficient for replication fork restart (255). *recF*, *recO*, or *recR* mutants alleviate the growth phenotype of a *rdgC* strain, suggesting that RdgC might function in blocking aberrant RecA loading in certain genetic backgrounds (255).

RecFOR, SSB, RecBCD and HU influence RecA's access to ssDNA

An underlying theme in this section is that SOS induction is mediated by RecA filament formation. The RecFOR, SSB and RecBCD proteins all influence SOS by affecting the accumulation of ssDNA *in vivo*. As mentioned above, the RecFOR proteins stimulate the loading of RecA onto ssDNA generated during replication of damaged templates (150, 151, 158, 320, 321, 328). *E. coli* strains that lack RecFOR function are delayed for SOS induction (231, 404). Genetic experiments have demonstrated that these proteins are in the same epistasis group, (328) and biochemical studies have shown that RecO and RecR, or RecFOR load RecA onto SSB covered ssDNA in purified enzyme assays (43, 338, 376, 377).

In undamaged cells, single strand binding protein (SSB) affects SOS induction by outcompeting RecA for ssDNA at the replication fork, thereby preventing SOS induction (43, 197, 202). There are approximately 7500–15,000 RecA monomers in *E. coli* when the SOS response is repressed (331, 357). In log phase cultures there are approximately 7000 SSB monomers (∼1750 tetramers), an *in vivo* observation suggesting that SSB must have a stronger affinity for ssDNA to allow for normal replication to proceed in undamaged cells (382). Indeed, SSB has a strong affinity for ssDNA and SSB prevents RecA binding to ssDNA *in vitro* (43, 338, 376, 377). It has also been shown *in vitro* that RecA will only displace prebound SSB from ssDNA if RecO and RecR are added to the reaction (43, 155, 338, 376, 377). In limited circumstances, SSB can aid in RecA filamentation by removing hairpins (or other secondary structures) from ssDNA (197).

As previously discussed, the RecBCD helicase/nuclease enzyme can have a positive affect on SOS induction. *E. coli* RecBCD and *B. subtilis* AddAB are enzymes that process double-strand breaks to yield a 3′ ssDNA segment that is required for RecA filament formation (9, 11, 64, 65, 92, 350).

Many bacteria, including *E. coli*, contain the histone-like protein HU. HU is a heterodimer composed of Hupα and Hupβ (172–175). HU is important for maintenance of DNA topology involved in several aspects of DNA metabolism, including replication initiation (38, 39). Although HU binds DNA non-specifically, HU binds to both recombination and replication intermediates with a higher affinity than it has for B-form DNA. Strains deficient for both the *hupA* and *hupB* genes show sensitivity to both UV and ionizing radiation. There are two possible reasons for this. One report shows that HU is important for SOS induction (252). A second report has shown the possibility of a direct role for HU in DNA repair. This report describes that HU binds preferentially to AP sites and contains AP lyase activity (196). However, more experiments are required to understand mechanistically how HU contributes to SOS.

POST-TRANSLATIONAL REGULATION OF SOS INDUCED PROTEINS

The SOS response is also regulated by post-translational protein modification. Interestingly, some of the first insights into regulation of the SOS response by post-translational modifications came from studies on λ prophage, which can induce its lytic cycle upon sensing ssDNA. Early work by Roberts and colleagues demonstrated that exposure of λ lysogens to UV-irradiation or mitomycin C results in a RecA-dependent cleavage of λcI, a

repressor of phage lytic genes, resulting in induction of the lytic cycle. Experiments using *recA*(Def) and λcI(Ind⁻) strains suggested that λcI cleavage activates expression of phage genes and that RecA acts as a regulator of the protease or was the protease itself (309). Subsequent studies established that λcI is cleaved between the Ala^{111}-Gly^{112} bond generating two nearly equal proteolytic fragments in an ATP/ssDNA dependent reaction (78, 79, 157, 332). This cleavage prevents the formation of a λcI homodimers that bind to λ operator sequences because the cleavage separates the operator binding domain and the dimer interface domain (217). These results led to the conclusion that RecA is activated for an ATP-dependent role in λ repressor cleavage when bound to ssDNA in a ternary complex. The ternary complex, the RecA/ssDNA nucleoprotein filament, is now understood to be a co-protease required to induce and stabilize a conformational change in λcI that brings the self-cleavage site in close proximity to the serine protease active site (187, 267).

As described earlier in this chapter, SOS controlled genes are induced when the LexA repressor undergoes an autoproteolytic cleavage event similar to that of λ repressor. Like λ repressor, the cleavage of LexA is facilitated by the RecA nucleoprotein filament on ssDNA (46, 157, 213, 214, 217, 218). Experiments using extracts from cells containing radiolabeled LexA demonstrated that the protein is cleaved nearly in half. The cleavage of the 22.7 kDa protein occurs between the Ala^{84}-Gly^{85} bond, and the kinetics suggest a more rapid cleavage event than λ phage (157, 218). *In vivo*, the half-life of LexA is approximately 1 hour in uninduced cells, however, cleavage begins one minute after UV exposure and is complete within 5 minutes. The *in vitro* kinetics of LexA cleavage are first order and are independent of protein concentration suggesting an intramolecular reaction with respect to the homodimer (331).

The domains necessary for RecA-mediated cleavage and autodigestion are located in the C-terminal domain of LexA (Fig. 3). Indeed, crystal structure analysis of the LexA C-terminus suggests that the protein exists in two states, non-cleavable and cleavable (227, 393). In the non-cleavable form, the cleavage site is positioned 20 Å away from the Ser-Lys dyad cleavage active site. In the cleavable conformation, the Ala^{84}-Gly^{85} bond is positioned to participate in the autoproteolytic cleavage reaction catalyzed by the Ser-Lys dyad. In the Ser-Lys dyad model of LexA cleavage, the uncharged Lys^{156} removes a proton from Ser^{119} creating a nucleophile to attack the Ala^{84}-Gly^{85} bond (209, 210, 306, 311). Isolation of *lexA*(Ind^{S}) mutants that increase the rate of LexA cleavage support the existence of two LexA structural conformations *in vivo* (312, 352). These results suggest that the RecA nucleoprotein filament does not participate directly in the proteolysis reaction, but instead induces a conformational change favoring LexA cleavage. For this reason RecA is termed a co-protease. In addition to the co-protease activity of RecA, full induction of the SOS response is ensured by ClpXP mediated degradation of LexA fragments preventing repressor activity mediated by the LexA N-terminal fragment (268).

UmuD also undergoes a similar Ser-Lys dyad catalyzed proteolysis event (Fig. 3) that regulates TLS and a DNA damage prokaryotic checkpoint (see Bacterial Cell Cycle Checkpoints). The catalytic core of UmuD shares structural homology to LexA and forms homodimers in solution (112, 284, 365). Like LexA, the proteolysis event is catalyzed by a Ser^{60}-Lys^{97} dyad that is within hydrogen bonding distance with the cleavage site, Cys^{24}-

Gly^{25}, in the presence of the RecA co-protease (53, 284, 341). Unlike LexA, UmuD structural studies support an intermolecular reaction due to the N-terminal arms folding in such a way as to then cleave sites in close proximity to the Ser-Lys dyad of the partner in the homodimer (365). The $UmuD_2$ proteolysis event, removes the unstructured N terminal 24 amino acids generating $UmuD'_2$. After cleavage the new N-terminus is able to move more freely and a large conformational change occurs presumably activating the protein for TLS (168, 284).

IDENTIFICATION OF GENES IN SOS NETWORK

To understand the breadth of *E. coli* responses to DNA damage, a genetic approach was used in a systematic search for genes induced as part of the SOS network. The Mu d1 bacteriophage (59), which generates chromosomal operon fusions to *lacZ*, was used to create a set of random transcriptional fusions. These fusion strains were screened for genes that expressed a higher level of β-galactosidase when treated with UV or mitomycin C (MMC). From this experiment a set of *din* (damage inducible) genes were isolated (182), whose expression was not detected in genetic backgrounds containing *recA* (Def) and *lexA* (Ind^-) alleles. Later genetic and biochemical studies showed that LexA was the direct repressor of the *din* genes (181). This technique was also used in a more directed experiment to generate fusions to genes suspected to be controlled by the SOS regulon. Such genes include $uvrA^+$ (183), $uvrB^+$ (115, 183), $sulA^+$ (160), $umuDC^+$ (17), $uvrD^+$ (12, 345), $himA^+$ (250), $ruvA^+$ and $ruvB^+$ (344), $recA^+$ (60) and $recN^+$ (222). At the time this chapter was written, 57 genes have been shown to be repressed by LexA (Table 1).

A computational search for LexA regulated genes was enabled by identifying a consensus sequence for the LexA box and the complete genome sequence of *E. coli* (113). In this study, LexA regulated genes were identified by searching the *E. coli* genome for potential LexA binding sites. These LexA regulated genes were then verified to be damage inducible, and LexA regulated *in vivo*. This work also showed that LexA bound several of these promoter regions *in vitro* (113).

While *lacZ* transcriptional fusions, and computational analysis were important breakthroughs in understanding the genes that comprise the SOS response, microarrays and chromatin immunoprecipitation followed by microarray analysis (ChIP-on-chip) now serve as a high-throughput method for monitoring changes in gene expression, and promoter occupation by LexA (75, 388). One microarray analysis (75) examined changes in gene expression following UV irradiation in wild-type and *lexA*(Ind^-) genetic backgrounds. These results confirmed the induction of known $lexA^+$ regulated genes, and also identified 17 previously unidentified $lexA^+$ regulated genes. In addition, genes up-regulated by a $lexA^+$-independent mechanism and genes down regulated in response to SOS induction were also identified. Transcripts expressed independently of LexA can be explained by downstream or secondary affects of genes regulated directly by LexA. For example, LexA may repress a gene that is required to regulate expression of a second gene. It is still unknown if transcripts downregulated by UV irradiation occur through a $lexA^+$- dependent or independent mechanism. Other microarray studies have examined the transcriptional response to UV and mitomycin C (184, 296).

While it has been known for many years that LexA acts as a transcriptional repressor of the SOS response, recent studies suggest that sole repression of the SOS response by LexA may be an over-simplification. The SOS regulatory system has been used to construct synthetic gene networks, and in *E. coli* some *lexA*$^+$ regulated genes have been shown to have another regulatory component (130, 193). For example, the *dinB*$^+$ gene is a member of the SOS regulon, which is repressed by *lexA*$^+$, but its expression is also regulated by the stress response sigma factor RpoS, thereby inducing *dinB*$^+$ transcript levels in stationary phase independently of LexA (203).

Similar efforts have been made to characterize the SOS response in a variety of other bacteria [for review (110)]. Microarray data show that *B. subtilis* contains a *recA*$^+$/*lexA*$^+$-dependent SOS system, although only 8 genes out of 62 induced by the SOS have analogous counterparts in *E. coli* (13). Interestingly, studies in *Mycobacterium tuberculosis* and *Myxococcus xanthus* imply both a *lexA*$^+$-dependent and an uncharacterized *lexA*$^+$-independent mechanism for induction of the DNA damage response (57, 302).

SINGLE CELL ANALYSIS OF THE SOS RESPONSE

The application of fluorescent microscopy to SOS studies has demonstrated the limitations of measuring SOS induction at the population level in cultures (51, 238). For example, when β-galactosidase activity is measured in cell culture using a *lacZ* transcriptional fusion to an SOS regulated promoter, the results represent a population average. In such experiments, it had not been clear if a given promoter's activity is similar in every cell or differentially expressed in subpopulations of cells (182, 324, 331). These models have been described as the "uniform expression model" or the "two population model," respectively (238). To determine SOS induction at the single cell level, *gfp*$^+$ was fused to the SOS regulated *sulA*$^+$ promoter. GFP fluorescence was measured in a comprehensive set of genetic backgrounds that have previously been shown to result in chronic SOS induction. Analysis of these results led to the conclusion that the "two population model" can explain most strains deficient or conditional for genes involved in DNA metabolism. The exception to this conclusion are strains deficient for *lexA*$^+$ or *recA*$^+$ because these cells are either never induced or induced constitutively giving a uniform gene expression pattern (238).

SOS MUTAGENESIS

Mutagenesis, induced by UV as well as a variety of chemical agents, is an active process (105, 120, 221, 262, 390–392, 408). This active cellular process involves specialized DNA polymerases, which are capable of inserting nucleotides opposite a misinstructional or noninstructional lesion, allowing continuation of replicative DNA synthesis. These polymerases, termed translesion DNA polymerases are the main contributors to the process referred to as SOS mutagenesis, error-prone repair, SOS repair, misrepair, and SOS processing. UV induced mutagenesis can be blocked by certain *lexA* and *recA alleles*, implying a role for SOS induced gene products in SOS mutagenesis (49, 258, 395, 405, 406).

UmuD´$_2$C (Pol V)-dependent mutagenesis

A screen for non-mutable *E. coli* strains lead to the discovery of the *umuD*$^+$ and *umuC*$^+$ genes. *umuD*$^+$ and *umuC*$^+$ are located in an operon, within the SOS regulon, and encode proteins with molecular weights of 15,000 and 45,000 Da respectively (107, 342). UmuD protein is present at ∼180 copies per uninduced *lexA*$^+$ cell and ∼2,400 copies per *lexA*(Def) cell (411). The levels of UmuC protein in a *lexA*(Def) background is ∼200 molecules per cell and was too low to be measured under non-SOS induced conditions (411). UmuD forms dimers, which undergo RecA mediated autocleavage, to form UmuD'$_2$ homodimers. It is these UmuD'$_2$ homodimers that function together with UmuC to form the active version of *E. coli* TLS polymerase Pol V (UmuD´$_2$C). Deletion of either the *umuD*$^+$ or *umuC*$^+$ genes abolishes the mutagenic affect of a wide-variety of agents including: UV, 4-nitroquinoline-1-oxide, and methyl methanesulfonate (88, 107, 120, 178, 342, 356, 391, 400, 407, 408). Strains defective in *umuC* or *umuD*, however, retain the ability to be mutated by certain agents including the methylating agent *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine (MNNG). MNNG generates O^6-methylguanine which has the potential to result in direct mispairing during replication because O^6-methylguanine can pair with either C or T. Although *umuD* or *umuC* strains are UV sensitive, it is a modest phenotype, and not nearly as sensitive as *uvr* mutants. In addition, Pol V dependent mutagenesis requires RecA to regulate the cleavage of UmuD to UmuD´ (24, 53, 269, 341, 368). Recent results have shown that two RecA molecules are important for mediating Pol V lesion bypass (289, 333). Taken together, RecA and Pol V collaborate to form a complex capable of lesion bypass. Finally, the molecular chaperones GroES and GroEL are required for Pol V dependent UV induced mutagenesis possibly functioning to help stabilize UmuC by facilitating correct folding (94, 95, 220). Consistent with this conclusion, the half-life of UmuC decreases in *groE* strains (95).

DinB (Pol IV)-dependent mutagenesis

Another *E. coli* TLS polymerase, Pol IV, encoded by *dinB*$^+$, was identified among a series of damage inducible (*din*) genes and plays a role in SOS mutagenesis (182). DinB has a molecular weight of ca. 40,000 Da, and is present at ∼250 molecules per *lexA*$^+$ cell and ∼2500 molecules per *lexA*(Def) cell (189). While *dinB* phenotypes have been more elusive than those of *umuDC*, *dinB*$^+$ is required for λ untargeted mutagenesis. Untargeted mutagenesis of bacteriophage λ DNA is observed when UV irradiated *E. coli* are transfected with unirradiated λ phage (52). DinB is also important for adaptive mutagenesis. Adaptive mutagenesis has been measured using reversion of a −1 frameshift in a *lacI lacZ* fusion. In this assay, cells are plated on minimal lactose medium, under non-lethal selection, resulting in the appearance of *lac*$^+$ revertants over several days (153). Although the mechanism by which adaptive mutations occur is controversial, it is clearly DinB-dependent, because *dinB* strains result in a 5–10 fold reduction in adaptive mutants (153). DinB activity is modulated by a host of other proteins *in vivo* (389). In particular, RecA, UmuD and UmuD´ have been shown to regulate the −1 frameshift activity of Pol IV *in vivo* and *in vitro* (137). These results demonstrate that RecA, UmuD and UmuD´ act as accessory factors for Pol IV, modulating the mutagenic capability of this polymerase. Furthermore, DinB allows for resistance to N^2-dG adducts including N^2-furfuryl-dG (169). It was shown that DinB

preferentially bypassed N^2-furfuryl-dG with higher proficiency than an undamaged dG, suggesting that DinB homologs are specialized for bypass of bulky N^2-dG adducts *in vivo* (169).

Pol II-dependent mutagenesis

DNA Pol II is encoded by the *polB*$^+$ (or *dinA*) gene, which is damage inducible (40, 294). Pol II translesion synthesis is often accurate across from 3, N(4) ethenocytosine adducts (5) and Pol II efficiently bypasses abasic as well as interstrand crosslinks (32, 176). Pol II contains the 3′–5′ proofreading exonuclease activity present in high fidelity polymerases, yet Pol II can be mutagenic. A rather striking observation is that Pol II is more mutagenic at AT rich sites rather than in GC rich sites which is unexpected for a proofreading polymerase (398). It was reasoned that Pol II has a preference for extension in AT-rich sequences owing to the higher mutation frequency (398).

Also, challenge of *E. coli* with N^2-acetylaminofluorene (AAF) results in −1 and −2 frameshift mutagenesis by both Pol II and Pol V (265). Although this review does not cover the topic of replication fork restart, it should be noted that Pol II has an established role in this process. The action of Pol II is coordinated with primosomal protein PriA and the RecFOR proteins (303–305).

BACTERIAL CELL CYCLE CHECKPOINTS

Cell cycle checkpoints have been well studied in eukaryotic organisms because of their importance in understanding cell cycle regulation and the clear links between the bypass of checkpoints and the development of cancer (14, 224, 301, 397). *E. coli* spatially regulates the cell cycle, i.e. DNA replication can occur at the ¼ and ¾ positions in the cell while cell division mechanisms occur at mid-cell (136, 200, 235, 319, 322, 340). This spatial separation of cell cycle events allows for initiation of a new round of replication before the previous round has completed (71, 93). The spatial regulation also allows arrest of certain cell cycle processes, but not necessarily arrest of all cell cycle processes (118). The lack of temporal cell cycle stringency has resulted in qualifying prokaryotic checkpoints as: ‘primitive checkpoints’ and ‘checkpoint-like’(48, 119, 273, 367).

The purpose of checkpoints, in both eukaryotes and prokaryotes, is to maintain genomic integrity and avoid cell death by preventing the overlap of cell cycle events. The cell is particularly vulnerable to loss of genomic integrity at ssDNA regions near stalled replication forks. Furthermore, formation of the RecA/ssDNA nucleoprotein filament results in the induction of prokaryotic checkpoints that prevent overlap of cell cycle events. The DNA damage, and cell division checkpoints are regulated by the SOS response specifically by inducing the *umuDC*$^+$ and *sulA*$^+$ (273, 369) gene products. Like their eukaryotic counterparts, these gene products are not necessary for the cell cycle events themselves but enforce proper execution, which is especially important following DNA damage.

The SulA-dependent DNA damage prokaryotic checkpoint

Expression of the cell division inhibitor SulA (also *sfiA*$^+$) is controlled by LexA and is up regulated following DNA damage. SulA directly prevents cell division by binding to FtsZ

(35, 72, 369). FtsZ, a tubulin homolog, forms a ring at midcell (Z-ring) providing a scaffold for other cell division proteins to bind and promote cytokinesis (401). X-ray crystallography data shows that SulA binds to FtsZ as a dimer (72). This direct interaction presumably prevents FtsZ polymerization into a Z-ring, thereby acting as a prokaryotic cell division checkpoint. The block to septation results in the formation of cellular filaments, cells that continue to grow but fail to divide, and was one of the first phenotypes observed in SOS induced cells.

The presumed purpose of the SulA-dependent checkpoint is to prevent distribution of damaged chromosomes to daughter cells. This allows sister chromosomes to be used for homologous recombination pathways that can be used to repair double-strand breaks and to tolerate DNA lesions. In addition, SulA helps temporally coordinate repair functions and cell division. Without proper coordination, nucleoids can be guillotined, meaning that the cell division plane closes on unsegregated chromosomes resulting in a double-strand break. This phenotype is observed in *xerCD, div, ftsK* and *sulA* mutants (30, 219, 394, 401). As mentioned above, FtsK is an SOS inducible ATP-dependent DNA pump that is required for cell division and chromosome localization under normal growth conditions. However, increased resistance to UV radiation and mitomycin C exposure have been observed after over-expression of FtsK (394). The mechanism for FtsK mediated increase in survival is not known.

The UmuDC-dependent DNA damage prokaryotic checkpoint

A model for a *umuDC*$^+$-dependent prokaryotic checkpoint was proposed on the basis of studies demonstrating cold sensitivity caused by UmuDC$^+$ overexpression (236, 237). UmuDC's role in this cold-sensitive growth phenotype is distinct from UmuDC's role in SOS mutagenesis (237, 274). A *umuD* missense mutation (S60A) results in a noncleavable UmuD that prevents SOS mutagenesis, but has no adverse effect on *UmuDC*$^+$-mediated cold sensitivity (274). Subsequent experiments with *umuD* (S60A) revealed that expression of the noncleavable UmuD protein resulted in increased survival following UV irradiation and a modest decrease in DNA replication in a *uvr*$^+$-dependent manner (273). The increase in UV resistance and a decrease in DNA replication occurred despite the inability of a noncleavable UmuD to participate in translesion synthesis. In addition, kinetics of UmuD cleavage to UmuD´ was comparable to the kinetics of UV-induced lesion removal by UvrA, and the kinetics of cleavage was UV dose dependent.

These observations led to the *umuDC*$^+$-dependent, DNA damage prokaryotic checkpoint model in which UmuD has two distinct roles. First, the $UmuD_2$ dimer in complex with UmuC delays the recovery of DNA replication and cell growth after DNA damage possibly by inhibiting Pol III at replication forks. This DNA damage checkpoint allows accurate repair of DNA damage before replication is attempted. If accurate repair mechanisms are insufficient, the eventual RecA-mediated cleavage of $UmuD_2$ to $UmuD'_2$ then permits $UmuD'_2C$ (DNA Pol V) to carryout TLS over any remaining damage (273).

The *umuDC*$^+$ DNA damage checkpoint model suggests that both $UmuD_2C$ and $UmuD_2'C$ have access to the replication fork and slow or arrest Pol III. Indeed, UmuD and UmuD´ have been shown to interact with various subunits of the Pol III holoenzyme (364). Affinity

chromatography has shown that $UmuD_2$ has a greater affinity for the β processivity clamp than does $UmuD'_2$. In contrast, $UmuD'_2$ interacts more strongly than $UmuD_2$ with the catalytic subunit, while both proteins interact equally with the epsilon proofreading subunit. Subsequent genetic analysis demonstrated that co-overexpression of β or epsilon with UmuDC abrogated the cold-sensitive phenotype (366).

INDUCIBLE GENE EXPRESSION INDEPENDENT OF THE CLASSICAL SOS REGULON

It has become increasingly clear that many bacteria mount a robust transcriptional response to DNA damage independently of *recA*$^+$ and *lexA*$^+$. Although a large proportion of the DNA damage-inducible genes in *E. coli* and *B. subtilis* are regulated by *recA*$^+$ and *lexA*$^+$ others are not, Table 1 (75, 144, 184). In both of these organisms, many genes that lack an identifiable SOS box are expressed following challenge with DNA damaging agents in *lexA* (Ind$^-$) or *recA* strains. In *E. coli*, transcription of approximately one third of the open reading frames in the genome is altered following mitomycin C challenge (184). This could be explained by the fact that mitomycin C is not specific for DNA and it reacts with other cellular components including proteins contributing to alterations in gene expression. Other DNA damaging agents such as UV irradiation are much more specific for DNA (102) and it is this difference that likley accounts for the gene expression data that was observed following challenge with MMC. In *B. subtilis*, the expression of 668 genes is altered following replication fork arrest with HPUra, 500 of which are regulated by *recA*$^+$ and/or *lexA*$^+$ (144). Most of these 500 genes are thought to be regulated indirectly since SOS boxes are located upstream of only a subset of these genes.

DnaA protein is required for the initiation of DNA replication and it acts as a transcription factor. DnaA is an example of a transcription factor that affects gene expression in response to DNA damage and replication fork arrest independent of the *lexA* and *recA* genes. In *B. subtilis*, DnaA regulates 12 genes following treatment with mitomycin C and 57 genes following replication fork arrest with the selective replicative polymerase inhibitor HPUra (13, 143, 144).

Microarrays have been used to characterize the DNA damage response in several bacteria including: *Mycobacterium tuberculosis*, *Myxococcus xanthus* and *Bdellovibrio bacteriovarus*. These studies have shown that damage-inducible gene expression, in these species can also occur independently of the *recA*$^+$ or *lexA*$^+$genes (57, 58, 87, 302). Taken together, the transcriptional response to DNA damage encompasses more than just *lexA*$^+$ *recA*$^+$ regulated genes.

THE DNA DAMAGE RESPONSE REGULATES VIRULENCE FACTORS

In several pathogenic bacteria, mobile genetic elements encode virulence factors. In addition, many of these elements are regulated by the DNA damage response [for review (180)]. In *Staphylococcus aureus*, bacteriophage φ11 and 80α are under control of SOS (139, 232, 233, 373–375). Replication and transfer of these phages results in horizontal gene transfer of virulence factors (373). *Vibrio cholerae* contains SXT, an integrative conjugative

element (ICE) that contains several genes encoding antibiotic resistance to chloramphenicol, trimethoprim, streptomycin and sulphamethoxazole. Transfer of SXT is regulated by the DNA damage response (25–28, 156). The element encodes SetR which interacts with the RecA/ssDNA nucleoprotein filament resulting in cleavage of SetR. SetR normally represses the expression of several activators that are required for SXT transfer. RecA/ssDNA cleavage of SetR thereby alleviates repression of the activators necessary for transfer of the element (27, 28). *V. cholerae* also encodes CTXϕ, a temperate filamentous phage that encodes cholera toxin (298, 299). LexA cleavage through interaction with RecA/ssDNA nucleoprotein filament is required for CTXϕ induction. The LexA binding site overlaps with the promoter region recognized by the alpha C-terminal domain of RNA polymerase preventing gene activation (298).

In enteropathogenic *E. coli*, the locus of enterocyte effacement (LEE) is SOS regulated and responds to positive regulation by Ler and negative regulation by LexA (243). The LEE locus also encodes the type III secretion system responsible for secretion of virulence-associated factors into host cells. The components of the type III secretion are encoded by the divergently transcribed LEE2 and LEE3 operons contained within LEE (108). LexA occupies the divergent promoter region repressing transcription of LEE2/3 (243). Furthermore, the expression of LEE2/3 requires a cleavable LexA. These examples demonstrate that the DNA damage response regulates the dissemination of antibiotic resistance genes, genes encoding the cholera toxin, and the type III secretion system in some bacteria.

CONCLUSIONS

The SOS response in *E. coli* is a complex genetic circuit that allows cells to sense damage to their genetic material and respond with both high and low fidelity repair. This chapter highlights many experiments that have shaped our understanding of the SOS response in *E. coli* and other organisms. We hope that readers have gained not only an appreciation for what is known about the response, but also an appreciation for the complexity of this response and the work that has yet to be done. Two of the major challenges will be to understand how cells coordinate DNA damage recognition with DNA replication, and the second will be to provide a structural basis for how protein-protein interactions contribute to regulation of the pathway. Other challenges in understanding the SOS response in *E. coli* will be to determine how the SOS response is coordinated with other physiological responses.

The analysis of SOS in other bacteria has opened an entirely new area of investigation. We think it is clear that many gram-positive and gram-negative bacteria respond to DNA damage by affecting gene expression, but the specific genes affected vary considerably from organism to organism. Detailed examination of SOS in a variety of bacterial species will considerably add to our knowledge of the mechanisms regulating SOS and the genes under SOS control. These studies will help determine how the SOS circuitry is plugged into other gene networks that allow for a given bacterium to thrive within it’s niche.

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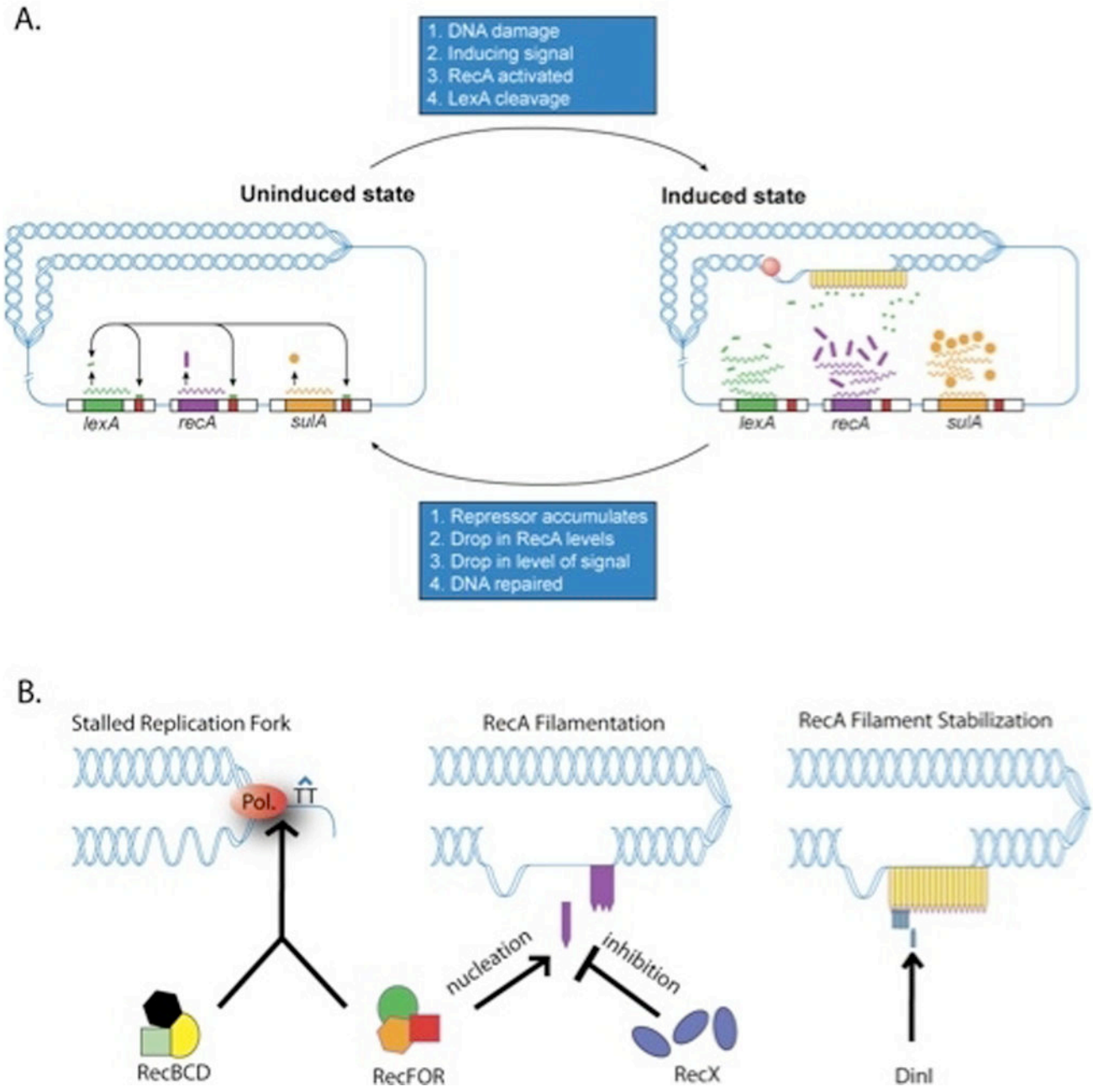

Fig. 1. A model for SOS induction

A. In the uninduced state, replication proceeds unperturbed and the limited amount of ssDNA present at the replication fork is not available for RecA binding. Transcription of *lexA*$^+$ (green), *recA*$^+$ (purple), *sulA*$^+$ (orange) and other SOS regulated genes is largely repressed. After DNA damage (red circle), RecA binds to the increasing amount of ssDNA in the cell creating the RecA/ssDNA nucleoprotein filament (purple and yellow). The RecA/ssDNA nucleoprotein filament acts as a co-protease to cleave LexA resulting in the expression of the SOS regulon. As the gene products of the SOS regulon repair the DNA damage, the cell will return to the uninduced state as normal replication proceeds and the

switch is reset. **B**. Generation and stabilization of a RecA nucleoprotein filament is regulated by a number of cellular factors. RecBCD and RecFOR can act at a stalled replication fork (left) to generate ssDNA for RecA binding. RecA binding and filamentation can be aided by RecFOR or prevented by RecX (center). Once formed, the RecA filament can be stabilized by DinI binding (right).

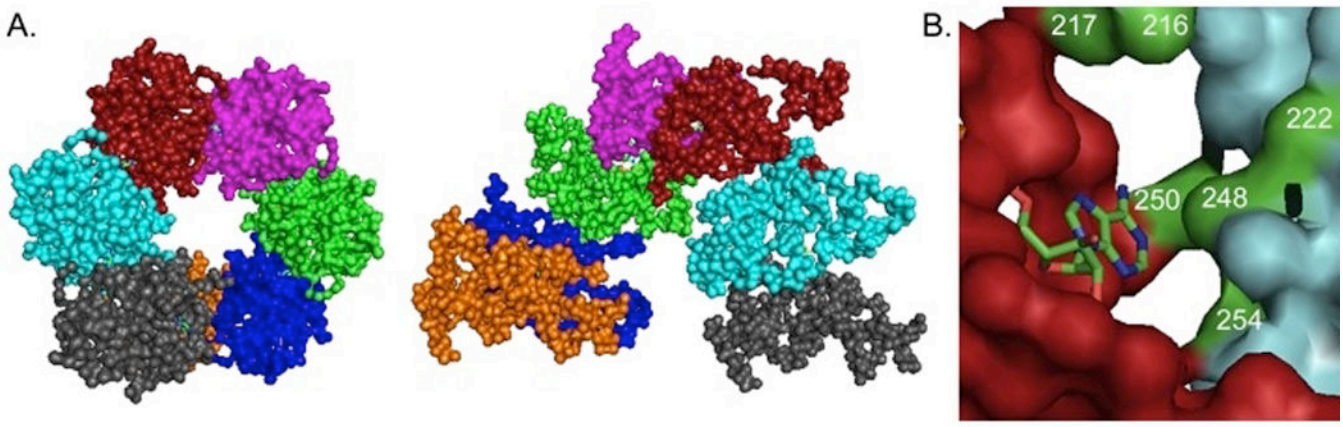

Fig. 2. Model of the RecA filament

Using electron microscopy, a model of the RecA filament was generated that positions the ATP between RecA subunits. **A**. The RecA filament is shown to display the DNA binding channel (left) and then subsequently turned 90º (right). **B**. An ATP molecule (shown) binds at the interface of two RecA subunits, positioning it to explain the cooperative nature of ATP hydrolysis observed for RecA-DNA filaments. Conserved residues in bacterial RecA proteins (green) are positioned along the subunit interface near the ATP binding pocket. The figure was generated using PyMOL and PDB file 1N03 (379, 380)

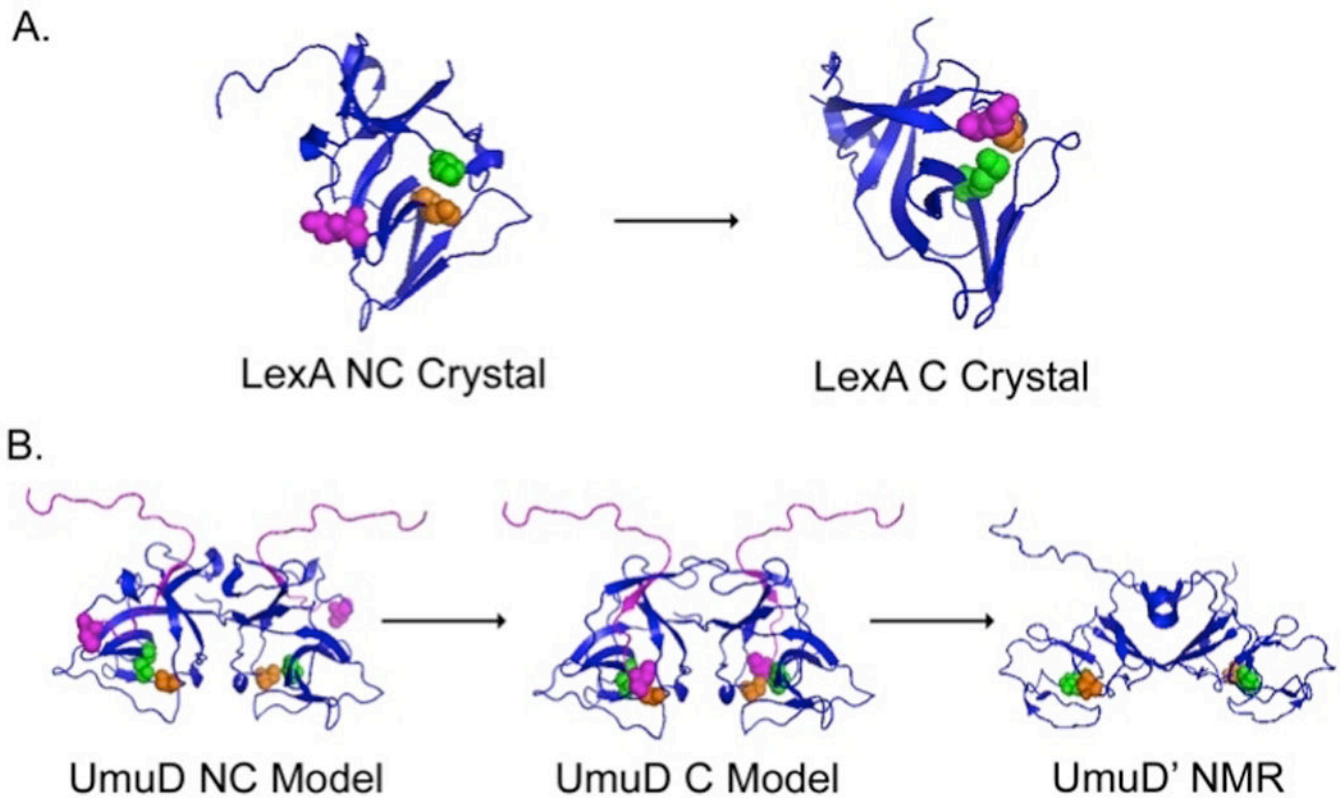

Fig. 3. Structural analysis of post-translationally modified SOS proteins reveals catalytically competent and non-competent protein conformations

LexA (**A**) and UmuD (**B**) proteins undergo a large rearrangement from a non-cleavable conformation (NC) to a cleavable conformation (C). **A**. LexA crystal structures indicate that the Ala^{84}-Gly^{85} residues (purple) can be positioned 20 Å away from Lys^{156} (green) and Ser^{119} (orange) in the NC form (left) to a position allowing for an autoproteolytic cleavage event in the cleavable form (right) (227). **B**. Full length models of the non-cleavable (left) and cleavable (middle) $UmuD_2$ dimer. The N-terminal arms of $UmuD_2$ (purple) fold to present the cleavage site (C24 purple spheres) to Ser^{60} (orange) and Lys^{97} (blue) (compare left and middle). NMR data suggest that after the cleavage event forming $UmuD'_2$ (right), the dimer undergoes a significant conformational change that consequently alters cellular activity (112, 284, 365).

Table 1

SOS regulated genes

LexA-dependent genes	Function	Identification as LexA dependent	LexA Box(es)[a]
polB (*dinA*)	−2 Frameshifts and replication restart after UV treatment (29, 126, 304, 305)	Mud1(Ap *lac*) (182)	−71 (75, 113)
dinB (*dinP*)	Translesion synthesis of N^2-dG adducts and −1 frameshifts (169, 188)	Mud1(Ap *lac*) (182)	−32 (75, 113)
hokE (*ybdY*)	Killing protein (113)	Northern Analysis (113)	−97 (75, 113)
uvrB	Involved in nucleotide excision repair (159)	UV resistance during Hfr mating; Mud1 (Ap *lac*) (115, 159, 182)	−92 (75, 113)
dinG	5′–3′ ssDNA helicase (195, 385, 387)	Galactokinase gene fusion (207)	−105/−34 (75, 113)
ftsK (*dinH*)	Chromosome segregation at cell division plane (96)	Galactokinase gene fusion (207)	−96 (75, 113, 207)
sulA	Inhibitor of cell division (132)	SOS chromtest; Mud1(Ap *lac*) (160, 295)	−42 (75, 113)
dinI	Stabilizes RecA/ssDNA filaments (386, 413)	Mud1(Ap *lac*); Suppressor *dinD68*; *lacZ* fusion (182, 413, 415)	−37 (75, 113)
umuCD	DNA pol V involved in SOS mutagenesis and translesion DNA synthesis (266, 286, 354)	LexA inhibition of *in vitro* transcription; MudI (17, 190)	−331,−351/−57,−37 (75, 113, 190)
yebG	Unknown	Operon Fusion (225)	−35 (75, 113, 225)
ruvAB	Holliday junction branch migration (RuvA DNA binding/RuvB helicase motor) (370, 371)	LexA repression of *in vitro* RNA pol. Assay; LacZ fusion (343, 344)	−67 (75, 113)
sbmC	DNA gyrase inhibitor (19, 63, 264)	Microcin resistance (19)	−32 (75, 113)
ssb	Single stranded binding protein (6, 245, 346)	S1 mapping; Galactokinase gene fusion (44)	−170 (113)
molR (*dinOsosF*)	Molybdate transport (205)	Northern Analysis (113)	−27 (75, 113)
recN	Involved in recombinational repair (222, 242, 290, 330, 396)	2D–gel electrophoresis; Mu (Ap lac) fusion (114, 222, 291)	−28, −46, −66 (75, 113)
recA	SOS regulation and mutagenesis/homologous recombination (36, 52, 77, 109, 148, 157, 198, 211, 213, 216, 218)	Dnase I protection assay; LacZ fusion (60, 218)	−77 (75, 113)
pcsA (*dinD*)	Unknown	Mud1(Ap *lac*) (182)	−61 (75, 113)
uvrD	DNA helicase II (272)	Complementation UV^s and MMS^s (234)	−74 (75, 113)
dinF	Unknown down stream of LexA	Mud1(Ap *lac*) (182)	−24,−45 (75, 113)
LexA	Transcriptional repressor of SOS genes (45, 46, 128, 157, 214, 218)	Dnase I protection assay (218)	−24,−45 (75, 113)
uvrA (*dinE*)	Involved in nucleotide excision repair (159)	UV resistance during Hfr mating; Mud1 (Ap *lac*) (159, 183)	−101/−168 (75, 113)
dinQ	Unknown	Northern Analysis (113)	−139 (113)
ydjQ	Putative UvrC homolog, function unknown (254)	Northern Analysis (113)	−33 (75, 113)
ysdAB (*tisAB*)	Toxic protein expressed under stress conditions (384)	Northern Analysis (113)	−142 (113)

LexA-dependent genes	Function	Identification as LexA dependent	LexA Box(es)[a]
ydjM	Inner membrane protein (83)	Northern Analysis (113)	−52 (113)
dinS	Putative transposase (113)	Northern Analysis (113)	−74 (113)
yigN	Unknown	Microarray (75)	−55 (75, 113)
ybfE	Unknown	Northern Analysis (113)	−136 (113)
yjiW (*dinLsosC*)	Unkown	Northern Analysis (113)	−95 (75, 113)
borD	Homolog of prophage protein expressed during lysogeny (21, 22)	Microarray (75)	ND
ybiN	Unknown	Microarray (75)	ND
grxA	Glutoredoxin; Hydrogen donor for ribonucleotide reductase (293)	Microarray (75)	ND
yccF	Unknown	Microarray (75)	ND
ymfD	Unknown	Microarray (75)	ND
ymfE	Unknown	Microarray (75)	−280
Lit	Protease for EF-Tu (134)	Microarray (75)	−193
intE	Predicted phage integrase	Microarray (75)	84, −192, −195 (75)
ymfG	Unknown	Microarray (75)	ND
ymfH	Unknown	Microarray (75)	ND
ymfI	Unknown	Microarray (75)	84
ymfJ	Unknown	Microarray (75)	ND
ycgH	Unknown	Microarray (75)	ND
ydeO	Unknown	Microarray (75)	−272
ydeS	Unknown	Microarray (75)	−43
ydeT	Unknown	Microarray (75)	ND
ydeR	Unknown	Microarray (75)	ND
arpB	Unknown	Microarray (75)	ND
yoaB	Unknown	Microarray (75)	−123
ogrK	Regulate gene transcription of phage P2 (145, 410)	Microarray (75)	−193, 8
yqgC	Unknown	Microarray (75)	−41, −193
yqgD	Unknown	Microarray (75)	ND
yhiJ	Unknown	Microarray (75)	ND
yhiL	Unknown	Microarray (75)	−63, −187
glvB	Unknown	Microarray (75)	−174
ibpB	Heat inducible chaperone (199)	Microarray (75)	ND
ibpA	Heat inducible chaperone (199)	Microarray (75)	−249
yifL	Unknown	Microarray (75)	ND

LexA-independent genes	Function	Identification as SOS induced
dinY	Mutant defective in Weigle reactivation of UV-irradiated bacteriophage λ (288)	Mu d1(Ap lac) (288)
dnaA	Initiation protein for chromosomal replication (399)	Transcriptional fusions; S1 nuclease mapping, immunoblot analysis (297)
dnaB	Replicative DNA helicase (204)	*lacZ* fusion (191)

LexA-dependent genes	Function	Identification as LexA dependent	LexA Box(es)[a]
dnaN	Pol III processivity factor; β-subunit (171)	*lacZ* fusion (171)	
dnaQ	Pol III proofreading factor; ε-subunit (171)	l*acZ* fusion (171)	
hga	2-Keto-4-hydroxyglutarate adolase; respiration recovery after UV exposure (106, 281)	2D–Gel Electrophoresis, Peptide Sequencing, and O_2 consumption (62)	
ihfA (himA)	Site-specific recombination (248, 249, 251)	*lacZ* fusion; Radiolabled 2D–Gele electrophoresis (250)	
nrdAB	Ribonucleotide reductase (121–125)	*lacZ* fusion (135)	
phr	DNA photolyase (327)	*lacZ* fusion (163, 283)	
hslVU	Protease of SulA (310, 337, 416, 417)	Microarray (75)	
cvpA	Colicin production (111)	Microarray (75)	
purF	Purine biosynthesis (313)	Microarray (75, 314)	
upp	Pyrimidine scavaging (8)	Microarray (75)	
rpoD	RNA polymerase sigma factor (263)	Microarray (75)	
dnaG	DNA primase (31, 349)	Microarray (31, 75)	
rpsU	Ribosomal subunit (82)	Microarray (75)	
yfaE	Unknown	Microarray (75)	
recX	Inhibitor of RecA (357)	Microarray (75)	
recQ	DNA helicase (378)	Suppression dnaE486; in vitro helicase assays (165)	
sfiC	Inhibition of cell division (81)	Cell Filamentation in *recAsfiA99*::Mu d(Ap *lac*) strain (81)	

[a] Distance from ATG start codon.

>Table 2

Potential SOS regulated genes[a]

Genes with potential SOS boxes	LexA Box(es) relative to promoter +1 start site
ydiM	−34
ilbL	−330
minC	−277
ycgJ	−262
yafL	−193
dinJ (*sosA*)	−32
ybiA	−105
tyrS (*dinNsosE*)	275
ORF within *yeeI*	−55, 118
ORF within *ycgM*	−57
mug (*tngygjF*)	−69
ORF within *ydbK*	−122
ygiS	−157
ORF within *ygiT*	−45
xylE	−23
ydbH	1
creA	−145
rob	−81
brnQ	−87
yiaO	−92
hofQ	−100
metE	−205
metR	−51
ORF within *ydcL*	−101
yhiX	−47
pshM	−89
ycgL	−57
rfaJ	−39
yjgN	−55
ybiT	−3
ilvD	−19
yecS	−73
ecpD	−79
ydeJ	−62
ycbU	−100
yfiK	−30
ymfM	−122, −222, −173
ymfN	−152, −312

Genes with potential SOS boxes	LexA Box(es) relative to promoter +1 start site
ymgF	−105
ymgH	6
yoaA	−24
yneL	−57
glvG	0, 211
glvC	214, 578
yfiE	−92

[a]Location of potential SOS box from Woodgate 2000 (113) and Courcelle 2001 (75)