The SOS Response of *Escherichia coli*

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89

INTRODUCTION

The SOS system was the first *Escherichia coli* regulatory network to be identified that is induced by DNA damage. It is the largest, most complex, and best understood DNA damage-inducible network to be characterized to date. The existence of the SOS system was first clearly postulated by Defais et al. (47), and this hypothesis was amplified and developed by Radman (47, 188, 189). The SOS system has been the subject of several major reviews, and these should be consulted for further details and references (69, 138, 177, 252, 253, 254, 269).

THE SOS RESPONSE

Exposure of *E. coli* to agents or conditions that damage DNA or interfere with DNA replication results in the induction of a diverse set of physiological responses termed the SOS responses. These responses are due to the induction of more than 20 genes or operons which have often been referred to as *din* (damage-inducible) genes (108). These SOS responses and genes are summarized in Table 1. The table includes genes whose products have known functions (for example, *polB* [formerly *dinA*], which encodes DNA polymerase II) but which have not yet been associated with observable physiological induced responses. Some SOS-regulated genes listed in Table 1 have been identified solely on the basis of their regulatory characteristics by the use of gene and operon fusion technology but have had no function ascribed to them yet. In the cases of some of the SOS genes, it is not clear that their induction contributes to cell survival under standard laboratory conditions.

Model for SOS Regulation

The expression of the genes in the SOS regulatory network is controlled by a complex circuitry involving the RecA and LexA proteins (69, 138, 177, 252–254). The basic regulatory mechanism of the SOS system is diagrammed schematically in Fig. 1. In an uninduced cell, the product of the *lexA* gene acts as the repressor of more than 20 genes, including the *recA* and *lexA* genes, by binding to similar operator sequences upstream of each gene or operon. Many of these SOS genes are expressed at significant levels even in the repressed state. The amount of RecA protein present in an uninduced cell, 7,200 molecules per cell (210), is evidently enough to satisfy the requirement for this protein in homologous recombination (104, 201).

In response to an SOS-inducing treatment or condition, a signal that leads to the expression of the SOS regulon is generated. A considerable body of evidence suggests that this signal consists of regions of single-stranded DNA. These may be generated when a cell attempts to replicate damaged DNA or under a variety of other circumstances. The binding of RecA to these regions of single-stranded DNA in the presence of a nucleoside triphosphate forms a nucleoprotein filament and converts RecA to an activated form (often referred to as RecA*). The interaction of activated RecA protein with the LexA protein results in the proteolytic cleavage of LexA: apparently, the activated RecA facilitates an otherwise latent capacity of LexA to autodigest. Activated RecA is also capable of mediating the cleavage of the repressors of the bacteriophages such as λ, P22, 434, and ϕ80, as well as the UmuD protein and its homologs (see below). The cleavage of LexA occurs at a particular Ala-Gly-peptide bond near the middle of the protein and generates

two polypeptide fragments. As the pools of intact LexA begin to decrease, various SOS genes, including the *recA* gene, are expressed at an increased level. Subsequently, the SOS responses mediated by the products of these genes begin to be observed. Genes with operators that bind LexA relatively weakly are the first to be expressed fully. If the inducing treatment is sufficiently strong, more molecules of RecA are activated, resulting in cleavage of more molecules of LexA. As the pools of LexA decline to very low levels, even genes whose operators bind LexA very tightly are expressed at maximal levels.

TABLE 1 SOS responses and genes of *E. coli*[a]

Induced physiological responses or gene function	Induced gene(s)	Reference(s)
E. coli		
Weigle reactivation of bacteriophages	*umuDC, recA, dinY*[b], *uvrA, uvrB*	3, 47, 105, 106, 178
Weigle mutagenesis of bacteriophages	*umuDC, recA*	252
UV mutagenesis of bacterial chromosome	*umuDC, recA*	3, 252, 269
Filamentation (inhibition of cell division)	*sulA* (*sfiA*)	90
uvr$^+$-dependent excision repair	*uvrA, uvrB, uvrD*	66, 108, 226
Long-patch repair	*uvrA, uvrB*	40, 41
Daughter strand gap repair	*recA, ruvAB?*	144, 146
Double-strand break repair	*recA, recN*	117, 184, 197, 209
Tandem duplication	*recA*	49
*Nar*I frameshift mutagenesis	*recA, umuDC* independent	152
Increase in pBR322 plasmid copy number	?	11
Rifampin-resistant pBR322 replication	?	154
Alleviation of restriction	*umuDC*, ?[b]	46, 86, 243
Inducible stable DNA replication	*recA*	153
Inhibition of DNA degradation by exonuclease V	recA, exi[b]	103, 182
Excision and transportation of Tn*5*	?	120
Induction DNA polymerase II	*polB* (*dinA*)	14, 98
Induction of various SOS loci	*dinB, dinD, dinF, dinG, dinH, dinI*	26, 108, 125–127, 148
Induction of SOS loci apparently not repressed directly by LexA	*dinY*[b], *recQ*[b], *dnaA*[b], *dnaN*[b], *dinQ*[b], *phr*[b], *nrdAB*[b]	125, 178
Phages and cryptic elements		
Prophage induction	Prophage genes	25, 85
Excision of element e14	?	79
Induction of defective retronphage (ϕR86)	?	112
ϕ186 induction	*tum*	121
Naturally occurring plasmids		
Induction of *umuDC* homologs (pKM101)	*mucAB*	61, 62
Induction of *umuDC* homologs (TP110)	*impAB*	147
Colicin production (ColE1)	*cea*	56, 57
Colicin production (ColA)	*caa*	142

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[b]The gene or locus is induced as part of the SOS response but does not appear to be regulated by LexA; in some cases, it is possible that the conclusion that the gene is under SOS control may be in error (see the text).
?, The induced gene(s) has not yet been identified. The relationship between many of these induced processes and survival is not understood.

As the cell begins to recover from the inducing treatment, e.g., by DNA repair, the inducing signal is eliminated and the RecA molecules are no longer in their activated state. The continued synthesis of

LexA molecules now leads to an increase in the pools of intact LexA. This in turn leads to repression of the SOS genes and a return to the uninduced state.

DEVELOPMENT OF THE MODEL FOR SOS REGULATION

Genetic Studies of *recA* and *lexA*

The initial evidence for the coordinate expression of the SOS responses grew out of genetic studies of the two key regulatory genes, *recA* and *lexA*. The first types of mutations identified were *recA*(Def) and *lexA*(Ind$^-$), each of which had the effect of preventing the induction of the set of responses now termed SOS responses (69, 89, 163, 188, 189, 251, 269). *recA*(Def) mutations were found to be recessive to *recA*$^+$, suggesting that the RecA product functions as a positively acting control element in SOS regulation. In addition to its role in SOS regulation, the RecA protein is absolutely required for all homologous recombination in *E. coli* and catalyzes synapsis and strand exchange between homologous molecules (115, 187, 194, 235, 264); *recA*(Def) mutants are completely deficient in homologous recombination. In contrast, *lexA*(Ind$^-$) mutants were found to be dominant to *lexA*$^+$, suggesting that the *lexA* product acts negatively in SOS regulation (32, 163). Unlike *recA* mutants, *lexA*(Ind$^-$) mutants are recombination proficient, a property which indicates that a deficiency in SOS regulation is not necessarily associated with a deficiency in homologous recombination.

The phenotypes of mutations located at the *recA* and *lexA* loci were often found to be complex and difficult to interpret, a fact reflected in the many names that have been used in the literature to describe alleles of these genes. The properties of most of these mutations (Table 2) can now be explained relatively easily in terms of the model described above.

Deduction of the Essential Elements of SOS Regulation

Studies of λ Induction and RecA Induction. The specific functions of the *recA* and *lexA* gene products in the regulation of the SOS system were initially deduced from studies of two particular SOS responses: (i) λ induction and (ii) the induction of what was termed protein X, which later was shown to be the 37.8-kDa RecA protein. These responses were particularly amenable to study, since the consequences of induction could be measured directly rather than having to be inferred from more complicated physiological responses.

The insight that proteolytic cleavage of a repressor could be involved in SOS regulation first came from studies of λ induction by Roberts and Roberts (191). They showed that treatment of a λ lysogen with UV or mitomycin resulted in the cleavage of the λ *c*I repressor and that this breakdown of the repressor correlated with the expression of phage genes. Since both λ induction and the induced cleavage of the λ repressor could be blocked by *recA*(Def) mutations, it was suggested that the RecA protein played a role in this process either by regulating a protease or by being a protease itself.

About the same time, Gudas and Pardee (81, 82) showed that induction of the synthesis of protein X by nalidixic acid could be blocked by *lexA*(Ind$^-$) mutations, as it could be by *recA*(Def) mutations (95). Furthermore, the synthesis of protein X could be induced by simply shifting a *lexA*(Ts) mutant, a *recA441* mutant, or a *lexA*(Ts) *recA*(Def) double mutant to an elevated temperature. On the basis of these observations, Gudas and Pardee proposed that LexA repressed the gene coding for protein X and possibly other SOS genes and that the RecA protein was involved in the inactivation of LexA. Because of the observation of Roberts and Roberts (191) that λ repressor was proteolytically cleaved at the time of SOS induction, Gudas and Pardee raised the possibility that LexA was also inactivated by proteolytic cleavage. Shortly afterward, several investigators (63, 80, 136, 157) demonstrated that "protein X" was actually the *recA* gene product and that RecA therefore played a role in its own induction.

The first *lexA*(Def) mutant was isolated by Mount (162) by screening for a derivative of a *lexA*(Ind$^-$) *recA441* strain that could not be lysogenized by λ. Strains carrying this *lexA*(Def) mutation also constitutively expressed other SOS responses including the high-level synthesis of the RecA protein (80). Of particular importance was the observation that *lexA*(Def) *recA*(Def) double mutants constitutively synthesized high levels of the (nonfunctional) RecA protein, a genetic observation that strongly suggested

that LexA functioned as a repressor of the *recA* gene and that the RecA protein was involved in the inactivation of the LexA protein at the time of SOS induction.

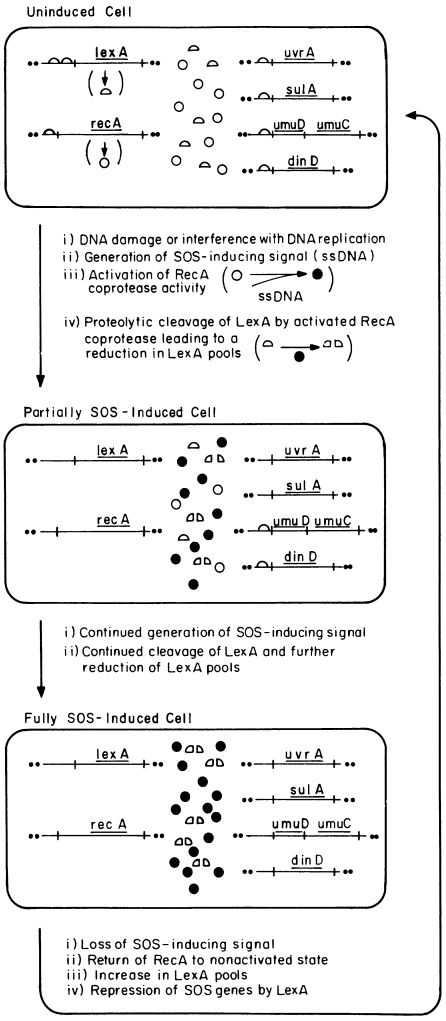

FIGURE 1 Model of the SOS regulatory system (adapted from reference 252). Open circles, nonactivated RecA molecules; solid circles, activated RecA molecules; semicircles, LexA molecules.

RecA-Mediated Cleavage of the LexA Protein. The protein that was required for the cleavage of the λ repressor was isolated by Roberts et al. (192, 193) from a strain carrying a *lexA*(Def) mutation and was shown to be the product of the *recA* gene. It was subsequently shown that purified RecA protein would mediate the cleavage of λ repressor in the presence of single-stranded DNA and ATP or a nonhydrolyzable analog of ATP (43, 44), with cleavage occurring at the Ala-111–Gly-112 peptide bond (87, 211). Since the RecA protein itself was capable of mediating the cleavage of a repressor and genetic studies suggested that RecA was involved in the inactivation of LexA, it seemed likely that the LexA protein was also cleaved in a RecA-dependent fashion at the time of SOS induction. This key element of the control circuit was established when the *lexA* gene product was identified as a 22.7-kDa protein that was shown to be cleaved in vitro in a RecA-mediated fashion and to function as the direct repressor of both the *recA* and *lexA* genes (20, 21, 135, 139).

Molecular Mechanism of LexA Cleavage

A recent body of work carried out primarily by Little and his colleagues has indicated that rather than acting as a classical protease, RecA apparently mediates LexA cleavage by facilitating an otherwise latent capacity of LexA to autodigest. This research was stimulated by the finding that specific cleavage of LexA

and λ repressors could occur in the absence of RecA. Incubation of highly purified LexA or λ repressor under mildly alkaline conditions in the presence of a divalent cation resulted in the cleavage of the same Ala-Gly bond that is normally cleaved at physiological pH only when activated RecA is present (131, 133). For both LexA and λ repressor, the key elements required for both RecA-mediated cleavage and autodigestion are located in the carboxyl-terminal domain of the protein (133, 211). Little and his colleagues have proposed that an uncharged form of Lys-156 helps to remove a proton from Ser-119, which then serves as the nucleophile to attack the Ala-84–Gly-85 bond of LexA (227); a second postulated role for Lys-156 could be to donate a proton to the α amino group when the peptide bond is broken. The model has been supported by analyses of the properties of *lexA* mutants (129, 130, 227) and by the demonstration that autodigestion can be inhibited by high concentrations of the serine protease inhibitor diisopropylfluorophosphate (195). In addition, it has been shown that the C-terminal cleavage product of LexA can act as a relatively efficient enzyme to cleave other molecules of a truncated LexA protein or intact LexA protein with a mutation (SA119) in its active site (111, 134). Despite the insight that the RecA-mediated cleavage of LexA occurs by a somewhat unusual mechanism, the logic of the regulatory circuit remains the same as that outlined above: RecA must be activated to effect the cleavage of LexA, and the resulting decrease in the pool of intact LexA protein in a cell leads to increased expression of the SOS genes.

TABLE 2 Properties of some important *recA* and *lexA* alleles[a]

A. Allele	Recombinase	Coprotease
recA$^+$	+	Inducible
Δ*recA*	−	Defective
recA430(Cpt$^-$) (formerly *lexB30*)	+	Defective (λ), partially defective (LexA), inducible (ϕ80)
recA441(Cpt^{Ts}) (formerly *tif-1*)	++	Constitutive (42°C), inducible (30°C)
recA730(Cpt^c)	++	Constitutive
recA718	+	Constitutive in *lexA*(Def), inducible in *lexA*$^+$
recA1203	−	Constitutive (LexA), inducible (λ)
recA1730	+[in *lexA*(Def)] −[in *lexA*$^+$]	Deficient (LexA), inducible (λ)
B. Allele	**Phenotypes**	**Biochemical change**
lexA3(Ind$^-$)	Defective in SOS induction, UV sensitive, dominant	Noncleavable LexA protein
lexA41(Ts) (formerly *tsl*)	Partial expression of SOS functions at 30°C, higher expression at 42°C, recessive	Noncleavable but unstable LexA
lexA51(Def) (formerly *spr*)	Constitutive expression of LexA-repressed genes	Defective LexA

[a]Reprinted from reference 69 with permission. Adapted from references 252 and 270.

Other proteins that undergo RecA-mediated cleavage, such as the repressors of bacteriophages 434, P22, and ϕ80 (59, 211) and UmuD and its homologs (see below), have been found to share homology with the carboxyl-terminal domains of LexA and λ repressor. Their cleavage appears to occur by a mechanism related to that of LexA and λ repressor, and all that have been tested similarly exhibit self-cleavage under alkaline conditions. Since activated RecA does not appear to be acting directly as a protease activity in these cleavage reactions but, rather, seems to be acting by stimulating the

autodigestion reaction and allowing it to proceed efficiently at physiological pH, the term "RecA coprotease" is used to refer to this activity (131).

Identification of Genes in the SOS Network

The experiments described above demonstrated the manner in which the RecA and LexA gene products regulate the *recA* and *lexA* genes and control the induction of λ. However, they did not indicate how SOS-inducing treatments led to the expression of the other SOS responses. Analysis of the regulation of these other SOS functions was complicated by the physiological complexity of many of the responses. In an effort to dissociate the physiological complexity of the SOS responses from the issue of their regulation, Kenyon and Walker (108) took advantage of the Mu d1 bacteriophage, a powerful tool constructed by Casadaban and Cohen (29) which made it possible to construct operon fusions in vivo in a single step. They screened a set of random Mu d1-generated fusions in the *E. coli* chromosome, searching for fusions which expressed β-galactosidase at higher levels in the presence of the DNA-damaging agent mitomycin than in its absence. By this procedure, a set of *din* (damage-inducible) loci (Table 1) were identified whose expression was increased by a variety of SOS-inducing treatments and was blocked by *recA*(Def) and *lexA*(Ind^-) mutations (108). Subsequent genetic and biochemical analyses were consistent with LexA being the direct repressor of the *din* genes (107).

One of the *din* mutants identified in this initial screen was as sensitive to UV killing as *uvr* mutants, which are defective in excision repair, and turned out to have a Mu d1 insertion in the *uvrA* gene (108). Another of the SOS-inducible loci identified in this initial screen, *dinA,* has been shown to be the *polB* gene, which encodes DNA polymerase II (14, 97, 98). The *dinF* gene has been sequenced (13), as has the *dinD* gene (148), but their functions are not known.

Subsequently, the Mu d1 bacteriophage played an important role in studies by a number of investigators in helping to identify genes which are members of the SOS regulatory network. Rather than being used to search for genes on the basis of their regulatory characteristics, as in the experiment described above, the bacteriophage was used to generate insertion mutations in genes suspected of being members of the SOS system. By this strategy, a number of genes were shown to be controlled by the SOS system, including *uvrA* (109), *uvrB* (66, 109) *sulA* (90), *umuDC* (3), *uvrD* (2, 226), *himA* (159), *ruvA* and *ruvB* (225), *recA* (30), and *recN* (145). Genetic analyses of the regulation of these were again consistent with LexA serving as the repressor of each of these genes. In addition, gene and operon fusions constructed in vitro have been used to study the regulation of the *lexA* (20) and *umuDC* (62, 223) genes as well as the plasmid-encoded *mucAB* genes (61). It has been discovered relatively recently that the copy number of the commonly used cloning vector, pBR322, increases in a $recA^+lexA^+$-dependent manner upon SOS induction (in other words, an increase in the copy number of pBR322 is an SOS response) (11). The existence of this unrecognized phenomenon may have complicated certain studies of SOS regulation employing pBR322-borne fusions, and it is possible (78, 174, 202) that certain genes such as *uvrC* (250), *phr* (94), and *ssb* (18) were thus incorrectly identified as being under SOS control. The $recA^+lexA^+$-dependent inducibility of plasmid-borne fusions to the *recQ* (102), *dinG* (126), and *dinH* (126) genes has also been reported, but to date LexA protein binding has been demonstrated directly only in the case of *dinG* (126).

As of the writing of this review, approximately 20 chromosomal genes have been shown to be members of the SOS regulon, and it seems likely that additional ones will be identified. To put this in some perspective, this means that on the order of 0.5% of the genes in *E. coli* are part of this complex regulatory system. In addition, a number of SOS-regulated genes have been identified on naturally occurring plasmids, bacteriophages, and transposons (Table 1).

LexA Binds to SOS Boxes and Inhibits Transcription

Genetic analyses of the regulation of the genes that are members of the SOS regulatory network have been consistent with LexA being the direct repressor of each. Purified LexA protein has been shown to bind to the operator sequences of most SOS genes and to inhibit transcription (19, 21, 69, 139, 205, 206, 213). Comparison of the sequences of the operators revealed that there was considerable homology among them, and they are often referred to as SOS boxes. The consensus sequence for an SOS box is

TA**CTGT**ATATATATA**CAG**TA (69). Not all of the bases shown in the consensus sequence for an SOS box are of equal importance. All the known SOS operators contain a consensus 5′-CTGT sequence. Furthermore, various operator-constitutive mutations that alter this sequence have been isolated (36, 158, 261, 262). In contrast, the center of the different operators is rather variable, with some preference for an alternating $(AT)_4$ sequence. It therefore seems likely that the CTGT sequence contains most of the information read by the LexA repressor upon its interaction with operator DNA, with the central T and G bases being absolutely required for efficient interaction with wild-type LexA repressor.

The various SOS genes differ with respect to the degree to which they are induced. Induction ranges from about 100-fold in the case of *sulA,* the most tightly repressed SOS gene identified so far, to only 4- to 5-fold in the case of *uvrA, uvrB, uvrD, ruvAB,* and *lexA* (213). The extent of repression may depend on at least four parameters: the operator strength, the localization of the operator relative to the promoter, the promoter strength, and the existence of additional, constitutive promoters. The location of the SOS boxes varies with respect to the transcription start site (69, 213). Some SOS boxes overlap with the –35 promoter region (*uvrA* and possibly *polB* and *ruvAB*), while others are situated between the –35 and –10 regions of the promoter (*recA* and *uvrB*). Some SOS boxes overlap with the –10 region of the promoter (*sulA, umuDC,* and *lexA*), while others are found downstream of the –10 region or even downstream of the +1 transcription start (*uvrD, cea,* and *caa*). Additionally, the number of operators ranges from a single operator observed with many SOS genes to three operators in the case of *dnaN.* Individual SOS boxes also vary with respect to their ability to bind LexA protein (213). In the case of the *uvrA* gene, in which the SOS box overlaps with the –35 region of the promoter, LexA binding seems to interfere with RNA polymerase at an early stage, preventing the formation of a closed RNA polymerase-promoter complex (10). However, it is possible that LexA protein inhibits other stages of transcription initiation for other SOS genes.

The twofold symmetry of the SOS boxes suggested that LexA protein binds as a dimer, and this inference has been supported by a variety of in vitro studies (214, 242). The ability of LexA protein to dimerize is critical to its ability to repress SOS-regulated genes in vivo. LexA protein consists of two structurally defined domains. These domains are joined by a hinge region which appears to be relatively flexible, since deletions within this region do not strongly impair DNA binding of the protein (137). The N-terminal domain (amino acids 1 to 84) of LexA protein specifically recognizes SOS boxes but does so with lower affinity than the intact protein (10, 92, 93, 110). The C-terminal domain of the protein contains the elements of the protein necessary for dimerization of LexA and thus indirectly increases DNA binding by allowing dimerization. Both the intact protein and the C-terminal domain form dimers in solution, with a rather low association constant ($2 \times 10^4 M^{-1}$) (212, 214). Recent experiments have indicated that the dimerization of LexA protein occurs after LexA monomers have become associated with the operator DNA (110).

The Ala-84–Gly-85 bond is located within the hinge region between the two domains. Thus, cleavage of this bond during SOS induction separates the two domains, thereby preventing the dimerization of LexA that is necessary for repression of SOS-regulated genes. The fact that dimerization occurs on the DNA leads to a high degree of cooperativity in DNA binding and therefore a steep binding curve, so that less LexA needs to be cleaved to give derepression of LexA-repressed genes (110).

The N-terminal domain of LexA protein shares some homology with DNA-binding proteins containing a helix-turn-helix motif (171). However, analysis of the sequence and structure (by two-dimensional nuclear magnetic resonance spectroscopy) of mutations affecting LexA binding and LexA-DNA contacts suggest that it is not a canonical helix-turn-helix protein but is at best a distant relative of this class of transcription factors (213). These results suggest that LexA protein interacts with one face of the DNA cylinder through contacts with the DNA backbone, while a protruding "reading head" probes the bottom of the major groove (where recognition takes place) (93).

THE SOS-INDUCING SIGNAL

For RecA to mediate the cleavage of LexA in vivo, it must be activated; simply overproducing RecA is not sufficient to cause the induction of the SOS responses (186, 246). This activation is reversible (31, 132). As discussed above, in vitro conditions that result in RecA-mediated cleavage of LexA protein and λ

repressor have been clearly defined: the RecA protein, ATP or a nonhydrolyzable analog of ATP, and single-stranded DNA are required. Furthermore, measurements of the in vitro rate of LexA cleavage have correlated closely with estimates of the in vivo cleavage rate, suggesting that the important components of the in vivo reaction have been identified (210). However, it has been considerably more challenging to infer the nature of the in vivo inducing signal that leads to RecA activation and subsequent LexA cleavage. Many of the agents that induce the SOS response are DNA-damaging agents, but this does not necessarily mean that the presence of a lesion in the DNA is the ultimate inducing signal, since DNA damage can have a number of additional consequences such as replication arrest, alterations in nucleoid structure, or altered superhelicity. Furthermore, blockage of replication or the presence of an abnormal replication fork could have secondary consequences, such as the generation of regions of single-stranded DNA or oligonucleotides that could serve as the ultimate inducing signal. Recent work has strongly supported the unifying view that the ultimate signal for SOS induction in vivo is the generation of regions of single-stranded DNA within the cell. Depending on the nature of the inducing agent, the generation of this single-stranded DNA may be independent of or dependent on DNA replication.

Most SOS-inducing agents do not directly cause breaks in DNA but, rather, create lesions that alter the chemical structure of the bases, which in turn may interfere with base pairing. Agents of this type include UV radiation and chemicals which react with DNA bases, such as activated derivatives of aflatoxin B_1 and dimethylbenzanthracene. It has been known for some time that UV radiation-induced lesions do not have to actually be present in the bacterial chromosome but will result in SOS induction if they are introduced into the cell on a DNA molecule such as an F or F′ plasmid; P1, M13, or λ bacteriophage DNA; or on Hfr DNA (16, 17, 45, 48, 74, 196). This phenomenon is known as indirect induction. The efficiency of SOS induction by such damaged DNAs is greatest if the damaged DNAs undergo DNA replication after being introduced into the bacterial cell (45, 233).

Evidence has been obtained indicating that the presence of UV radiation-induced lesions in DNA is not sufficient to cause SOS induction but, rather, that the SOS-inducing signal arises when the cell attempts to replicate the damaged DNA, thereby generating single-stranded regions. Initial evidence for this model was provided by Salles and Defais (200) using a *dnaC28*(Ts) *uvrB* double mutant. The *dnaC28*(Ts) mutation makes the strain temperature sensitive for the initiation of DNA replication; if the cells are shifted to 42°C (the restrictive temperature), they complete the existing round of replication but are not able to initiate another. A *uvrB* mutation inactivates the UvrABC endonuclease activity (see below), which initiates nucleotide excision repair of UV radiation-induced lesions. Raising the temperature of the *dnaC28*(Ts) *uvrB* double mutant inhibited the induction of RecA protein by UV radiation, whereas some RecA induction occurred in a *dnaC28*(Ts) *uvrB*$^+$ strain following exposure to higher doses of UV light (200). These results suggested that the mere presence of UV radiation-induced lesions was not sufficient to cause SOS induction in a cell lacking UvrABC endonuclease activity and that DNA replication of the damaged template was required to generate the SOS-inducing signal. Furthermore, it was suggested (200) that *uvr*$^+$-dependent SOS induction observed in the absence of replication resulted from the removal of pyrimidine dimers and the appearance of small gaps that could be processed into an SOS-inducing signal.

These results (200) were extended by Sassanfar and Roberts (210) in a study in which LexA cleavage was directly measured in the same strains. They found that if the *dnaC uvrB* cells were UV irradiated 70 min after the shift to the restrictive temperature, no LexA cleavage occurred, whereas 70% of the protein was cleaved within 10 min at the permissive temperature. This result indicated that replication of the damaged DNA template was required to produce the inducing signal which activated RecA protein for LexA cleavage. Furthermore, under conditions where DNA replication can occur, the initial rates of LexA cleavage were the same in *uvr*$^+$ and *uvr* strains, implying that the action of the UvrABC endonuclease is not important for the generation of the SOS-inducing signal under ordinary physiological conditions. However, *uvr* mutants remained SOS induced for a much longer time than wild-type strains did, indicating the important role of nucleotide excision repair in the removal of these lesions. In a recent study, a persistent SOS-inducing signal was observed in UV-irradiated *uvr*$^+$ *E. coli* cells. This has been attributed to the excision of one member of a pair of closely spaced photoproducts to yield a gap

opposite a lesion (22). Such a structure cannot be repaired by ordinary *uvrA*$^+$*B*$^+$*C*$^+$-dependent excision repair.

A number of temperature-sensitive *dna* mutants, in which the elongation phase of DNA replication is inhibited at the restrictive temperature, exhibit SOS induction when shifted to higher temperatures (216, 269). However, it has been suggested (210) that in these mutants the disintegration of the immobilized and thus unstable replication fork at the restrictive temperature gives rise to gaps and breaks where replicating DNA has been exposed to nuclease action. Evidence supporting this view has been provided in the case of a *dnaE486*(Ts) mutant (210). Similarly, it has been suggested (167) that *priA* mutants are induced for the SOS response because they lack the PriA protein, a component of the primosome, thereby resulting in a less stable or less efficient replication fork that is defective in its management of the single-stranded lagging template strand. The expression of the SOS response in certain *uvrD* mutants may be due to single-stranded regions generated at the replication fork because of defects in the UvrD helicase protein (169).

DNA replication on damaged templates leads to the production of segments of single-stranded DNA. These are generated when DNA synthesis reinitiates downstream of the lesion at the beginning of the next Okazaki fragment (198). It is the binding of RecA protein to these single-stranded regions that is postulated to result in its activation and hence the induction of the SOS response (200, 210). At a UV radiation dose of 5 J/m^2, which introduces approximately 250 pyrimidine dimers per *E. coli* genome equivalent, a replication fork moving at a rate of 1,000 nucleotides per s at 30°C would be expected to encounter a pyrimidine dimer every 2 to 3 s (210). The observed lag of approximately 1 min after UV irradiation before LexA cleavage begins suggests that it takes some time for single-stranded DNA to be generated and for RecA protein to assemble on it (132). Neither photoreactivation nor nucleotide excision repair would be significant on this timescale. Even with lower doses of UV radiation exposure, the time required for the replication fork to travel between lesions may be negligible compared with the time required for reinitiation of the fork downstream from a lesion. According to this model, the fork would continuously encounter lesions, leaving gaps that are filled with activated RecA protein that mediates LexA cleavage. LexA cleavage would cease when the gaps are filled by daughter strand gap repair (69) and the lesions are removed by nucleotide excision repair (69).

RecA protein is not activated by single-stranded regions that are normally present on the lagging strand of the replication fork in undamaged cells. The explanation for this may relate to the kinetics of RecA polymerization and lagging-strand replication. It is possible that RecA protein cannot polymerize on this DNA, or cannot displace single-strand-binding protein (SSB) from it, before the DNA is covered again by replication (210). This view suggests that the ability of *recA*(Cpt) and *recA*(Cpt^{Ts}) mutants to express the SOS responses in the absence of exogenous DNA damage is due to the altered RecA protein encoded by these mutants becoming activated by polymerizing on these lagging-strand gaps during their relatively short half-life. The higher effective affinity of RecA441(Cpt^c) protein for DNA, relative to wild-type RecA protein (180), is consistent with this view. In addition, the fact that the RecA730 protein displaces SSB from single-stranded DNA more efficiently than does RecA441, which in turn displaces SSB from single-stranded DNA more efficiently than does RecA$^+$ (123), also supports this model. An alternative suggestion is that some RecA mutants may exhibit constitutive coprotease activity because they can be activated by an expanded range of nucleotide and polynucleotide effectors such as tRNA and rRNA (258, 259).

In the case of SOS induction by nalidixic acid, there is strong evidence that the critical event is the generation of regions of exposed single-stranded DNA in the cell. Nalidixic acid inhibits DNA gyrase (72, 238) and causes double-strand breaks in DNA (52, 231). However, this is not sufficient for SOS induction, and subsequent processing of the DNA by the RecBCD nuclease is required (81, 104). Although this enzyme both degrades and unwinds DNA from double-strand breaks in vitro, only the unwinding activity of RecBCD, which generates single-stranded DNA, is required for nalidixic acid to function as an SOS inducer (33).

In the special case of ϕ80 induction, certain oligonucleotides such as d(G-G) stimulate repressor cleavage. This finding was first made in a study in which the derepression of a ϕ80 repressor-controlled

reporter gene was measured in permeabilized cells exposed to potential inducing signals (96). The oligonucleotides have been shown to interact with the ϕ80 repressor itself rather than with RecA protein and therefore exert a specific effect on ϕ80 repressor cleavage but not on LexA cleavage and hence not on SOS induction (60).

RecA-MEDIATED CLEAVAGE ACTIVATES UmuD

Recent work has revealed a new dimension to the SOS response —posttranslational activation of the UmuD protein by RecA-mediated cleavage. As described below, *umuD* function is required for most UV and chemical mutagenesis. When the *umuD* gene and its plasmid-borne homolog, *mucA,* were sequenced, the surprising observation was made that the deduced amino acid sequences of the UmuD and MucA proteins shared significant homology with the carboxyl terminus of LexA protein and of λ repressor (175). This led Perry et al. (175) to propose that the UmuD and MucA proteins may interact with activated RecA protein and that this interaction might result in a proteolytic cleavage of these proteins that would activate or unmask the function(s) required for mutagenesis. Furthermore, since there is very limited homology between the amino acids of UmuD and MucA protein on the N-terminal side of their putative cleavage sites, it seemed possible that this constituted a nonfunctional or expendable domain. On the basis of comparisons of amino acid sequences, the cleavage site of UmuD was predicted to be Cys-24–Gly-25 (175). Although both λ repressor and LexA protein have Ala-Gly cleavage sites, ϕ80 repressor was subsequently found to have a Cys-Gly cleavage site. The hypothesis that UmuD protein may become activated by RecA-mediated cleavage was consistent with a number of observations which raised the possibility that RecA protein had an additional role in mutagenesis besides mediating the cleavage of LexA protein (3, 12, 28, 64, 65, 69, 119).

UmuD Is Cleaved In Vivo and In Vitro in a RecA-Mediated Fashion

The demonstration that UmuD protein is cleaved in vivo in a RecA-dependent fashion after cells have been exposed to an SOS-inducing treatment (222) was made by using an experimental approach very similar to that initially used (191) to demonstrate the cleavage of λ repressor in vivo. Antibodies to UmuD protein were isolated and used in immunoblotting experiments to show that UV irradiation of the cells resulted in the conversion of UmuD protein to a smaller form (referred to as UmuD′). The molecular weight of UmuD′ was similar to the predicted molecular weight of the postulated C-terminal fragment of UmuD (175). This in vivo cleavage of UmuD protein was not observed in *lexA*(Def) *recA*(Def) or *lexA*(Def) *recA430*(Cpt^-) cells but was observed in the absence of an SOS-inducing treatment in *lexA*(Def) *recA730*(Cpt^c) cells. This suggested that UmuD protein was cleaved as a consequence of an interaction with activated RecA protein, similar to the way in which LexA and λ repressor undergo RecA-mediated cleavage.

RecA-mediated cleavage of UmuD protein was also demonstrated in vitro (27). In these studies, it was observed that, just as with λ repressor and LexA protein, purified UmuD protein was proteolytically cleaved to yield UmuD′ when incubated with RecA protein, single-stranded DNA, and ATP-γ-S, but the cleavage of UmuD protein was less efficient than that of LexA protein. The bond cleaved was subsequently shown (272) to be the Cys-24–Gly-25 bond previously predicted on the basis of the homology with LexA and λ repressor (175). UmuD protein can be cleaved by RecA or RecA441(Cpt^{Ts}) protein but not by RecA430 protein, consistent with the in vivo observations (222). It was also shown that UmuD protein shares another characteristic with λ repressor and LexA, namely autodigestion at alkaline pH (27).

Activation of UmuD by RecA-Mediated Cleavage

To investigate the role of UmuD cleavage in UV radiation-induced mutagenesis, a special derivative of a plasmid carrying the $umuD^+$ gene was constructed (166) in which overlapping termination (TGA) and initiation codons (ATG) were introduced at the site in the *umuD* sequence that corresponds to the cleavage site (Cys-24–Gly-25). The plasmid carrying this engineered form of *umuD* gene thus encoded two polypeptides corresponding almost exactly to those that would normally be produced by RecA-

mediated cleavage of UmuD at the Cys-24–Gly-25 bond. When the plasmid encoding the two polypeptides was introduced into a nonmutable *umuD44* strain, it restored the UV mutability of the cell to that of a *umuD*$^+$ cell. This observation ruled out the possibility that the purpose of UmuD cleavage was to inactivate UmuD protein. It was also observed that a plasmid encoding only the peptide corresponding to the small N-terminal fragment failed to complement the UV radiation nonmutability of a *umuD* strain whereas a plasmid encoding only the large C-terminal fragment (UmuD′) did restore UV mutability. This observation strongly indicated that UmuD′ is both necessary and sufficient for the role of UmuD protein in UV radiation mutagenesis. Similar conclusions were later reached by using a lower-copy-number plasmid encoding UmuD′ and UmuC proteins and strains carrying the *umuD24* insertion mutation (4).

To test the hypothesis that RecA-mediated cleavage activates UmuD protein for its role in mutagenesis, plasmids encoding either the two UmuD polypeptides or just the C-terminal polypeptide were introduced into a *lexA*(Def) *recA430*(Cpt$^-$) strain (166). Such strains are nonmutable by UV light despite the fact that they express the *umuD*$^+$ and *umuC*$^+$ genes constitutively at high levels. Both plasmids made *lexA*(Def) *recA430*(Cpt$^-$) cells UV mutable again. Since the UmuD protein was not cleaved in *recA430* mutants (222), these results indicated that the nonmutability of *lexA*(Def) *recA430*(Cpt$^-$) cells was due solely to their failure to cleave UmuD protein and hence that RecA-mediated cleavage of UmuD protein to yield UmuD′ activates UmuD protein for its role in mutagenesis.

Further evidence that the mechanism of RecA-mediated cleavage of UmuD is mechanistically similar to the RecA-mediated cleavage of LexA protein was provided by the observation that Ser-60 → Ala and Lys-97 → Ala mutations (166) block UmuD cleavage in vivo. These mutations correspond to the Ser-119 → Ala and Lys-156 → Ala mutations that block LexA cleavage (8).

SOS Mutagenesis Is Regulated Both Transcriptionally and Posttranslationally

Collectively, the results described above indicate that RecA protein carries out two mechanistically related roles in UV radiation and chemical mutagenesis: (i) transcriptional derepression of the *umuD*$^{+C+}$ operon by mediating the cleavage of LexA protein, and (ii) posttranslational activation of UmuD protein by mediating its cleavage (Fig. 2). Since both of these events require the presence of activated RecA protein, which is the cell's internal indicator that it has suffered DNA damage, the biological purpose of this regulatory system is apparently to give the cell an extra measure of control as to whether and to what extent it should express activities necessary for UV radiation and chemical mutagenesis.

FINE-TUNING IN THE SOS SYSTEM

Once a cell has been exposed to an SOS-inducing treatment, several factors influence whether a given SOS response will be expressed: (i) the amount of inducing signal that is generated and its persistence, which in turn influences the amount of RecA protein that is activated and the length of time that it stays activated; (ii) the rate at which the repressor of a particular SOS gene is cleaved when it interacts with activated RecA protein; (iii) the affinity of the repressor for the operator of a particular SOS gene; (iv) the level of expression of a given SOS gene; (v) the level of expression of a given SOS gene that is required for its gene product to have a physiologically manifestable consequence; and (vi) whether a second RecA-mediated cleavage is required for the response to be observed.

Intermediate States of Induction

Although the SOS system can exist in two extreme states, fully repressed and fully induced, it can also exist in any of a number of other states which are intermediate between these two extremes. As discussed above, cleavage of LexA protein occurs very rapidly after an SOS-inducing treatment and the lowest concentration of LexA protein that results represents an equilibrium between LexA cleavage mediated by activated RecA protein and synthesis of intact LexA molecules (210). Furthermore, the various SOS-regulated genes differ with respect to the affinities with which their operators bind LexA protein, the number of operators, and other specific details of the regulation. Hence, the extent to which a given gene is expressed following a particular SOS-inducing treatment is dependent on the degree to which the LexA protein pool has been decreased in response to a given SOS-inducing treatment. The fact that LexA

dimerization occurs on the DNA leads to a high degree of cooperativity and therefore a steep binding curve, so that less LexA must be cleaved to give derepression of LexA-repressed genes (110). Furthermore, cooperative binding of LexA protein to multiple SOS boxes, as in the case of *recN* (213), leads to full induction within a narrower range of change of LexA protein concentration. The genes that bind LexA protein most weakly are fully induced in response to even weak SOS-inducing treatments, whereas the genes that bind LexA protein most tightly are fully induced only in response to stronger SOS-inducing treatments. The SOS boxes in the *lexA, uvrA, uvrB,* and *uvrD* genes bind LexA protein more weakly than does the operator in the *recA* gene, whereas the SOS boxes in *sulA* and *umuDC* bind LexA protein more tightly (213). Thus, relatively weak SOS-inducing treatments lead to increased expression of uvr^+ gene-dependent excision repair functions. However, other SOS responses, such as the accumulation of large amounts of RecA protein, *sulA*-dependent filamentation (see below), and the induction of *umuDC*-dependent translesion synthesis (see below), do not occur unless the cell receives a stronger SOS-inducing treatment. This feature of the regulatory system allows *E. coli* cells to utilize certain SOS-regulated functions, such as nucleotide excision repair, in order to recover from DNA damage without a commitment to a full-fledged SOS response.

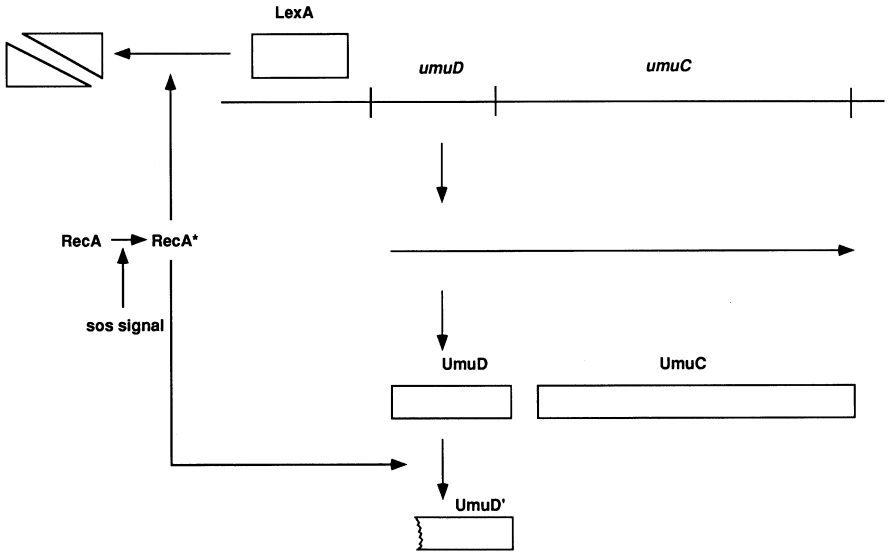

FIGURE 2 Posttranslational activation of UmuD by RecA-mediated cleavage.

The repression of the *lexA* gene by LexA protein has three effects on SOS induction. First, it extends the range, in terms of inducing signal, over which the system can establish an intermediate state of induction and thus express only a subset of the SOS responses. Second, since the affinity of LexA protein for the *lexA* operator is weak relative to the operators of other genes, such as the *recA* gene, the system is buffered against significant levels of induction by a very limited inducing signal. Third, it speeds the return to the repressed state once the levels of inducing signal begin to decrease (19–21, 132, 139).

The rate at which various proteins undergo RecA-mediated cleavage is also critical to the fine-tuning of the SOS response. For example, λ repressor is cleaved much more slowly than LexA protein when it interacts with activated RecA protein. This may favor the survival of the phage by ensuring that lysogenic induction does not take place until levels of DNA damage exceed the repair capacity of the other inducible responses. The fact that UmuD protein is cleaved more slowly than LexA helps ensure that the active form of UmuD protein, which is required for UV radiation-induced mutagenesis, is not produced unless the cell has experienced a significant SOS-inducing treatment. In addition, Table 1 lists some genes that appear to be under SOS control but which are not repressed by LexA. It is possible that a different repressor for those genes, which can be cleaved in a RecA-mediated fashion, will be identified.

Finally, it is possible that various SOS-regulated genes will also be subject to additional control by other regulatory systems. For example, the *cea* gene, which encodes colicin E1, is regulated by both the

SOS system and the cyclic AMP (cAMP)/cAMP receptor protein catabolite repression system (56). This dual-control system results in a delay during SOS induction that may achieve the physiological purpose of limiting the natural production of colicin E1 (which is lethal to the cells that produce it) to those cells that have suffered a catastrophe and most probably would not survive anyway (203).

REGULATION AND PHYSIOLOGICAL ROLES OF SOS GENES

The relationship between a physiological response and a gene function can be complex. Certain subsets of SOS responses, such as Weigle mutagenesis of UV-irradiated bacteriophages and UV mutagenesis of the bacterial chromosome, seem to have similar genetic requirements and thus may represent different physiological manifestations of the same induced pathway (106, 237, 252, 269). Other sets of apparently different SOS responses could turn out to be related at a biochemical level. Studies of the genetic dependence of at least one SOS response, Weigle reactivation of UV-irradiated bacteriophages, have indicated that the physiological response consists of at least two components, a *umuDC*-dependent component (106, 237) and a *uvrA*-dependent component (3); it is possible that certain other SOS responses will turn out to exhibit similar complexity. Particularly difficult types of responses to study are those in which the RecA gene product plays more than one role; for example, it plays at least three roles in UV mutagenesis (5, 6, 53, 54, 65, 166) and it plays both regulatory and mechanistic roles in the phenomenon of induced stable DNA replication (113, 122).

The regulation of a number of SOS genes has been examined in detail, and insights have been gained into the physiological role of their gene products. Progress on representative SOS responses is briefly summarized below.

uvr$^+$-Dependent Excision Repair

Howard-Flanders et al. (88) identified unlinked mutations, termed *uvrA, uvrB,* and *uvrC,* which prevented the excision of pyrimidine dimers and rendered cells very sensitive to UV irradiation; *uvrA, uvrB,* and *uvrC* mutants were also very sensitive to killing by a wide variety of other DNA-damaging agents such as mitomycin, 4-nitroquinoline-1-oxide, and psoralen plus near-UV light. The *uvrA, uvrB,* and *uvrC* gene products have been identified as 114,000-, 84,000-, and 70,000-Da proteins, respectively, and are subunits of the complex UvrABC endonuclease, which initiates excision repair of pyrimidine dimers and other bulky lesions (6, 116, 117, 119, 126, 143, 153, 154). The *uvrD* gene encodes helicase II (1, 155, 168, 249), which is also required for excision repair.

As mentioned above, the SOS box of the *uvrA* gene overlaps with the –35 region of the promoter and is thought to interfere with transcription at an early stage of initiation by blocking the formation of a closed RNA polymerase-promoter complex (10). In the absence of SOS induction there are ca. 25 UvrA molecules per cell, and after SOS induction there are ca. 250 UvrA molecules per cell (218, 249). In vitro studies of the *uvrB* gene have shown that it has two adjacent promoters (206, 248), which initiate transcripts at +1 and –31, respectively. Footprinting experiments identified a LexA-binding sequence that overlaps the upstream promoter (206). Although LexA inhibited transcription from the upstream promoter only in vitro (206), S1 mapping studies have shown that LexA regulates the action of both promoters in vivo (248). An uninduced cell has ca. 250 UvrB molecules, whereas an SOS-induced cell has approximately 1,000 UvrB molecules (218). Although the LexA protein apparently binds to a DNA fragment carrying one of the *uvrC* promoters (234), the *uvrC* gene does not appear to be regulated by LexA (67, 78, 161). The *uvrD* gene is under SOS regulation, and its SOS box is located downstream of the promoter (55). The expression of *uvrD* is increased ca. four- to sixfold upon SOS induction.

The UvrABC endonuclease has been purified intact and has also been reconstituted from separately purified subunits; it makes two endonucleolytic incisions, one on each side of the lesion, generating an oligonucleotide of 12 to 13 bases (118, 124). The mechanism of incision (for reviews, see references 69, 128, 204, 218, and 249) involves the binding of dimeric UvrA to UvrB in solution to form a $UvrA_2UvrB$ complex that searches the DNA for base damage. When damage is encountered, the $UvrA_2UvrB$ complex locally unwinds and kinks the DNA by 130°. The UvrA protein then dissociates, and a stable UvrB-DNA complex is formed in which the DNA is primed for incision. The UvrC protein then associates with the UvrB-DNA complex and makes the two incisions referred to above. The *uvrD* gene product, helicase II, is

required for the release of the oligonucleotide fragment and of UvrC from the postincision complex. The incision step is followed by repair synthesis, carried out by DNA polymerase I, which fills in the excision gaps. The remaining nick is sealed by DNA ligase. The repair patches that are produced are heterogeneous in size, with 99% of the patches being approximately the size of the gap generated by the UvrABC endonuclease and 1% being 1,500 nucleotides or more in length (42). The process of long-patch repair is inducible and is controlled by the SOS regulatory circuit (41). Short-patch synthesis begins immediately after UV irradiation and is virtually completed before the synthesis of the majority of the long patches (41). The nature of the induced function(s) that leads to long-patch repair synthesis has not yet been determined.

The discovery of the inducibility of the *uvrA, uvrB,* and *uvrC* genes was initially surprising since, for a number of years, the *uvr* genes had been widely regarded as being constitutively expressed and not being under the control of the SOS regulatory circuit (189). However, the inducibility of the *uvr* genes is consistent with a variety of studies that have suggested that *uvr*-dependent excision repair can be induced by DNA-damaging treatments (41, 217). The initial sense that these genes were not inducible was due to the facts that they are expressed at significant basal levels in uninduced cells and that the basal level of expression is not affected very much by *recA*(Def) or *lexA*(Ind$^-$) mutations.

SOS Mutagenesis

In *E. coli,* mutagenesis by UV and a variety of chemical agents such as 4-nitroquinoline-1-oxide and methyl methanesulfonate is not a passive process but, rather, requires the intervention of an active cellular system that processes damaged DNA in such a way that mutations result (58, 69, 141, 165, 252, 253, 254, 269). There is now fairly widespread agreement that the mechanism responsible for such mutagenesis involves a DNA polymerase inserting nucleotides opposite a misinstructional or noninstructional lesion and then continuing synthesis. This process has been referred to as SOS mutagenesis, error-prone repair, SOS repair, misrepair, and SOS processing. The insight that specialized cellular functions are required for SOS mutagenesis came from experiments showing that UV mutagenesis could be blocked by certain *lexA* and *recA* alleles (23, 163, 266, 267) and from experiments indicating that cellular functions had to be induced by DNA damage for mutations to arise as a consequence of DNA damage (47, 69, 252, 260, 268, 269). SOS mutagenesis requires the functions of three genes, *umuD, umuC,* and *recA,* that are inducible and regulated as part of the SOS network. However, the *umuDC* operon is the only SOS control locus that must be induced for SOS mutagenesis (158, 232).

Mutations in the *umuD* and *umuC* genes (47, 62, 69, 106, 223, 237, 252, 260, 268, 269) abolish the ability of *E. coli* cells to be mutated by a wide variety of agents such as UV, 4-nitroquinoline-1-oxide, and methyl methanesulfonate. Such cells do, however, retain the ability to be mutated by certain agents such as *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine, which introduce directly mispairing lesions. *umuD* and *umuC* mutants are somewhat sensitive to killing by UV but are by no means as sensitive as *uvr* mutants. The *umuD* and *umuC* genes have been cloned (33, 128) and have been shown to code for proteins with molecular weights of ca. 15,000 and 45,000, respectively (62, 223). The two genes are located in an operon, and a variety of techniques including the use of operon and gene fusions have been used to show that the *umuDC* operon is inducible and regulated by the SOS control circuit (3, 62, 69, 223). UmuD protein is present at ~180 copies per cell in uninduced *lexA*$^+$ strains but is present at ~2,400 copies per cell in a *lexA*(Def) strain (271). The level of UmuC protein in a *lexA*(Def) cell (200 molecules per cell) is about 12-fold lower than that of UmuD protein and was too low to be measured in uninduced *lexA*$^+$ cells (271). Both UmuD and UmuD′ proteins are homodimers (272).

Homologs of *umuD* and *umuC* are found on some naturally occurring plasmids. The most intensively studied of these are present on plasmid pKM101, which has played a major role in increasing the sensitivity of Ames *Salmonella typhimurium* (official designation, *Salmonella enterica* serovar Typhimurium) strains used for detecting mutagens and carcinogens (156). pKM101 carries two genes, *mucA* and *mucB,* that can suppress the nonmutability of *umuD* and *umuC* strains (69, 219, 252, 255,

273). Like the *umuD* and *umuC* genes, the *mucA* and *mucB* genes are organized in an operon that is repressed by LexA, and they code for products of ca. 15,000 and 45,000 Da, respectively (176).

As described above, the UmuD protein is activated for its role in SOS mutagenesis by a RecA-mediated cleavage. Analogously to UmuD, MucA protein has been shown to be cleaved at its Ala-26–Gly-27 bond (240) in a RecA-mediated fashion (84, 220), and the C-terminal polypeptide MucA′ has been shown to be active in UV radiation mutagenesis (220). This cleavage was shown to be much more efficient than that of UmuD protein and to be almost as efficient as LexA cleavage (84). In addition, evidence has been presented suggesting that the intact UmuD protein may be more than simply an inactive form that is converted to the activated form, UmuD′, upon RecA-mediated cleavage (8). Rather, the intact form may play an active negative role in modulating the ability of *E. coli* to carry out SOS mutagenesis and may be particularly important in shutting off the capacity of a cell to carry out SOS mutagenesis as it begins to recover from DNA damage (8).

In addition to the UmuD′ and UmuC proteins, SOS mutagenesis requires a third, as yet poorly understood function of RecA beyond its abilities to mediate LexA and UmuD cleavage (6, 53, 54, 65, 166, 173). Furthermore, the functions of the GroES and GroEL molecular chaperones are also required (50, 51, 140). DNA polymerase I is not required, but the possibility that it could participate if present has not been excluded (7). DNA polymerase II activity is increased sevenfold in SOS-induced cells (15), and the SOS inducibility of DNA polymerase II activity has been explained by the discovery (14, 34, 98) that the *polB* gene is identical to the *dinA* gene, one of the SOS-inducible loci identified by the use of operon fusions (107, 108). DNA polymerase II is not generally required for SOS mutagenesis (98, 108, 114), although one report has appeared describing a circumstance in which DNA polymerase II appears to be required (241). Some genetic evidence has been obtained indicating that DNA polymerase III or some modified form of DNA polymerase III is required (24, 35, 68, 100, 239).

A biochemical system for SOS mutagenesis with purified components has been reported by Echols and his colleagues (190). On the basis of genetic evidence implicating UmuD′, UmuC, RecA, and DNA polymerase III, these components were used in an assay designed to bypass a single abasic lesion at a defined site in a primed template. The UmuC protein used in the assay was purified in 8 M urea and renatured by dilution and dialysis (272). When all of these proteins were present, a limited amount of bypass synthesis was observed similar to that observed in vivo with a single-stranded vector carrying a single AP site (124). The requirement for UmuD′, UmuC, and RecA proteins was observed irrespective of whether the form of the DNA polymerase III holoenzyme contained ε, the proofreading subunit. DNA polymerase I did not exhibit bypass synthesis in the presence of UmuD′, UmuC, and RecA proteins, whereas DNA polymerase II, together with polymerase III processivity proteins, exhibited at best marginal bypass synthesis. Interestingly, intact UmuD protein inhibited bypass (190), consistent with the hypothesis (8) that the intact form of UmuD protein might function as an inhibitor of SOS mutagenesis.

In addition, an in vitro system has recently been developed for UV radiation mutagenesis (37, 38). It consists of two stages. First, a UV-irradiated plasmid carrying the *cro* gene of bacteriophage λ is incubated with a soluble protein extract prepared from SOS-induced *E. coli* cells. Second, a bioassay in a *recA* deletion strain is used to detect mutations produced in the *cro* gene during the first stage. The use of this system has allowed the identification of two pathways for UV mutagenesis (37, 38). The first pathway depends on DNA replication and requires the *recA* and *umuC* gene products. The second pathway was revealed by enzymatically removing pyrimidine dimers from the plasmid DNA at the end of the first stage and prior to the bioassay. This treatment caused a large increase in the frequency of mutations detected in the bioassay. This photoreactivation-stimulated in vitro mutagenesis was dependent on the nucleotide excision repair genes *uvrA, uvrB,* and *uvrC* and was partially dependent on *uvrD.* It did not, however, require the functions of the *umuC* and *recA* genes. The second mutagenic pathway occurred in the absence of plasmid DNA replication. Although not dependent on DNA polymerase I or II, it was dependent on DNA polymerase III but was not inhibited by antibodies against the β subunit of DNA polymerase III holoenzyme. The fact that the processivity subunit is not required is consistent with a mechanism for the second mutagenic pathway in which DNA polymerase III fills in short single-stranded

DNA gaps (38). Sequencing of mutations arising via this second pathway revealed a spectrum similar to that of in vivo UV mutagenesis (38).

Double-Strand Break Repair

Double-strand breaks in DNA can be created by the action of various physical and chemical agents, the most widely studied of which is ionizing radiation. Pretreatment of *E. coli* with either X rays or UV radiation was shown to result in an induced resistance to killing by X rays or γ rays. This induced resistance was under SOS control and required new protein synthesis (183–185, 228). The discovery that the capacity to repair double-strand breaks caused by γ rays was an inducible SOS function (117) suggested that increased resistance resulted from an enhanced capacity to carry out double-strand break repair. It also indicated that the inducible inhibition of DNA degradation after X irradiation (182) is probably caused by the inducible repair of double-strand breaks (117).

The inducible repair of double-strand breaks introduced by ionizing radiation or mitomycin requires the presence of another DNA duplex that has the same base sequence as the broken double helix (116). *E. coli* cells grown in medium that supports rapid cell growth initiate new rounds of replication prior to completing the first round and, as a consequence, have multiple replication forks and thus multiple copies of most of their genome. Such cells can carry out double-strand break repair. In contrast, *E. coli* cells grown on a very poor medium (for example, one in which aspartate serves as the carbon source) do not have multiple initiation forks. They cannot carry out double-strand break repair, although they can efficiently repair single-strand breaks.

The repair of DNA double-strand breaks in *E. coli* exposed to ionizing radiation, mitomycin, or UV radiation requires a functional *recA* gene (116, 117, 207, 256). In addition, in vitro experiments with model substrates have shown that RecA protein can promote strand exchanges past double-strand breaks (265). In wild-type *E. coli,* the repair of double-strand breaks is also dependent on *recB* and *recC* function (229, 230, 256). It seems likely that this reflects a role for the *recBCD*-encoded exonuclease V in the generation of the 3′ ends.

A number of genes associated with recombinational processes (*recN, recF, recJ, radA,* and *uvrD*) have also been found to influence double-strand break repair to some extent (207). The *recN* gene is of particular interest, since its expression is regulated by the SOS response (145, 197) and its product is required for the repair of double-strand breaks (181, 208, 209) but not for the repair of daughter strand gaps (208, 209).

Daughter Strand Gap Repair

When DNA synthesis occurs in cells that have been exposed to UV irradiation, the newly synthesized DNA has a lower molecular weight than newly synthesized DNA from unirradiated cells (198). The low molecular weight is due to gaps or discontinuities in the nascent strand. These gaps apparently arise when replication is blocked at a pyrimidine dimer or other bulky lesion and then resumes at some site past the lesion, presumably at the next site for the initiation of an Okazaki fragment. *E. coli* has a strategy for repairing these gaps that has been referred to as daughter strand gap repair or postreplicational repair (for a review, see reference 69). During this type of repair, the gaps are filled and the discontinuous strands are joined into molecules of the same size (198). The mechanism by which this occurs results in stretches of parental DNA becoming covalently attached to daughter strands, indicating that a recombinational strand exchange is involved (199). These strand exchanges occur at a frequency approaching one per daughter strand gap repair (199). In excision-deficient cells, pyrimidine dimers remain in the DNA during this process but become equally distributed between parental and progeny strands as a result of the strand exchanges (70, 71).

A number of genes have been implicated in the tolerance of DNA damage associated with discontinuous synthesis and gap filling of daughter strand DNA (83, 229, 230). Four classes of mutations appear to cause deficiencies in daughter strand gap repair: *recA*(Def), *ruv, lexA*(Ind$^-$), and *recF.* RecA protein is thought to polymerize on the single-stranded DNA in the daughter strand gap to form a right-handed helical filament. This RecA filament could then promote a search of the sister duplex for homologous contacts via the formation of a three-stranded intermediate. Base pairing within the

heteroduplex would then serve to properly align the homologous sequences and initiate strand transfer. RecA protein could then drive strand exchange 5′ → 3′ relative to the single-stranded gap to form a Holliday junction.

The deficiency in daughter strand gap repair seen in *lexA*(Ind$^-$) mutants appears to be a consequence of the inability of such cells to increase the synthesis of proteins required for this type of recombinational repair: the products of *recA, ruvAB,* and possibly others. Recent results have indicated that the RecO, RecR, and possibly the RecF proteins serve as RecA accessory proteins that help RecA overcome inhibition by SSB and utilize SSB/single-stranded DNA complexes as substrates (247). This hypothesis is supported by the observation that the *recA803* allele (which is able to partially suppress the deficiencies of a *recF* mutant in the repair of daughter strand gaps) encodes a RecA derivative (257) that competes more effectively with SSB for binding to single-stranded DNA than does the wild type (151). This RecA derivative may be better able to participate in daughter strand gap repair without the intervention of RecF protein. A role for RecF protein as a RecA accessory protein would also account for the impaired SOS induction observed in a *recF* mutant (244).

The *ruvAB* operon is repressed by LexA protein and is regulated as part of the SOS response (9, 224, 225). RuvB protein is a DNA-dependent ATPase (99) and, when present at saturating amounts under high Mg^{2+} concentration, is able to promote branch migration without RuvA protein, indicating that it is the catalyst for branch migration (164). Visualization by electron microscopy has shown that RuvB binds circular duplex DNA to form ring-like structures that associate in pairs (236, 263). RuvB binds to RuvA protein, which interacts with RuvB in solution (221), and then binds specifically to Holliday junctions (172) to form a RuvAB-Holliday junction complex (173). It appears that the primary function of RuvA is to target the RuvB enzyme to the site of the junction, where it promotes ATP-dependent branch migration. The branch migration promoted by RuvA and RuvB proteins is significantly faster and much more energy efficient (245) than that promoted by RecA protein (194). Furthermore, RuvAB-mediated branch migration can bypass UV-induced lesions present in DNA at levels that inhibit RecA-mediated strand exchange (245). The fact that *ruv* mutants are sensitive to UV light, mitomycin, and ionizing radiation (143, 170), taken together with their known biochemical roles in homologous recombination, including their ability to promote branch migration on damaged DNA, makes RuvA and RuvB proteins attractive candidates for carrying out a portion of the branch migration that occurs during the repair of daughter strand gaps. The fact that the *ruvAB* operon is induced as part of the SOS response is consistent with this point of view.

Filamentation

E. coli cells exposed to SOS-inducing treatments continue to elongate but fail to septate and thus form filaments; this response is particularly acute in *lon* mutants (73, 76). *sulA* mutations were identified by their ability to suppress this SOS-induced filamentation (73). The inducibility and SOS control of the *sulA* gene was established by the use of a Mu d1 fusion (90); as mentioned previously, a LexA box is located upstream of the *sulA* coding region (39). The *sulA* gene product functions as an inducible inhibitor of septation (75, 77, 91, 215). The *lon* gene product is an ATP-dependent protease (75, 77) that degrades the SulA protein in vivo. Consequently, the SulA protein is very unstable, with a half-life of about 1 min in wild-type cells so that it accumulates to inhibitory levels only when its synthesis is increased by full induction of the SOS response (160). The target of the SulA protein is FtsZ, a key cell division protein. Specific mutations in *ftsZ* or overproduction of the FtsZ protein prevents the inhibition of septation by the SulA protein (101, 149, 150). Interestingly, the *lon* gene is a member of the heat shock regulatory network (179), and some SOS-inducing treatments can also induce at least some of the heat shock genes (118); the physiological significance, if any, of the relationship is not yet clear.

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