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Genetics

Inducibility of a gene product required for UV and chemical mutagenesis in *Escherichia coli*

(*umuC* gene/*recA*/*lexA* regulation/operon fusion/SOS functions)

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ABSTRACT **The product of the *umuC* gene is required for UV and chemical mutagenesis in *Escherichia coli*. By the use of the Mud(Ap, *lac*) bacteriophage, we have obtained an operon fusion of the *lac* structural genes to the promoter/regulatory region of the *umuC* gene. The strain containing the *umuC*::Mud(Ap, *lac*) fusion was identified on the basis of its UV nonmutability. Strains containing this putative null allele of *umuC* were (*i*) nonmutable by UV and other agents, (*ii*) slightly UV sensitive, and (*iii*) deficient in their ability to carry out Weigle reactivation of UV-irradiated bacteriophage λ. The UV nonmutability of the strain could be suppressed by a derivative of the mutagenesis-enhancing plasmid pKM101. β-Galactosidase synthesis in *umuC*::Mud(Ap, *lac*) fusion strains was inducible by UV and other DNA-damaging agents. Genetic analysis of the regulation of β-galactosidase in *umuC*::Mud(Ap, *lac*) strains suggests that the *lexA* protein is the direct repressor of the *umuC* gene and that a function of the *recA* protein, probably its protease activity, is required for the removal of the *lexA* repressor at the time of *umuC* induction.**

In *Escherichia coli*, mutagenesis by agents such as UV light, methyl methanesulfonate (MeMes), and 4-nitroquinoline-1-oxide (4NQO) is not a passive process. Rather, there exists a cellular system that processes the DNA damage in such a way that mutations result. Mutagenesis is not a necessary consequence of DNA damage; if this system is inactivated, no mutations result (1–4).

This "mutagenesis system" is inducible. Its activity is observed in wild-type cells only after treatments that either damage DNA or block replication (1). This feature is perhaps best illustrated by the fact that UV-irradiated bacteriophage are only slightly mutated unless the cells that they infect have been exposed to such an inducing treatment (5, 6). In addition to increasing the mutation frequency of UV-irradiated bacteriophage, treatment of host cells with low levels of DNA-damaging agents also increases the fraction of surviving phage (5, 6). These inducible mutagenesis and reactivation activities have been called Weigle or W mutagenesis and W reactivation, respectively (2).

The ability of *E. coli* or its bacteriophage to be mutated by UV and chemical agents can be blocked by mutations at three bacterial loci, *recA*, *lexA*, and *umuC* (1, 3, 4). These mutations simultaneously reduce or eliminate W reactivation. Because of the association of an inducible mutagenesis activity with what appears to be an inducible repair activity, it has been proposed that mutations result from the operation of an "error-prone repair" system (1, 2). To date, the biochemical mechanism of these processes has not been established (7, 8), nor have the effects on mutagenesis and survival been rigorously shown to result from the same process.

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The *recA* and *lexA* proteins coordinately regulate the diverse set of SOS phenomena that occur when cells are treated with various DNA-damaging agents. In addition to the induction of error-prone repair, these include the induction of lambdoid prophage, the induction of the *recA* protein, and filamentous growth (1). The *recA* and *lexA* proteins regulate not only their own synthesis but also the expression of a set of cellular *din* (*d*amage-*in*ducible) genes (9) [including *uvrA* (9, 10), *uvrB* (10, 11), and *sfiA* (12)] whose products are apparently required for at least some of these inducible responses. Although it is clear the *recA* and *lexA* proteins are involved in the regulation of the SOS responses, it has not been established whether these proteins play additional mechanistic roles in some of the SOS responses. In particular, it is not yet clear whether the *recA* or *lexA* gene products participate in the actual processing of DNA damage that gives rise to mutations.

In contrast to the pleiotrophic effects of the *lexA* and *recA* mutations, *umuC* mutations (3) specifically eliminate UV and chemical mutagenesis and reduce the efficiency of W reactivation. Thus, it is possible that the *umuC* gene product may play a key mechanistic role in the process of error-prone repair.

To better understand the molecular basis for the inducibility of the *umuC*$^+$-dependent mutagenesis and repair activities, we have isolated an operon fusion of the *umuC* promoter to the β-galactosidase structural gene. In doing so, we have obtained a putative null allele of the *umuC* gene. In this report, we describe the phenotype of this *umuC* mutant and analyze the regulation of the *umuC* gene.

METHODS AND MATERIALS

Strains. Bacterial strains used were all derivatives of *E. coli* K-12. Bacteriophage P1 transductions were essentially as described by Miller (13). The plasmids pGW200 (pKM101*mucl2*::Tn5) and pGW249 (pKM101*bla455*::Tn5) were introduced into fusion strains by mating and selection on appropriately supplemented minimal plates containing kanamycin (25 μg/ml) (14).

Media. Bacteria were routinely grown in Luria broth and LB agar (13). Supplemented M9/glucose plates and liquid medium (13) were used for mutagenesis and UV-survival measurements (14) and for β-galactosidase assays (13).

Isolation of Nonmutable Fusion Strains. The screening procedure was adapted from that used by Kato and Shinoura (3). Ampicillin-resistant colonies of strain GW1101 containing random Mud(Ap, *lac*) insertions (9) were replicated onto two plates containing low levels (1 μg/ml) of histidine. These plates were then exposed to three 2-J/m^2 doses of UV light at 10-hr intervals and those that displayed a nonmutable phenotype (0–1 His$^+$ papillae) on both replica plates were further characterized.

Abbreviations: MeMes, methyl methanesulfonate; 4-NQO, 4-nitroquinoline-1-oxide; MeNNG, *N*-methyl-*N'*-nitro-*N*-nitrosoquanidine.

RESULTS

Isolation and Mapping of a *umuC-lac* Fusion. A fusion of the *lac* structural genes to the promoter/regulatory region of the *umuC* gene was obtained by using the Mud(Ap, *lac*) operon fusion vector (15). Mud(Ap, *lac*) is a derivative of the temperate bacteriophage Mu, which integrates into the bacterial chromosome with no appreciable site specificity (16, 17). The phage carries the lactose structural genes but no promoter capable of initiating their transcription. However, when this phage integrates in a bacterial transcriptional unit, the *lac* genes can be expressed as a result of continued transcription into the phage genome. Such an insertion creates an operon fusion in which the synthesis of β-galactosidase has been placed under the control of the cellular regulatory locus. Moreover, the insertion of Mud(Ap, *lac*) in a gene, or proximal to it in its transcriptional unit, generates a mutation that generally results in the loss of function of that gene.

Our first step in obtaining a *umuC*::Mud(Ap, *lac*) fusion was to screen random insertions of Mud(Ap, *lac*) in the *E. coli* chromosome for those that made the cell nonmutable by UV. The bacterial strain we used for this screen had its own *lac* genes deleted and carried an ochre *his*$^-$ (18) and an ochre *arg*$^-$ mutation, each of which was revertable by UV. In addition, the strain carried a *uvrA*$^-$ mutation that inactivated the accurate *uvrA*$^+$-dependent excision repair pathway and increased the sensitivity of the cells to UV mutagenesis (1). Colonies containing random insertions of Mud(Ap, *lac*) were replica plated to supplemented minimal plates containing a low concentration of histidine, and the plates were UV irradiated. After screening 17,000 independent Mud(Ap, *lac*) insertions, we were able to identify 11 mutants that had a complete or partial inability to carry out UV-induced *his*$^-$ to His$^+$ reversion. Of these, six probably contained Mud(Ap, *lac*) insertions in histidine biosynthetic genes as they still gave rise to UV-induced Arg$^+$ revertants at a normal frequency.

The approximate position of the Mud(Ap, *lac*) insertions in the remaining five "UV-nonmutable" strains was determined by Hfr "quick-mapping" experiments (19). One of these insertions was subsequently mapped to the *umuC* locus (3, 20) by P1 transduction. Previously, we had isolated an insertion of the transposable element Tn5 (kanamycin resistance) that is ≈65% cotransducible with the known *umuC36* mutation. Transduction of this Tn5 from a *umuC*$^+$ strain into the nonmutable strain containing Mud(Ap, *lac*) resulted in loss of the Mud(Ap, *lac*) phage 50% of the time (12/24). All of those kanamycin-resistant transductants that had lost the Mud(Ap, *lac*) phage regained their ability to be mutated by UV. When this same Tn5 was transduced from a *umuC*$^-$ strain into the nonmutable Mud(Ap, *lac*) strain, none of the transductants that had lost Mud(Ap, *lac*) (0/25) regained the ability to be mutated by UV.

On the basis of this mapping data and the phenotypic characterization described below, we conclude that the UV nonmutability of this strain is due to an insertion of Mud(Ap, *lac*) in the *umuC* gene itself or proximal to it in the same transcriptional unit.

Properties of the *umuC*::Mud(Ap, *lac*) Mutant. The strains used are summarized in Table 1. As shown in Fig. 1, the strain carrying the *umuC*::Mud(Ap, *lac*) mutation was nonmutable with UV as are the known *umuC* mutants. An additional property of *umuC* mutants is that their nonmutability and their deficiency in W reactivation can be suppressed by the introduction of the drug-resistance plasmid pKM101 (21). This plasmid, in a *recA*$^+$*lexA*$^+$-dependent fashion, increases both the susceptibility of cells to mutagenesis and their resistance to killing by UV (22). We have previously suggested that a pKM101-encoded gene termed *muc* (*m*utagenesis::*UV* and *c*hemical) may be an analog of the chromosomally encoded *umuC* gene (14, 21). Introduction of pGW249, a kanamycin-resistant *muc*$^+$ derivative of pKM101 (14), into the *umuC*::Mud(Ap, *lac*) strain suppressed the UV nonmutability of this strain (Fig. 1). Moreover, a *muc*$^-$ Tn5 insertion mutant of pKM101 that fails to suppress the UV nonmutability of known *umuC* mutants (14) similarly failed to suppress the UV nonmutability of the *umuC*::Mud(Ap, *lac*) strain (Fig. 1). In addition, the *umuC*::Mud(Ap, *lac*) mutation is recessive; the introduction of an F′*umuC*$^+$ episome made the strain mutable by UV again (data not shown).

umuC mutations generated by ethyl methanesulfonate mutagenesis cause a modest increase in the sensitivity of cells to

Table 1. Bacterial strains

Strain	Relevant markers	Source
GW1000	*lacΔU169, tif-1, sfiA11, his-4*	This laboratory
RB800	*malE*::Tn*5*, *lexA3*	R. Brent
GW1102	As GW1000, but *malE*::Tn*5*	P1·RB800 × GW1000
AB1886	*uvrA6*	
GW1101	As GW1102, but *mal*$^+$, *uvrA6*	P1·AB1886 × GW1102
GW1103	As GW1101, but *umuC*::Mud(Ap, *lac*)	This paper
GW1104	As GW1103, but *uvrA*$^+$, *malE*::Tn*5*	P1·RB800 × GW1103
GW1105	As GW1103, but *uvrA*$^+$, *malE*::Tn*5*, *lexA3*	P1·RB800 × GW1103
DB6659	*srl*::Tn*10*, *recA56*	D. Botstein
GW1106	As GW1103, but *uvrA*$^+$, *malE*::Tn*5*, *recA56*, *srl*::Tn*10*	P1·DB6659 × GW1104
DM1187	*spr-51*	D. Mount (21)
GW1107	As GW1103, but *uvrA*$^+$, *spr-51*	P1·DM1187 × GW1105
GW1108	As GW1103, but *uvrA*$^+$, *spr-51, recA56, srl*::Tn*10*	P1·DB6659 × GW1107
GW1060	As GW1000, but *uvrA215*::Mud(Ap, *lac*)	Ref. 10

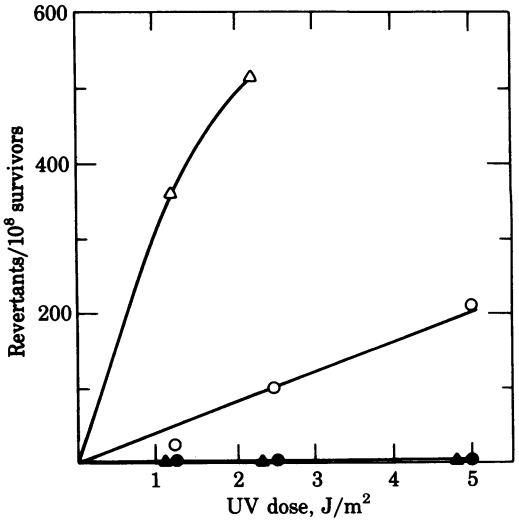

FIG. 1. UV nonmutability of a *umuC*::Mud(Ap, *lac*) strain and suppression of the nonmutability by a pKM101 derivative. Exponentially growing cultures of cells in supplemented M9/glucose medium were UV irradiated and plated on supplemented M9/glucose plates containing histidine (1 μg/ml) (22). His$^+$ revertants were counted after 2 days of incubation at 30°C. ○, GW1101 [*umuC*$^+$]; ●, GW1103 [*umuC*::Mud(Ap, *lac*)]; △, GW1103 (pGW249) [*umuC*::Mud(Ap, *lac*)/pKM101 *bla455*::Tn*5*]; ▲, GW1103 (pGW200) [*umuC*::Mud(Ap, *lac*)/pKM101 *muc12*::Tn*5*].

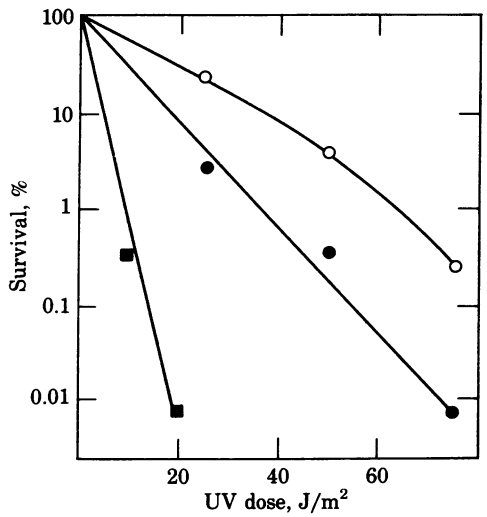

FIG. 2. Effect of the *umuC*::Mud(Ap, *lac*) mutation on resistance to UV killing. Exponentially growing cultures of cells were UV irradiated and plated on supplemented M9/glucose plates. ○, GW1000 (*uvrA*⁺*umuC*⁺); ●, GW1104 [*uvrA*⁺, *umuC*::Mud(Ap, *lac*)]; ■, GW1060 [*uvrA215*::Mud(Ap, *lac*), *umuC*⁺].

killing by UV (3). As shown in Fig. 2, a *uvrA*⁺ derivative of the *umuC*::Mud(Ap, *lac*) insertion mutant was slightly more UV sensitive than the corresponding *uvrA*⁺*umuC*⁺ strain, yet was by no means as sensitive as a *uvrA*::Mud(Ap, *lac*) mutant that lacks the major excision repair pathway (10).

The other distinguishing phenotype of *umuC* mutants is their reduced ability to carry out the induced reactivation of UV-irradiated λ phage (W reactivation) (3). The *umuC*::Mud(Ap, *lac*) strain was similarly deficient in W reactivation (Fig. 3). The residual inducible phage reactivation seen in *umuC* mutants has been previously shown to be *uvrA*⁺ dependent (21). Although the *umuC*::Mud(Ap, *lac*) strain was deficient in the W-reactivation response it was still proficient in other SOS responses such as the induction of λ prophage and of *recA* protein.

Induction of *umuC* Expression by UV. As shown in Fig. 4, UV irradiation induced the synthesis of β-galactosidase in a *umuC*::Mud(Ap, *lac*) fusion strain. As Mud(Ap, *lac*) appears to be inserted within the *umuC* transcriptional unit, this provides direct evidence that the synthesis of the *umuC* gene product is induced by DNA damage. As expected, the induction of the *umuC* gene product did not require the *uvrA*⁺/*B*⁺/*C*⁺-dependent endonucleolytic activity; the expression of the *umuC*::Mud(Ap, *lac*) fusion was also highly UV inducible in the original *uvrA*⁻ background.

Control of *umuC* Expression. The mutability of *umuC*⁺ cells is dependent on the function of the *recA* and *lexA* proteins (1, 9). These proteins are known to regulate the expression of a variety of damage-inducible genes. Current genetic and biochemical evidence indicates that the *lexA* protein represses multiple cellular genes (10, 12, 23, 24) and that induction occurs when the *recA* protein proteolytically cleaves the *lexA* protein in response to DNA damage (25). To determine whether the *umuC* gene is likewise controlled by the *recA* and *lexA* proteins, we introduced *recA*⁻ and *lexA*⁻ (uninducible repressor) mutations into the *umuC-lac* fusion strain. As shown in Fig. 4, induction of β-galactosidase was abolished.

In an effort to further analyze this *recA*⁺ *lexA*⁺ dependence, we examined the effect of a putative null mutation of *lexA*, termed *spr* (23), on *umuC* expression. Introduction of the *spr* mutation into the *umuC*::Mud(Ap, *lac*) strain resulted in high-level constitutive synthesis of β-galactosidase; no further increase in β-galactosidase synthesis was seen after UV-irradiation (Fig. 4). Thus, the *lexA* protein appears to play a negative regulatory role in the control of the *umuC* gene. When a *recA*⁻ mutation was subsequently introduced into the *spr umuC*::Mud(Ap, *lac*) strain, high-level constitutive synthesis of β-galactosidase was still observed; once again, no increase in β-galactosidase expression was seen on UV irradiation (Fig. 4). Thus, once *lexA* activity is eliminated from a cell, *recA* function is no longer needed for *umuC* expression. These observations suggest that the *lexA* protein is the direct repressor of the *umuC* gene and that induction occurs when, in response to DNA damage, the *lexA* protein is cleaved by the *recA* protease (25).

In this analysis, we have assumed that the *umuC*::Mud(Ap, *lac*) mutant we isolated resulted from a simple insertion of Mud(Ap, *lac*) into the *umuC* transcriptional unit. The formal possibility exists that the insertion of Mud(Ap, *lac*) into *umuC* was accompanied by a Mu-mediated deletion or rearrangement that resulted in the promoter of some other gene being fused to the *lac* genes of Mud(Ap, *lac*). We consider this unlikely as

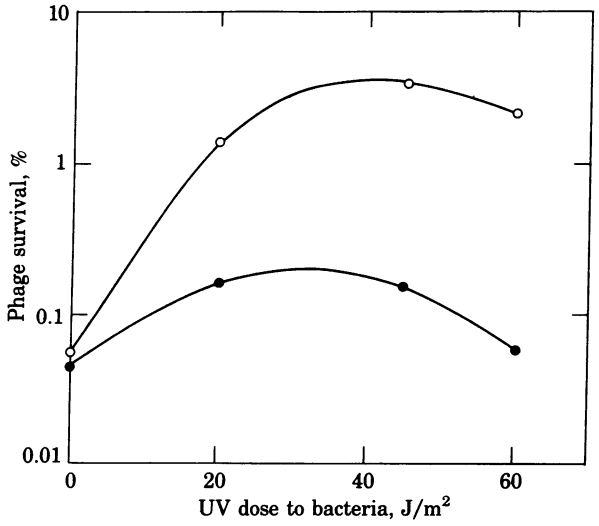

FIG. 3. Weigle reactivation of UV-irradiated bacteriophage. UV-irradiated (300 J/m²) λ were adsorbed to UV-irradiated bacteria and plated on a lawn of a *uvrA recA* indicator strain as described (20). ○, GW1000 (*umuC*⁺); ●, GW1104 [*umuC*::Mud(Ap, *lac*)].

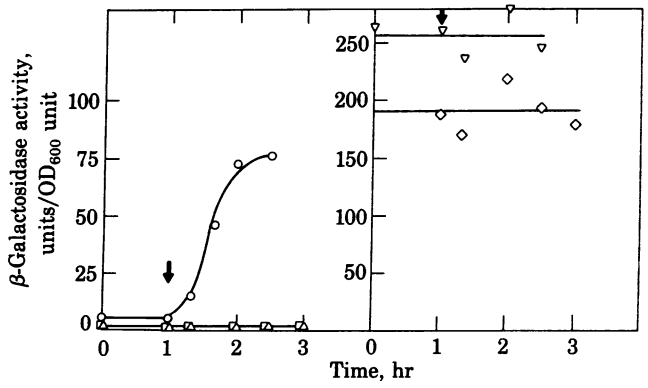

FIG. 4. Kinetics of UV induction of β-galactosidase in the *umuC*::Mud(Ap, *lac*) fusion strain and its derivatives. Cells were grown in supplemented M9/glucose medium at 30°C. Cells were UV irradiated (10 J/m²) at the time indicated by the arrow. Aliquots (1 ml) were removed periodically, and total β-galactosidase activity in the culture was determined essentially as described by Miller (13). Cell density was determined by measuring OD_{260}. ○, GW1104 [*umuC*::Mud(Ap, *lac*)]; △, GW1105 [*umuC*::Mud(Ap, *lac*), *lexA3*]; □, GW1106 [*umuC*::Mud(Ap, *lac*), *recA56*]; ▽, GW1107 [*umuC*::Mud(Ap, *lac*), *spr-51*]; ◇, GW1108 [*umuC*::Mud(Ap, *lac*), *spr-51*, *recA56*].

Table 2. Induction of β-galactosidase in a *umuC*::Mud(Ap, *lac*) fusion strain by various agents

Agent	Dose	β-Galactosidase, units/OD_{600} unit
—	—	5.6
MeMes	0.02 μl/ml	30.0
4NQO	5 μg/ml	64.7
MeNNG	0.25 μg/ml	31.3
Mitomycin C	0.25 μg/ml	67.3

An exponentially growing culture of GW1104 was split into several aliquots. One aliquot was untreated, and chemicals were added to the others to the concentrations shown. The cells were then incubated at 30°C for 2 hr, and the β-galactosidase activity was determined.

the *umuC*::Mud(Ap, *lac*) fusion was identified not on the basis of its regulatory characteristics but rather by its nonmutable phenotype and the observed regulation of β-galactosidase is consistent with physiological and genetic studies of $umuC^+$-dependent phenomena.

Induction of *umuC* Expression by Other Agents. We have also examined the ability of other DNA-damaging agents besides UV to induce β-galactosidase synthesis in the *umuC*::Mud(Ap, *lac*) fusion strain. MeMes, 4NQO, *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MeNNG), and mitomycin C all proved to be effective inducers (Table 2). Reversion of the ochre arg^- mutation by these first three agents was largely $umuC^+$-dependent (Table 3). Mitomycin C was not a particularly effective mutagen, at least for this particular reversion, yet it was a highly effective inducer of *umuC*. It is interesting to note that MeNNG, at 0.25 μg/ml, was able to cause induction of *umuC*. This is the same range of concentration of MeNNG that induces the "adaptive response" in related strains. The adaptive response, once induced, specifically prevents mutagenesis and killing by methylating and ethylating agents (26, 27).

The induction of the SOS phenomena and the expression of damage-inducible genes can be triggered by a variety of agents that damage DNA. Although the mechanism by which this induction occurs is not fully understood, it is likely that these agents lead to an increase in the concentration of an effector of the *recA* protein (such as single-stranded DNA). The agents tested here are inducers of the general set of SOS responses, and it is likely that their effect on *umuC* induction reflects their ability to generate an intracellular effector of the *recA* protein.

DISCUSSION

Treatment of cells with DNA-damaging agents induces a $umuC^+$-dependent system that can process DNA damage in such a way that mutations result. By isolating a fusion of the *umuC* promoter to the β-galactosidase structural gene, we have shown that the inducibility of this system is due at least in part to the induction of the *umuC* gene product.

Table 3. Nonmutability of a *umuC*::Mud(Ap, *lac*) strain with various agents

Agent	Dose	His^+ revertants	
		GW1000 ($umuC^+$)	GW1104 [*umuC*::Mud(Ap, *lac*)]
—	—	12	3
MeMes	1 μl	598	5
4NQO	60 μg	73	1
MeNNG	10 μg	228	16
Mitomycin C	20 μg	7	2

An 0.1-ml aliquot of an exponential culture was added to 2 ml of top agar containing the chemical and poured on a supplemented M9/glucose plate containing histidine at 1 μg/ml. His^+ revertants were counted after 3 days of incubation at 30°C.

The genetic analysis presented here indicates that the *lexA* protein directly represses the *umuC* gene. By similar genetic analyses and, in some cases, by biochemical experiments, this protein has now been shown to repress a number of cellular genes, including the *lexA* gene itself (24), *recA* (23), *uvrA* (10), *sfiA* (12), and the *dinA*, *dinB*, and *dinD* genes (ref. 9; unpublished results). Induction of these gene products occurs when the *recA* protein is proteolytically activated in response to DNA damage and cleaves the *lexA* repressor (25). Apparently, the use of a single regulatory protein such as the *lexA* or *crp* (28) proteins to control multiple cellular genes provides bacterial cells with an efficient mechanism for coordinate expression of genes that have diverse functions.

The demonstration that the *umuC* gene product is inducible may help to clarify the role of the *lexA* and *recA* proteins in mutagenesis. The nonmutability (29) of $lexA^-$ [uninducible repressor (25)] mutants is probably due at least in part to their inability to induce the *umuC* gene product. It is unlikely that the *lexA* protein functions mechanistically in mutagenesis as cells carrying putative null alleles of *lexA* (*spr* mutations) are fully mutable. In contrast, the *recA* protein appears to have a second function in addition to inactivating the *lexA* repressor protein. As shown above, cells carrying *spr* mutations synthesize high levels of *umuC* gene product in the absense of the *recA* protein; however, they are nonmutable. This requirement for *recA* function could be for its protease activity (30)—either to inactivate a second repressor or to proteolytically modify some protein. Alternatively, the requirement could be for those biochemical activities that have been associated with the *recA* role in homologous recombination (31, 32).

The inducibility of the bacterial mutagenesis system implies that, for agents such as UV, MeMes, and 4NQO to be effective mutagens, they must have at least two properties: (*i*) they must induce the *umuC* protein and (*ii*) they must introduce premutagenic lesions into DNA. The requirement for *umuC* (and possibly *recA*) induction is indicated by the nonmutability of cells carrying $lexA^-$ mutations. The need for premutagenic lesions can be inferred from a number of experiments—for example, the demonstration that the mutation frequency of bacteriophage infecting induced host cells is much higher when the phage have been irradiated (33). Thus, the efficiency of various mutagens is a reflection not only of their ability to introduce premutagenic lesions but also of their ability to induce the bacterial mutagenesis system that processes them. In addition, this suggests that certain combinations of mutagens may act synergistically.

The *umuC* mutation isolated in this study is likely to be a null allele. The mutation is recessive and was detected after screening a relatively modest number (17,000) of random Mud(Ap, *lac*) insertion mutants. The simplest interpretation of such a null allele is that the *umuC* gene product is an active participant in the processing of DNA damage that results in mutations. Moreover the inference that a nonmutable phenotype can result from a *loss* of cellular function suggests that the DNA damage resulting from UV and many chemical mutagens is not intrinsically mutagenic in bacteria. As the cells of many higher organisms, including humans, can be mutated by UV and many of these same chemicals, it seems reasonable to argue that these organisms possess analogous processing systems.

The phenotype of the *umuC* insertion mutant is similar to that of cells carrying *umuC* point mutations. In addition to becoming nonmutable, the cells are somewhat more sensitive to DNA damage and lose a component of the inducible W-reac-

tivation system. The association of the repair and mutagenesis deficiencies of the *umuC* mutant suggests that both the effects on mutagenesis and on recovery from UV damage may result from a single activity of the *umuC* protein.

Finally, it is interesting to note that the remaining component of W reactivation in a *umuC* mutant is abolished by the introduction of a *uvrA* mutation (21). The *uvrA* protein functions in the major excision repair pathway and, like the *umuC* gene product, is induced by DNA damage in a *recA*$^+$*lexA*$^+$-dependent fashion (9, 10).

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