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Genetics

groEL and *dnaK* genes of *Escherichia coli* are induced by UV irradiation and nalidixic acid in an *htpR*$^+$-dependent fashion

(SOS/heat shock/gene regulation)

JUDY HEILIG KRUEGER AND GRAHAM C. WALKER

Biology Department, Massachusetts Institute of Technology, Cambridge, MA 02139

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ABSTRACT **Two proteins with molecular weights of 61,000 and 73,000 were found to be induced by UV light in *Escherichia coli* mutants in which the SOS responses are constitutively expressed. The induction of these proteins by UV light and nalidixic acid was shown to be independent of the *recA*$^+$ *lexA*$^+$ regulatory system. Analysis of these proteins by two-dimensional gel electrophoresis and comparison with the "heat-shock" proteins of *E. coli* revealed that the M_r 61,000 protein comigrated with the *groEL* gene product, that the M_r 73,000 protein comigrated with the *dnaK* gene product, and that other heat-shock proteins were also induced. The induction of groEL and dnaK by UV light and nalidixic acid is controlled by the *htpR* locus. The results suggest that the regulatory response of *E. coli* to agents such as UV light and nalidixic acid is more complex than previously thought.**

Over the past several years there has been a considerable increase in our understanding of how *Escherichia coli* responds to DNA damage. Two independent regulatory networks have been identified that are induced by damage to the cell's DNA—the SOS response (1) and the adaptive response (2).

Of the two, the adaptive response seems to be the simpler. It is induced by exposure to methylating or ethylating agents but not by agents such as UV irradiation or 4-nitroquinoline-1-oxide (3). Two proteins have been shown to be induced in this response, the O^6-methylguanine-DNA methyltransferase and a 3-methyladenine glycosylase (4); the product of the *ada* gene regulates their induction (4).

The SOS response seems to be more complex (1). It is induced by agents and conditions that either damage DNA or interfere with DNA replication. Typical inducing agents are UV irradiation, nalidixic acid, and mitomycin C. The expression of genes in the SOS network is controlled by two regulatory elements, the recA and lexA proteins. The lexA protein serves as the repressor of each of the *din* (*d*amage-*in*ducible) genes (5) that have been identified to date (1); *lexA*(Def) mutations that eliminate *lexA* function cause the high-level constitutive expression of *din* genes (1, 6). After SOS-inducing treatments, a protease activity of the recA protein is activated that then cleaves the lexA protein leading to the induction of the *din* genes (1). To date, at least 15 chromosomal *din* genes have been identified that are regulated by the lexA and recA proteins, and it seems likely that more genes will be found to be members of the SOS regulatory network.

In this paper, we report that the response of *E. coli* to UV irradiation and nalidixic acid is even more complex than previously thought. These agents induce the expression of several genes that are not regulated by the lexA and recA proteins but rather by a different regulatory system.

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MATERIALS AND METHODS

Bacterial strains used are listed in Table 1. Early log cultures grown at 30°C were labeled with [^{35}S]methionine (5 μCi/ml, final concentration for one-dimensional gels; 30 μCi/ml, final concentration for two-dimensional gels; 1 Ci = 37 GBq) for 5 min and chased for 1 min after various treatments (6). Cell extracts were prepared and the proteins were separated on 10–12% NaDodSO$_4$/polyacrylamide gels as described by Laemmli (10). Two-dimensional gel electrophoresis was carried out as described by O'Farrell (11). Extracts were prepared as for one-dimensional gels and were then diluted 1:3 with sample dilution buffer (12). Fluorographic exposures using Kodak XAR5 film were made of gels treated with EN^{3}HANCE (New England Nuclear).

RESULTS

Induction of a M_r 61,000 Protein by UV Irradiation. During the characterization of *E. coli* strains containing *lexA*::Tn*5*-(Def) mutations (6), we used NaDodSO$_4$/polyacrylamide gel electrophoresis to examine the proteins synthesized in [^{35}S]methionine-labeled cells to confirm that the recA protein was being synthesized constitutively, an expected phenotype of cells deficient in lexA protein (8). Fig. 1 shows the patterns of proteins observed in *lexA*$^+$ and *lexA*::Tn*5* cells that had been pulse-labeled with and without prior UV irradiation (100 J/m^2). As expected, the synthesis of the recA protein (M_r, ≈40,000) was induced by UV irradiation in the *lexA*$^+$ strain (lanes a and b), but in the *lexA*::Tn*5* strains (lanes c–j), the recA protein was expressed at high levels without irradiation.

However, in addition, we were surprised to find an easily visible protein band (M_r, 61,000) induced by UV light not only in the *lexA*$^+$ strain but also in the *lexA*::Tn*5* strains. This suggested that there is a UV-inducible gene in *E. coli* that is not repressed by lexA protein and, therefore, that this gene differs from all the other UV-inducible *E. coli* genes that have been characterized to date (1). In spite of this difference, there was a formal possibility that the induction of the M_r 61,000 protein was an SOS response, because a gene repressed by some other recA-cleavable repressor besides lexA (i.e., a conceptual analog of the λ repressor) would be expected to be induced by UV irradiation. We did note one characteristic feature that distinguished the induction of the M_r 61,000 protein from the induction of the recA protein, which was that the recA protein could be induced by doses of UV light from 10 to 100 J/m^2, while the M_r 61,000 protein was only induced by higher doses (50–100 J/m^2). During their study of recA induction, Gudas and Pardee (13) reported that nalidixic acid-treatment of *E. coli* B/r caused the induction of a M_r 60,000 protein that separated with a membrane fraction, and it seemed possible that the M_r 61,000 protein induced in our experiments was the same protein that they had observed.

Table 1. Bacterial strains

Strain	Markers	Source or ref.
AB1157	F⁻, *thr-1*, *leu-6*, *proA2*, *his-4*, *argE3*, *thi-1*, *lacY1*, *galK2*, *ara-14*, *xyl-5*, *mtl-1*, *tsx-33*, *rpsL*, *supE44*	*
JM12	as AB1157, but *recA441*, *supE*⁺(?)	(7)
DM1187	F⁻, *thr-1*, *leu-6*, *proA2*, *his-4*, *galK2*, *rpsL*, *ilv(ts)*, *recA441*, *sulA11*, *lexA51*(Def)	(8)
SC122	F⁻, *lac(am)*, *trp(am)*, *pho(am)*, *mal(am)*, *rpsL*, *sup4*^{ts}	(9)
K165	as SC122, but *htpR(am)*	(9)
GW1000	*recA441*, *sulA11*, *lacU169*, *thr-1*, *leu-6*, *his-4*, *argE3*, *ilv(ts)*, *galK2*, *rpsL31*	(5)
GW4701	as GW1000, but *htpR(am)*, *malPQ*::Tn*5*	†
GW2725	as GW1000, but *dinF1*::Mud(Ap, *lac*) *lexA71*::Tn*5*	(6)
GW2701	as GW1000, but *dinD1*::Mud(Ap, *lac*) (pGW600)	(6)
GW2706	as GW2701, but *lexA72*::Tn*5*	(6)
GW2707	as GW2701, but *lexA71*::Tn*5*	(6)
GW2708	as GW2701, but *lexA73*::Tn*5*	(6)

*A. J. Clark.
†K. H. Paek and G. C. Walker.

Induction of a M_r 61,000 Protein by Temperature Shift of a *recA441* Strain. We first decided to examine the induction of this protein after a different SOS-inducing treatment that is thought to lead to the activation of the recA protease in the absence of DNA damage. In a *recA441*(*tif-1*) strain, the SOS responses are turned on by growth at 42°C, an effect potentiated by the presence of adenine. In Fig. 2, samples were pulse-labeled 20 and 40 min after raising the temperature of a *recA441* strain from 30°C to 42°C. In addition to the recA protein, a M_r 61,000 protein was induced by the temperature shift in a *recA441* background; the addition of adenine seemed to stimulate the synthesis of both proteins at the 20-min point. If the M_r 61,000 proteins shown in Figs. 1 and 2 are indeed the same, then this protein can be induced by two different treatments known to induce the SOS response—UV irradiation and a temperature shift of a *recA441* strain.

Induction of the M_r 61,000 Protein is *recA*⁺ *lexA*⁺ Independent. To test whether the induction of this M_r 61,000 protein was part of the *recA*⁺ *lexA*⁺ regulatory system, we examined its synthesis after UV irradiation in two *recA* mutants. In both *recA13* and *recA56* strains, the *recA* gene product failed to be induced by UV irradiation as expected, but the M_r 61,000 protein was still induced (data not shown).

This result indicated that the induction of the M_r 61,000 protein by UV light does not depend on the activity of the recA protein and therefore that the gene coding for this protein is not part of the *recA*⁺ *lexA*⁺ regulatory circuit. This conclusion was also consistent with our observation that the M_r 61,000 protein was induced by UV irradiation in a *lexA3*(Ind⁻) strain. If the M_r 61,000 protein induced by heat in Fig. 2 is the same as that induced by UV light, these results implied that the induction of the protein after a temperature shift from 30°C to 42°C is independent of the *recA441* allele and thus that the protein can be induced simply by a temperature shift.

Comparison with Heat-Shock Proteins. In *E. coli*, a group of at least 13 proteins are induced after a heat shock (14). Within a few minutes of the temperature shift, the synthesis rates increase about 2- to 50-fold (14). In addition, their heat induction appears to be dependent on a regulatory locus called either *htpR* (14) or *hin* (15), because a strain, K165 (9), carrying an amber mutation in *htpR* shows greatly decreased synthesis of the heat-shock proteins at 42°C. In K165, the mutation appears to be suppressed at 30°C by the *supF*^{ts} it carries. At 42°C, the mutation is no longer suppressed and the cells can no longer form colonies. Only some of the heat-shock proteins have been identified, including the products of the *groEL* and *groES* genes (14, 16, 17) (required for morphogenesis of λ), *dnaK* (18) (defective in λ DNA replication), *lysU* (19) (alternative lysyl-tRNA synthetase), and *rpoD* (20) (σ-subunit of RNA polymerase).

We decided to directly compare the proteins made in UV-irradiated cells and heat-shocked cells (Fig. 3). The cells in lane d of Fig. 3 were labeled 5 min after a shift to 50°C. At this high temperature, the majority of proteins synthesized in substantial amounts are heat-shock proteins (21). As in previous experiments, the M_r 61,000 protein was induced 20 min after UV treatment (lane c), and, interestingly, it comigrated with one of the major heat-induced proteins, the product of the *groEL* gene. [In lanes a–c, the recA protein is being synthesized constitutively because this strain contains a *lexA*(Def) allele.] From this fluorogram, it became obvious that another protein besides the M_r 61,000 protein can be induced by UV irradiation in a *lexA*(Def) strain. This protein comigrates with one of the larger heat-induced proteins (M_r, ≈73,000), the dnaK protein.

To determine whether the two UV-induced proteins are

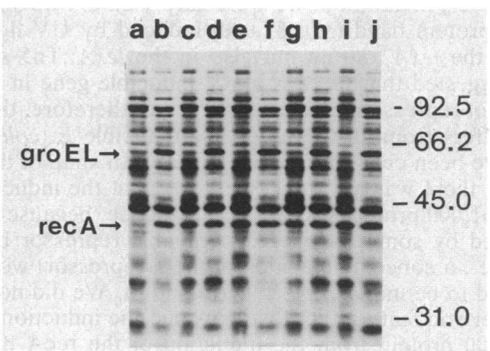

FIG. 1. Proteins from *lexA*⁺ (GW2701) and *lexA*(Def)::Tn*5* strains synthesized after UV irradiation. Cultures were labeled 30 min after irradiation (100 J/m²). Equal amounts of acid precipitable counts were applied to each lane. Molecular weights (×10⁻³) and mobility of standards are indicated on the right. Arrows indicate recA protein and M_r 61,000 protein. Lanes: a, GW2701 control; b, GW2701 irradiated; c, GW2706 control; d, GW2706 irradiated; e, GW2707 control; f, GW2707 irradiated; g, GW2708 control; h, GW2708 irradiated; i, GW2725 control; j, GW2725 irradiated.

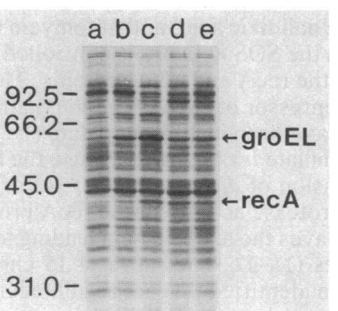

FIG. 2. Proteins from a *recA441* strain synthesized after a temperature shift from 30°C to 42°C. A culture of JM12 was divided and a portion was shifted to 42°C. Adenine (100 μg/ml, final concentration) was added to indicated samples at the time of the temperature shift. Molecular weights (×10⁻³) and mobility of standard proteins are indicated on the left. Arrows indicate the recA protein and M_r 61,000 protein. The time of labeling after temperature shift is indicated in parentheses. Lanes: a, JM12 control; b, JM12 (20 min); c, JM12 (20 min) with adenine; d, JM12 (40 min); e, JM12 (40 min) with adenine.

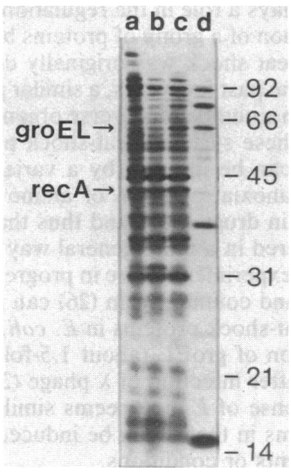

FIG. 3. Comparison of proteins made after UV irradiation (100 J/m^2) and after a temperature shift from 30°C to 50°C. Equal amounts of acid-precipitable counts were applied to each lane. Molecular weights ($\times 10^{-3}$) and mobility of standard proteins are indicated on the right. Arrows indicate the positions of the recA protein and the M_r 61,000 protein. The time of labeling after treatment is indicated in parentheses. Lanes: a, DM1187 control; b, DM1187 irradiated (2 min); c, DM1187 irradiated (20 min); d, AB1157 at 50°C (5 min).

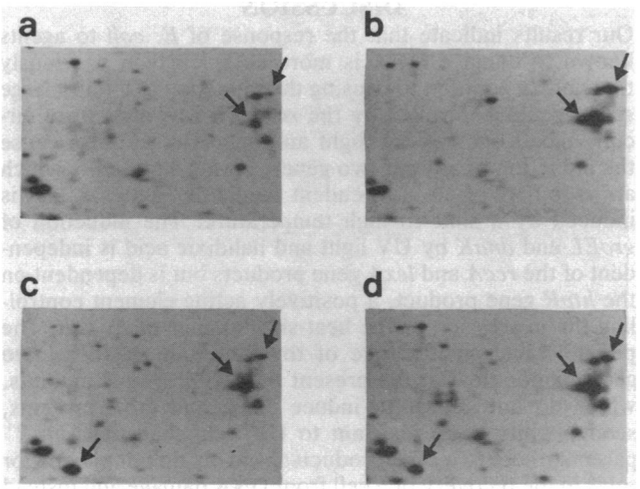

FIG. 4. Two-dimensional gel electrophoresis of [^{35}S]methionine-labeled extracts of strain GW1000 synthesized under various conditions. Equal amounts of acid-precipitable counts were applied to each gel. Only regions of the gels corresponding to a pH gradient of 5.2–5.9 (horizontal dimension; acidic side is on the right) and to a molecular weight range of 38,000–90,000 (vertical dimension; largest proteins are at the top) are shown. Arrows map the position of the recA protein (M_r, 40,000), groEL protein (M_r, 61,000), and dnaK protein (M_r, 73,000). The time of labeling after treatment is indicated in parentheses. (*a*) Control, 30°C; (*b*) 42°C (5 min); (*c*) irradiated, 100 J/m^2 (20 min); (*d*) nalidixic acid, 40 μg/ml (10 min).

indeed the products of the *groEL* and *dnaK* genes, labeled proteins from either UV-irradiated or heat-shocked cells were separated by two-dimensional electrophoresis. The positions of the groEL and dnaK proteins after a similar separation have been described (14). The results in Fig. 4 show that the M_r 61,000 protein induced after heat has the same isoelectric point and molecular weight as the heat-induced groEL protein. In addition, the UV-induced M_r 73,000 protein comigrates with dnaK protein. Fig. 4 also shows the effect of nalidixic acid treatment on the synthesis levels of various proteins. The recA protein, the M_r 61,000 groEL protein, and the M_r 73,000 dnaK protein are all induced by nalidixic acid.

Induction of groEL and dnaK by UV Irradiation and Nalidixic Acid is *htpR*$^+$ Dependent. The induction of heat-shock proteins after a temperature shift is blocked in strains carrying the *htpR*(*am*) allele. We used a derivative of GW1000 into which the *htpR* allele from strain K165 had been transduced (unpublished results) to investigate the effects of this mutation on UV light and nalidixic acid induction of the M_r 61,000 and 73,000 proteins. GC3217, the parent of GW1000, contains an unmapped amber suppressor whose pattern of suppression is different from that of one of its early progenitors, AB1157 (which contains *supE44*) (P. Foster, personal communication). The GW1000 *htpR* derivative is temperature sensitive (unpublished results) and fails to induce heat-shock proteins after a temperature shift to 42°C (Fig. 5). The induction of the M_r 61,000 and 73,000 proteins by both UV light and nalidixic acid is also greatly decreased in the GW1000 *htpR* strain, although recA protein continues to be induced by the treatments. Thus, as with induction by heat shock, the induction of these two proteins by UV light and nalidixic acid appears to be under *htpR* control. Another protein slightly smaller than the groEL protein was also induced by the addition of nalidixic acid, but its increased synthesis was not affected in an *htpR* strain.

As can be seen in Figs. 4 and 5, a temperature shift to 42°C is more effective than UV light or nalidixic acid in induction of groEL and dnaK proteins, and nalidixic acid seems slightly more effective than UV light. This parallels the time required for maximal induction of the two proteins by the different treatments: 5–10 min for a temperature shift (15), 10–15 min for nalidixic acid treatment, and 20–25 min for UV irradiation.

Sensitivity of *htpR* Mutants to UV Light. The *htpR* allele appears to prevent both induction of the heat-shock proteins after a shift to high temperature and growth at high temperature. Because the UV induction of *groEL* and *dnaK* is also decreased in an *htpR* strain after UV irradiation, we investigated whether *htpR* strains were more sensitive to UV irradiation. When we compared the survival after various doses of UV light of two *htpR*$^+$ strains, GW1000 and SC122, with their *htpR* derivatives, GW4701 and K165, we found the *htpR* strains to be slightly more resistant to UV irradiation.

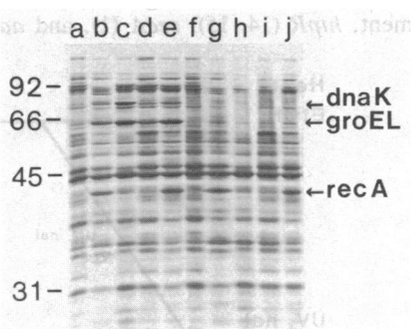

FIG. 5. Comparison of proteins synthesized from *htpR*$^+$ (GW1000) and *htpR* (GW4701) strains after various treatments. Cultures were pulse-labeled after either UV irradiation (100 J/m^2), a temperature shift (30°C to 42°C), or addition of nalidixic acid (40 μg/ml, final concentration). Equal amounts of acid-precipitable counts were applied to each lane. Molecular weights ($\times 10^{-3}$) and mobility of standard proteins are indicated on the left. Arrows indicate the positions of the *recA*, *groEL*, and *dnaK* gene products. The time of labeling after treatment is indicated in parentheses. Lanes: a, GW1000 control; b, GW1000 irradiated (20 min); c, GW1000 at 42°C (5 min); d, GW1000 with nalidixic acid (5 min); e, GW1000 with nalidixic acid (15 min); f, GW4701 control; g, GW4701 irradiated (20 min); h, GW4701 at 42°C (5 min); i, GW4701 with nalidixic acid (5 min); j, GW4701 with nalidixic acid (15 min).

DISCUSSION

Our results indicate that the response of *E. coli* to agents known to damage DNA is more complex than previously thought. In addition to causing the induction of a fairly large set of genes controlled by the *recA*$^+$ *lexA*$^+$ regulatory circuit, agents such as UV light and nalidixic acid also cause the induction of at least two genes, *groEL* and *dnaK*, which are members of an independent regulatory network that is induced by a shift to high temperature. The induction of *groEL* and *dnaK* by UV light and nalidixic acid is independent of the *recA* and *lexA* gene products but is dependent on the *htpR* gene product, a positively acting element controlling the expression of the heat-shock genes of *E. coli*. The physiological significance of the induction of these two genes is not clear at the present time. Since *htpR* mutants, which do not appear to induce dnaK and groE proteins, seem slightly more resistant to UV light than their *htpR*$^+$ parents, these two gene products probably do not play major roles in the recovery of a cell from DNA damage and instead may function in some other cellular process.

In addition to the *groEL* and *dnaK* gene products, Neidhardt *et al.* (14) have found 11 other proteins from *E. coli* that are induced in an *htpR*$^+$-dependent fashion after a temperature shift. Nine of these proteins are identified by an alphanumeric name indicating their position on two-dimensional gels. On our two-dimensional gels, we were also able to detect the induction of several other proteins by UV light and nalidixic acid that had mobilities on the two-dimensional gels that corresponded to those of the B25.3, F84.1, G93.0, C62.5, and either C15.4 (*groES*) or C14.7 or both (not distinguished on our gels) (data not shown). These other proteins induced by UV light and nalidixic acid have not been characterized in detail, but it seems likely that they are heat-shock proteins and that their induction is *htpR*$^+$ dependent.

Our present knowledge of the responses of *E. coli* to agents that damage DNA is summarized in Fig. 6. As discussed here, at least a subset of the SOS-inducing treatments induce the heat-shock response, and evidence has been presented previously that a subset of the agents inducing the adaptive response also induces the SOS response (22, 23). It seems likely that the inducing signal for the SOS system involves single-stranded DNA and a nucleotide triphosphate; the nature of the inducing signal for the other two systems is presently unknown. It is interesting that a positively acting control element, *htpR* (14, 15), *recA* (1), and *ada* (unpublished results), plays a role in the regulation of each system.

The phenomenon of a group of proteins being synthesized in response to heat shock was originally described in *Drosophila* (24). In the past few years, a similar phenomenon has been described in a number of diverse organisms (25). It now appears that in these systems heat-shock proteins (or some subset thereof) can be induced by a variety of treatments (recovery from anoxia, addition of amino acid analogues, ethanol, or certain drugs, etc.) and thus that these proteins could be considered in a more general way as "stress" proteins. While our experiments were in progress, it was reported that ethanol and coumermycin (26) can induce at least a subset of the heat-shock proteins in *E. coli*. In addition a 2- to 3-fold induction of groEL (about 1.5-fold for dnaK) has been described after infection of λ phage (27, 28). Thus the heat-shock response of *E. coli* seems similar to that of eukaryotic organisms in that it can be induced by a variety of different treatments or conditions.

The degradation of two abnormal proteins has been shown to be decreased in an *htpR* strain at both low and high temperatures (C. Gross, personal communication), suggesting that the *htpR* gene product may regulate protease activity in some fashion. Since one SOS-induced protein, the *sulA* gene product, is proteolytically degraded (29), it is possible that the degradation of some SOS-induced proteins by *htpR*-controlled protease(s) could be involved in the recovery of cells from an SOS-inducing treatment.

Pellon and co-workers (21, 30) have reported an interesting series of observations relating heat shock to changes in nucleoid structure. Although their significance is still unclear, they might provide a clue as to how and why heat-shock proteins are induced by DNA damage. They observed that brief heat treatment at 50°C causes a change in the sedimentation coefficient of the bacterial nucleoid, suggesting the unfolding of the chromosome, a response that is also brought about by treatment with classes of DNA damaging agents or gyrase inhibitors (31–34). Thus, unfolding of the chromosome might play a role in the generation of an inducing signal for the heat-shock response or, alternatively, certain of the heat-shock proteins might play a role in the restoration of the unfolded chromosome to its original state. Furthermore, Pellon and co-workers observed that an apparent intermediate in the repair of the unfolded chromosome cosediments with a fast-sedimenting peak of proteins enriched in groEL (but not dnaK).

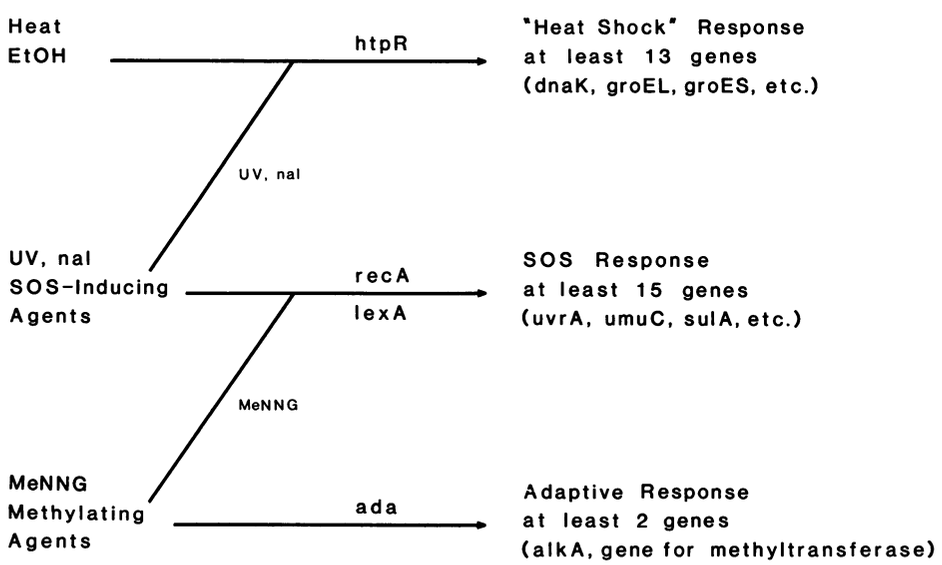

FIG. 6. Three regulatory networks of *E. coli* that can be induced by agents that damage DNA. nal, Nalidixic acid; MeNNG, *N*-methyl-*N'*-nitro-nitrosoguanidine.

Note Added in Proof. While this paper was in press, we learned that Baluch *et al.* (35) had observed the induction of *groEL* by UV light in the course of studying the effect of rifampicin on *recA* induction.

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