JOURNAL OF BACTERIOLOGY, Jan. 1989, p. 99–103
0021-9193/89/010099-05$02.00/0

Vol. 171, No. 1

Altered Induction of the Adaptive Response to Alkylation Damage in *Escherichia coli recF* Mutants

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Received 21 July 1988/Accepted 27 September 1988

Escherichia coli recF **mutants are hypermutable when treated with methyl methanesulfonate (G. C. Walker, Mol. Gen. Genet. 152:93–103, 1977). In this study, methylation hypermutability of *recF* mutant strains was examined, and it was found that *recF*$^+$ is required for normal induction of the adaptive response to alkylation damage. Although this regulatory effect of *recF* mutations results in reduced levels of enzymes that specifically repair methyl lesions in DNA, it only partially explains the hypermutability. Further examination showed that methylation hypermutability of *recF* mutant strains required a functional *umuDC* operon, a component of the SOS response. These results lead to the hypothesis that methylation hypermutability results from the effects of *recF* mutations on the induction of both the SOS response and the adaptive response.**

The adaptive response of *Escherichia coli* to alkylation damage involves four known genes arranged in three transcriptional units, the *ada-alkB* operon and the *alkA* and *aidB* genes (for a review, see references 18 and 32). This response is induced when cells are treated with alkylating agents (primarily methylating agents) and the induced activities specifically repair alkylation lesions in DNA. This repair is accomplished by enzymes that either remove methyl groups from modified sites or remove methylated bases from DNA. Induction requires a wild-type *ada* gene (14) and occurs when Ada protein transfers methyl groups from methylphosphotriesters in the DNA backbone to itself. Methylated Ada protein then binds to a sequence adjacent to the promoter and stimulates transcription of the *ada-alkB* operon, the *alkA* gene, and presumably also the *aidB* gene (22, 28). The results presented here show that a wild-type *recF* gene is required for normal induction of adaptive response genes.

Mutations in the *recF* gene are pleiotropic, affecting recombination, DNA repair, expression of the SOS response, and mutagenesis. The effects of *recF* mutations on chromosomal recombination are seen in *recB recC sbc* mutants (12); in this genetic background, recombination requires the wild-type *recF* gene. *recF* mutations also have effects on DNA metabolism in wild-type cells; *recF* is required for recombination between plasmids (8, 13) and for mutagenesis and repair of UV damage to DNA (1, 4, 6, 7, 11, 12, 15, 23, 24, 40). Many of the DNA repair defects associated with *recF* mutations can be ascribed to their effect on induction of the SOS response, a damage-inducible DNA repair response (5, 6, 21, 33–35). The SOS response is induced when RecA protein is activated by DNA damage. Activated RecA then stimulates cleavage of LexA protein, thereby derepressing the SOS genes, which are under the control of the LexA repressor protein (19, 20, 39, 41). Mutations in *recF* decrease the induction of the SOS response and result in increased sensitivity to DNA-damaging agents (6, 21, 29, 34, 35). The role of *recF* in this regulation is, however, not clear at present. Walker (38) noted that the *recF143* mutation also affected mutagenesis by methyl methanesulfonate (MMS), resulting in hypermutability. This study relates *recF143*-mediated hypermutability to *recF* effects on the induction of both the adaptive response and the SOS response. A model based on the regulatory effects of *recF* mutations on these two responses is proposed to explain *recF*-mediated hypermutability.

MATERIALS AND METHODS

Bacterial strains. All bacterial strains used in this study are listed in Table 1.

Mutagenesis and lethality. Mutagenesis was performed essentially as described by Walker (38). Overnight culture (0.1 ml; approximately 10^8 cells) was added to 2 ml of top agar, which contains all required nutrients at high concentrations, except arginine. Top agar contained agar (0.6%); E salts (31); glucose (4%); histidine, leucine, proline, and threonine (1 mg/ml each); thiamine (2 μg/ml); and arginine (0.05 M). Just prior to the addition of cells, MMS or *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG) was added at the specified concentration. Top agar containing the mutagen and cells was then poured onto a minimal E salts plate containing 2% glucose. When required, mutagens were diluted in dimethyl sulfoxide. To determine the initial cell titers and the lethal effects of the mutagenic treatment, diluted cells were plated under conditions identical to those used to examine mutagenesis. The limited amount of arginine present was sufficient to allow Arg$^-$ cells to form small colonies only when small numbers of cells were plated. When large numbers of cells were plated, only a few divisions occurred before the arginine was depleted, thereby inhibiting growth of Arg$^-$ cells. Arg$^+$ revertants that arise in the population can continue to grow and form colonies on the lawn of Arg$^-$ cells. All incubations were carried out at 37°C for 5 days.

β-Galactosidase assays. β-Galactosidase activity was determined as previously described (36). All incubations of Mu dl(Ap^r *lac*)-containing cells were carried out at 30°C. β-Galactosidase assays were performed with extracts obtained 3 h after the addition of the methylating agent. At this time both *recF*$^+$ and *recF143* mutant strains exhibited maximal amounts of activity (data not shown). To rule out the possibility that *recF* mutations altered the kinetics of adaptive response gene induction rather than the extent of induction, β-galactosidase activity was assayed periodically for 5 h after the addition of MMS. In these experiments *recF* mutants exhibited lower levels of activity at all time points than their isogenic *recF*$^+$ parent strain (data not shown). All

TABLE 1. Bacterial strains

Strain	Relevant genotype	Source or reference
AB1157[a]	Wild type	2
JC9239	*recF143*	12
JC10990	*recF332*::Tn*3* *tnaA*::Tn*10*	3
MV1161[b]	Wild type	36
MV1563[c]	*aidB2*::Mu dl(Ap^r *lac*)	36
MV1571	*alkA51*::Mu dl(Ap^r *lac*)	36
MV1601[d]	*alkB52*::Mu dl(Ap^r *lac*)	37
MV1942[e]	*alkA51*::Mu dl(Ap^r *lac*) *recF143*	This study
MV1944[f]	*alkB52*::Mu dl(Ap^r *lac*) *recF143*	This study
MV2007[g]	*ada-10*::Tn*10*	This study
MV2100[h]	*aidB2*::Mu dl(Ap^r *lac*) *recF143*	This study
MV2111[i]	*umuC36*	This study
MV2113[j]	*recF143 umuC36*	This study
MV2115[k]	*ada-10*::Tn*10 umuC36*	This study
MV2123[l]	*aidB2*::Mu dl(Ap^r *lac*) *recF332*::Tn*3*	This study
MV2125[m]	*alkA51*::Mu dl(Ap^r *lac*) *recF332*::Tn*3*	This study
MV2127[n]	*alkB52*::Mu dl(Ap^r *lac*) *recF332*::Tn*3*	This study

[a] AB1157 contains the following mutations: *thr-1 ara-14 leuB6* Δ(*gpt-proA*)*62 lacY1 tsx-33 supE44 galK2 hisG4 rfbD1 mgl-51 rpsL31 kdgK51 xyl-5 mtl-1 argE3 thi-1*.

[b] MV1161 is a spontaneous *rfa-550* derivative of AB1157 (36).

[c] All MV strains used in this study, except MV2113, are derivatives of MV1161.

[d] *alkB52*::Mu dl(Ap^r *lac*) was formerly designated *aidD6*::Mu dl(Ap^r *lac*).

[e] MV1942 is a *tnaA300*::Tn*10 recF143* transductant of MV1571. It was constructed by transduction of MV1571 with P1.MV1232 (*tnaA300*::Tn*10 recF143*) (33), selecting for tetracycline resistance (Tet^r), and then screening for UV sensitivity.

[f] MV1944 is a *tnaA300*::Tn*10 recF143* transductant of MV1601. Its construction was similar to that of MV1942.

[g] MV2007 is an *ada-10*::Tn*10* transductant of MV1161. It was constructed by transduction of MV1161 with P1.GW5352 (17) (*ada-10*::Tn*10*Δ16, Δ17), selecting for Tet^r, and then screening for MNNG hypermutability and sensitivity.

[h] MV2100 is a *tnaA300*::Tn*10 recF143* transductant of MV1563. Its construction was similar to that of MV1942.

[i] MV2111 is a *zcf*::Tn*5 umuC36* transductant of MV1161. It was constructed by transducing MV1161 with P1.NR8001 (*zcf*::Tn*5 umuC36*) (obtained from B. W. Glickman, York University, Toronto, Ontario, Canada), selecting for kanamycin resistance, and then screening for UV nonmutability.

[j] MV2113 is a *zcf*::Tn*5 umuC36* transductant of JC9239. Its construction was similar to that of MV2111.

[k] MV2115 is a *zcf*::Tn*5 umuC36* transductant of MV2007. Its construction was similar to that of MV2111.

[l] MV2123 is a *tnaA300*::Tn*10 recF332*::Tn*3* transductant of MV1563. It was constructed by transducing MV1563 with P1.JC10990 (*tnaA300*::Tn*10 recF332*::Tn*3*) (3), selecting for Tet^r, and then screening for UV sensitivity.

[m] MV2125 is a *tnaA300*::Tn*10 recF332*::Tn*3* transductant of MV1571. Its construction was similar to that of MV2123.

[n] MV2127 is a *tnaA300*::Tn*10 recF332*::Tn*3* transductant of MV1601. Its construction was similar to that of MV2123.

experiments were repeated three to eight times, and representative data are shown.

RESULTS

Effect of *recF143* on methylation mutagenesis. The data shown in Fig. 1A and B confirm that the *recF143* mutation results in hypermutability upon MMS treatment and show that hypermutability also occurs upon MNNG treatment. No lethality was detected at the MMS or MNNG concentrations used (data not shown). MMS and MNNG methylate DNA by different mechanisms (16) and produce different spectra of lesions in DNA. MNNG methylates oxygen sites in DNA to high levels relative to nitrogen sites, whereas MMS is relatively poor at oxygen methylation (26). Mutagenesis resulting from treatments with these two methylating agents differs: MNNG mutagenesis is *umuDC* independent and is due largely to mispairing of O^6-methylguanine during replication, whereas MMS mutagenesis appears to be partially due to error-prone, *umuDC*-dependent processing of lesions that block replication (10, 25, 39).

Effect of *recF143* on adaptive response gene induction. One possible explanation for increased methylation mutagenesis is that *recF* mutations may affect the expression of the adaptive response genes of *E. coli*. To test this possibility, we introduced the *recF143* mutation into strains containing fusions of Mu dl(Ap^r *lac*) to the three known adaptive response genes or operons, *ada-alkB*, *alkA*, and *aidB*. These *recF143* mutants, and their *recF*$^+$ counterparts, were then tested for induction of β-galactosidase activity upon treatment with methylating agents.

MNNG induction of *ada-alkB*::Mu dl(Ap^r *lac*) and *alkA*::Mu dl(Ap^r *lac*) fusions was reduced by the *recF143* mutation to approximately 30% of the level seen in isogenic *recF*$^+$ strains (Fig. 2). The *recF143* mutation also decreased induction of *aidB*::Mu dl(Ap^r *lac*) (Fig. 2), a gene that is also regulated by *ada* but which requires higher levels of alkylation for its induction (36; M. R. Volkert, F. H. Gately, and L. I. Hajec, Mutat. Res., in press).

MMS induction of *recF*$^+$ and *recF143* derivatives of the three fusion mutants was also tested. The *recF* mutation reduced MMS induction of all three genes (Fig. 2). To determine whether the effects of *recF* on adaptive-response gene induction were specific to the *recF143* allele or were a general effect of *recF* mutations, we transduced *recF332*::Tn*3* into each of the fusion strains. *recF332*::Tn*3* is a mutation resulting from Tn*3* insertion between codons 24 and 25 of the 357-amino-acid-encoding *recF* gene (3). Results of these experiments were essentially identical to the results obtained by using the *recF143* mutation (data not shown), thereby ruling out explanations invoking a partially active RecF missense protein.

These results suggest that the hypermutability of the *recF143* strain is due to decreased expression of the adaptive response genes. This leads to the prediction that *recF* mutant strains would exhibit levels of mutagenesis intermediate between a *recF*$^+$ strain and an *ada-10*::Tn*10* mutant strain, because *recF* mutants are partially inducible and therefore presumably contain modest amounts of adaptive response enzymes. A *recF*$^+$ strain is normally inducible and therefore contains high levels of adaptive response enzymes, and an *ada-10*::Tn*10* mutant is completely blocked in *alkA* and *aidB* induction (37) and presumably contains no Ada protein (17). This prediction was fulfilled when MNNG mutagenesis was compared in these three strains (Fig. 1A). However, when MMS mutagenesis was compared (Fig. 1B), the *recF* mutant strain exhibited higher levels of mutagenesis than the *ada-10*::Tn*10* derivative did in the dose ranges tested. Since MMS mutagenesis in these three strains does not correlate with the predicted levels of adaptive-response repair enzymes, these results are not consistent with the simple model that the hypermutability of *recF* mutant strains is due to decreased induction of the adaptive response.

Role of *umuDC* in *recF*-mediated methylation hypermutability. MMS and MNNG differ in that MMS mutagenesis is partially dependent on the *umuDC* operon, a component of the SOS response, whereas MNNG mutagenesis is *umuDC* independent in wild-type strains (10, 25). When the *umuC36* mutation was introduced into the *recF*$^+$, *recF143*, and *ada-10*::Tn*10* strains, all strains showed decreased levels of MMS mutagenesis as anticipated (Fig. 1). Moreover, the *umuC36 recF143* mutant strain exhibited a level of mutagenesis intermediate between that of the *umuC36 recF*$^+$ and

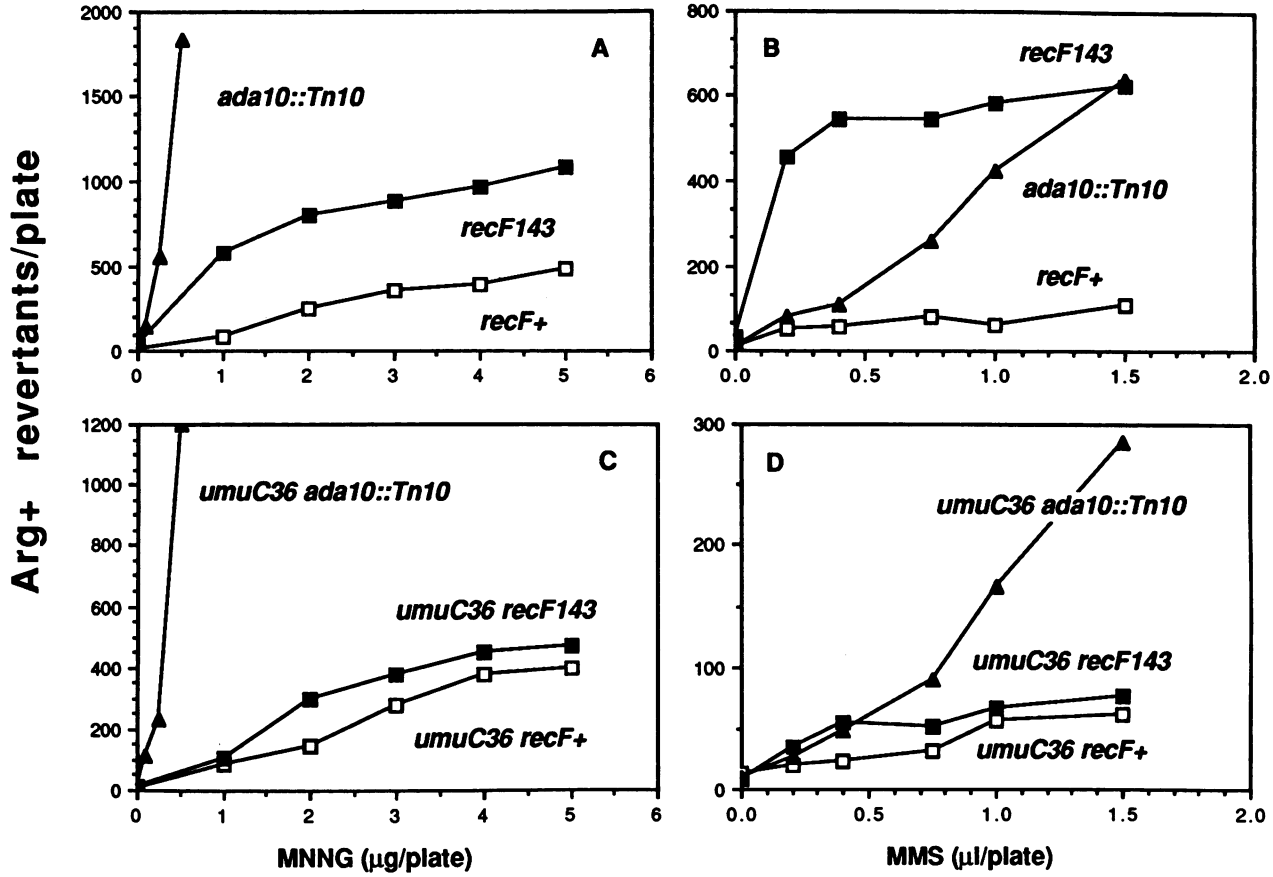

FIG. 1. Methylation mutagenesis. (A and B), Mutagenesis in *recF*$^+$ (□), *recF143* (■), and *ada-10*::Tn*10* (▲) strains; (C and D), mutagenesis in *umuC36* derivatives of *recF*$^+$ (□), *recF143* (■), and *ada-10*::Tn*10* (▲) strains. MNNG mutagenesis is shown in panels A and C, and MMS mutagenesis is shown in panels B and D. Strains used were AB1157 (*recF*$^+$), JC9239 (*recF143*), MV2001 (*ada-10*::Tn*10*), MV2111 (*umuC36 recF*$^+$), MV2113 (*umuC36 recF143*), and MV2115 (*umuC36 ada-10*::Tn*10*).

umuC36 ada-10::Tn*10* strains. These results suggest that methylation hypermutability of *recF* mutant strains is due in part to the reduced expression of the adaptive response; however, its full extent requires the function of the *umuDC* operon. MNNG hypermutability also appears to be partially *umuDC* dependent in *recF143* and *ada-10*::Tn*10* mutants; however, no reduction in MNNG mutagenesis could be detected when the *umuC36* mutation was introduced into the *recF*$^+$ strain (Fig. 1).

***umuDC* dependence of *recF143*-mediated spontaneous hypermutability.** *recF143* mutant strains exhibit a higher frequency of spontaneous mutations (27). Measurements of spontaneous mutations from a total of seven different experiments showed that the *recF*$^+$ parent strain yielded 11 ± 4 spontaneous mutants per plate, whereas the *recF143* mutant strain yielded 42 ± 8 spontaneous mutants per plate. This elevated level of spontaneous mutagenesis is dependent on the *umuDC* operon, since it was not seen when the *umuC36* mutation was introduced; the *umuC36 recF*$^+$ and *umuC36 recF143* mutant strains yielded 9 ± 3 and 10 ± 1 spontaneous mutants per plate respectively.

DISCUSSION

The results of this study show that the *recF* gene of *E. coli* is required for normal induction of the adaptive response to alkylation damage. This reduced ability to induce the adaptive response can account for only a portion of the hypermutability. The expression of SOS response genes is also implicated in methylation hypermutability of *recF* mutant strains, and its *umuDC* dependence suggests that *umuDC* processing of methyl lesions is required for the hypermutability to be fully expressed.

An explanation for the role of *umuDC* in this hypermutability stems from the result that *recF* mutations do not completely block all SOS gene induction (21, 29, 34). There are differences among individual SOS genes with respect to the severity of the effect of *recF* on induction; induction of some SOS genes is blocked completely by *recF* mutations, expression of others is reduced, and some SOS genes appear to be induced normally (29; M. Volkert, unpublished observations). The *umuDC* operon is among the SOS genes whose induction is unaffected by *recF* mutations (29). I propose that the hypermutability of *recF* mutant strains seen when their DNA is damaged by methylating agents is due to effects on expression of both the adaptive response and SOS genes. In *recF* mutants the reduced expression of the adaptive response genes causes more lesions to remain in the DNA. These lesions are then preferentially processed by the mutagenic *umuDC* pathway, which is induced to a high level relative to other (nonmutagenic) SOS damage processing pathways in the *recF* mutant cell. In the wild-type cell, the lesions would more probably be processed, for example, by recombinational repair, which requires both *recA* and *recF* (11, 40).

Most MNNG hypermutability resulting from the *recF* mutation is eliminated when the *umuC36* mutation is intro-

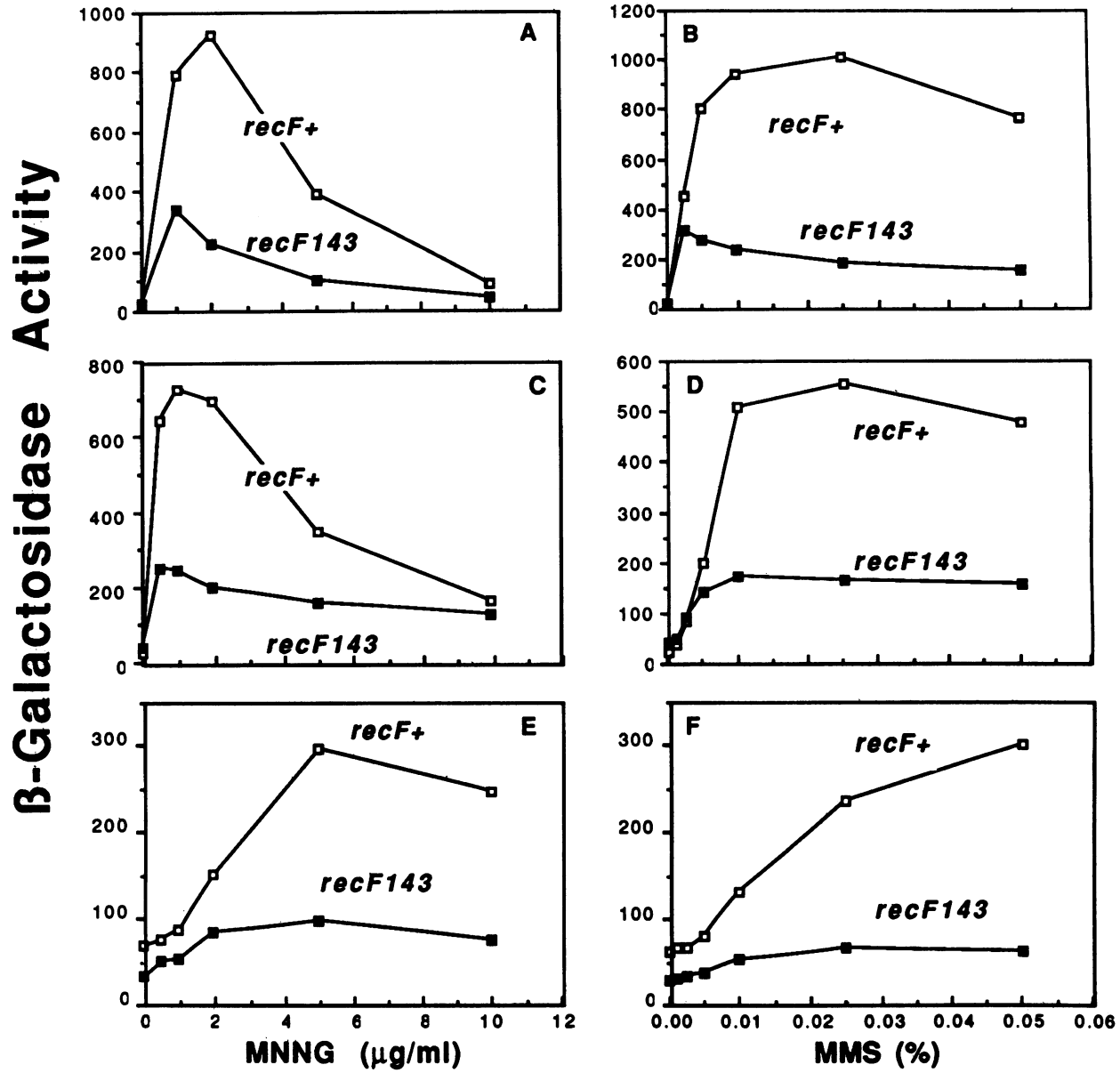

FIG. 2. Effect of *recF143* on induction of adaptive response genes. (A and B), Induction of *alkB52*::Mu dl(Ap^r *lac*) in *recF*$^+$ (□) and *recF143* (■) strains; (C and D), induction of *alkA51*::Mu dl(Ap^r *lac*) in *recF*$^+$ (□) and *recF143* (■) strains; (E and F) induction of *aidB2*::Mu dl(Ap^r *lac*) in *recF*$^+$ (□) and *recF143* (■) strains. MNNG induction is shown in panels A, C, and E, and MMS induction is shown in panels B, D, and F. Strains tested were MV1601 and MV1944 (panels A and B), MV1571 and MV1942 (panels C and D), and MV1563 and MV2100 (panels E and F).

duced. This suggests that MNNG mutagenesis, which is largely *umuDC* independent in wild-type strains (10, 25), becomes *umuDC* dependent in a *recF* mutant strain. Thus, the *recF* mutation not only causes MMS lesions to be preferentially processed by the *umuDC* pathway, but also channels MNNG lesions into this pathway. A similar channeling of MNNG lesions into *umuDC*-dependent pathways occurs in *alkA* mutants (10).

The observation that the *recF* gene of *E. coli* affects the expression of both the SOS and adaptive responses provides a direct link between these two regulons. Such a regulatory link was suggested by the results of Defais et al. (9), who noted that the expression of the adaptive response reduced the ability to subsequently induce the SOS response. The results of Vericat et al. (30) show that this competition between the adaptive and SOS responses is complex. They tested three SOS genes, *recA*, *sulA*, and *umuDC*, and found that *recA* and *sulA* expression was reduced by prior induction of the adaptive response, whereas *umuDC* expression was not. Since the SOS genes whose induction is reduced by adaptive response expression are also the SOS genes that require *recF*$^+$ for their induction (29), it is possible that these two responses compete for RecF protein, thereby limiting the amount available for expression of the second response.

ACKNOWLEDGMENTS

I thank Laurel Hajec for expert technical assistance and Anthony Poteete, Martin Marinus, Laurel Hajec, Zdenka Matijasevic, and

Suzanne Deschenes for helpful discussions during this work and for critical comments on the manuscript.

This work was supported by Public Health Service grant GM37052 from the National Institutes of Health.

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