Mutations in *uvrD* Induce the SOS Response in *Escherichia coli*

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We have isolated three new mutations in *uvrD* that increase expression of the *Escherichia coli* SOS response in the absence of DNA damage. Like other *uvrD* (DNA helicase II) mutants, these strains are sensitive to UV irradiation and have high spontaneous mutation frequencies. Complementation studies with *uvrD* showed that UV sensitivity and spontaneous mutator activity were recessive in these new mutants. The SOS-induction phenotype, however, was not completely complemented, which indicated that the mutant proteins were functioning in some capacity. The viability of one of the mutants in combination with *rep-5* suggests that the protein is functional in DNA replication. We suggest that these mutant proteins are deficient in DNA repair activities (since UV sensitivity is complemented) but are able to participate in DNA replication. We believe that defective DNA replication in these mutants increases SOS expression.

The SOS response is induced when *Escherichia coli* suffers DNA damage from physical agents such as UV light or mutagenic chemicals such as mitomycin C (25). Induction of this response results in the expression of a diverse set of cellular activities that includes an increased capacity for DNA repair, enhanced mutagenesis, and inhibition of cell division (25). The SOS response is regulated by RecA and LexA gene products. LexA represses the approximately 20 genes responsible for the SOS activities. When DNA damage occurs, RecA is activated by an inducing signal and is able to effect LexA repressor cleavage. Destruction of this repressor allows expression of the SOS regulon.

What constitutes the inducing signal and how it is generated by DNA damage is unknown. Several conditionally lethal mutations cause cells to constitutively induce the SOS response. These mutations are found predominantly in genes whose products affect DNA replication such as *lig* (DNA ligase), *dnab* (*DnaB* helicase [12]), and *dnae* (polymerase subunit of Pol III holoenzyme) (19). Possible signal molecules that may interact with RecA include single-stranded DNA, oligonucleotides, or nucleotide cofactors (7).

The *uvrD* gene is regulated by the SOS response (22). Mutations in this gene confer a variety of phenotypes. The *uvrD3* allele was isolated by Ogawa et al. (18) as a mutant sensitive to UV light and methyl methane sulfonate. A spontaneous mutator conferring UV sensitivity was isolated by Siegel (20) and designated *mutU4*. A similar mutation was isolated independently as *uvrE* (23). While looking for recombination-deficient mutations in *recBC sbcB* strains, Horii and Clark (11) isolated *recLi52*, which is not a spontaneous mutator. Subsequently, these mutations have all been found to reside in a single locus, *uvrD*, and share the common phenotype of UV sensitivity (21). The product of the *uvrD* gene plays roles in several pathways of DNA metabolism that include the SOS-regulated repair functions, excision repair and RecF recombination repair, as well as methyl-directed mismatch repair. Identification of DNA helicase II as the product of the *uvrD* gene uncovered its role in DNA replication as one of the known *E. coli* DNA helicases that unwind duplex DNA (13, 17). Previous studies indicate that *uvrD rep* double mutants are inviable or very unstable, suggesting an interaction between these two gene products during replication (24, 20).

To understand alterations within the cell that may be involved in generating an SOS-inducing signal, we isolated mutants which constitutively expressed SOS functions in the absence of DNA damage and which mapped at several loci. These mutants are viable at all temperatures, causing SOS induction during conditions of viable growth. In this report, we describe the isolation and characterization of one class of such mutants bearing three new alleles of *uvrD*.

**MATERIALS AND METHODS**

Media. Strains were routinely grown in L broth containing 10 g of Bacto-Tryptone (Difco Laboratories), 5 g of yeast extract (Difco), and 10 g of NaCl per liter. Solid media also contained 15 g of Difco agar. 1X minimal medium for β-galactosidase assays was prepared as described elsewhere (16) and supplemented with 0.5% Casamino Acids (Difco) if the strain contained an auxotrophic marker. LC medium for P1 transduction was L medium supplemented with 25 mM CaCl₂, 0.005% thymidine, and 0.2% glucose. MacConkey agar (Difco) was prepared according to the directions of the manufacturer. Antibiotics, when required, were used in the following concentrations: 20 μg/ml for tetracycline, 80 μg/ml of ampicillin, and 100 μg/ml of streptomycin, and 25 μg of kanamycin per ml. Unless otherwise specified, mitomycin C was used at 0.25 μg/ml.

**Chemicals.** N-Methyl-N'-nitro-N-nitrosoguanidine (MNNG) and o-nitrophenyl-β-d-galactopyranoside were purchased from Sigma Chemical Co.

**Plasmids, bacteriophage, and strains.** Table 1 lists *E. coli* strains used in this work. Plasmid pVMK35 was obtained from S. Kushner (13). All bacterial genetic nomenclature and map positions for alleles are in accordance with the current version of the *E. coli* genetic map of Bachmann (2). Strains were constructed by standard P1 *vir* transductions (16). Transductants were selected on the appropriate antibiotic media, which also contained 5 g of sodium citrate per liter, or on minimal media (plus citrate) when selecting an amino acid marker. Selection for Tn10 excision was performed by the Bochner method (8), while precise excisions were selected on or screened on the appropriate minimal or MacConkey indicator media. Strains bearing Mu d(Amp Lac) gene fu-
**TABLE 1. E. coli K-12 strains and markers**

| Strain    | Genetic markers                        | Source or reference     |
|-----------|----------------------------------------|-------------------------|
| DM1901    | HfrH lacU169 relA1 thi-1 lexA55        | Huisman and             |
|           | malB::Tn9 suA::Mu d(Ap lac) (Mu)       | D’Ari, 1981             |
| DM7012    | lexA3 z305::Tn10 malB45                | This laboratory         |
| KP281     | As NO120 but lexA71::Tn5               | K. Peterson             |
| KP479     | mutL::Tn10                               | K. Peterson             |
| N014-4    | uvrD3                                  | H. Ogawa                |
| N056      | HfrH(?) lacU169 relA1 thi-1 lexA5      | This work               |
|           | malB::Tn9 suA::Mu dXICam) (Mu)         |                         |
| NO57      | As NO56 but Δ(srr-recA306::Tn10        | This work               |
| NO64      | As NO56 but λ r344 cl (Ind) lexA +     | This work               |
| NO120     | As NO56 but malB (KanR)                 | This work               |
| NO139     | As NO120 but uvrD244 metE163::Tn10     | This work               |
| NO140     | As NO120 but metE163::Tn10             | This work               |
| NO173     | As NO120 but uvrD244 fad751::Tn10      | This work               |
| NO184     | As NO139 but metB TetR (uvrD244)       | This work               |
| NO197     | As NO120 but uvrD242 metE163::Tn10     | This work               |
| NO198     | As NO120 but uvrD243 metE163::Tn10     | This work               |
| NO199     | As NO120 but metE163(TetR)             | This work               |
| NO221     | As NO140 but uvrD3 metB                 | This work               |
| NO222     | As NO140 but metB                      | This work               |
| NO223     | NO19rpVMK35 (uvrD244/uvrD*)            | Transformation           |
| NO224     | NO19rpVMK35 (uvrD*uvrD*)               | Transformation           |
| NO225     | NO19rpVMK35 (uvrD242/uvrD*)            | Transformation           |
| NO226     | NO19rpVMK35 (uvrD243/uvrD*)            | Transformation           |
| NO248     | As NO184 but lexA3 z305::Tn10 malB45   | This work               |
| NO249     | As NO184 but Δsrr-recA306::Tn10        | This work               |
| NO250     | As NO197 but metB TetR (uvrD242)       | This work               |
| NO251     | As NO198 but metB TetR (uvrD243)       | This work               |
| NO266     | As NO120 but mutL::Tn10                | This work               |
| NO267     | As NO184 but mutL::Tn10 (uvrD244)      | This work               |
| NO268     | As NO250 but mutL::Tn10 (uvrD242)      | This work               |
| NO269     | As NO251 but mutL::Tn10 (uvrD243)      | This work               |
| NO276     | As NO120 but rep5 metE163::Tn10        | This work               |
| NO278     | As NO276 but rep5 metE163::Tn10        | This work               |
| NO280     | As NO276 but uvrD244 (rep5)            | This work               |
| PM5       | rep5 relA1 spoT1 thi-1                 | B. Bachmann             |
| RK4349    | metE163::Tn10 pro-3 entA403 his-218    | B. Bachmann             |
|           | metB I xyl rpsL109 Δduc-6 supE44        |                         |
| RS3087    | fad751::Tn10 relA1 spoT1 thi-1 HfrH    | B. Bachmann             |

* Result of backcross, metE163::Tn10 source was RK4349.  
* Result of backcross, fad751::Tn10 source was RS3087.  
* Selection of Met + on minimal medium.  
* Bochner selection of NO140.  
* uvrD3 met + source was N14-4.  
* Donor was DM7012.  
* Donor was NO57.  
* Donor was KP479.  
* rep5 donor was PM5; metE163::Tn10 donor was RK4349.  
* Donor was NO184.  
* fad751::Tn10 is in the fadABC cluster.

**Mutant isolation strategy.** To monitor SOS expression in cells and provide a screen for SOS-constitutive mutants, we constructed a strain bearing a *sulA::Mu d(Ap Lac)* fusion (4). Since *sulA* is regulated by the SOS response, the Mu d fusion allowed us to monitor SOS induction. Strains bearing the fusion were Lac + when SOS was induced and Lac - when the SOS regulon was repressed. Lac phenotype was scored on MacConkey lactose plates and measured quantitatively by β-galactosidase assays. In addition, the mutation in *sulA* prevented lethal filamentation when SOS was induced. Therefore, mutagenized cultures of the *sulA::Mu d strain* (NO64) were plated on MacConkey lactose plates to screen for Lac + colonies as possible SOS-constitutive mutants.

**MNNG mutagenesis.** Mutagenesis by MNNG treatment was similar to mutagenesis by previously described methods (1). NO64 was grown to mid-log phase and suspended in 0.1 M sodium citrate (pH 5.5). MNNG, dissolved in 0.1 M citrate, was added to the cells at a final concentration of 100 μg/ml. The culture was incubated for 20 min at 37°C. The mutagenized culture was diluted 1:100 in L broth, dispensed into 10 separate culture tubes (to isolate independent mutants), and grown overnight at 32°C. Cells were spread onto MacConkey lactose plates to screen for Lac + colonies.

**β-Galactosidase assays.** β-Galactosidase assays were performed by the method of Miller (16). Overnight cultures grown in the presence of chloramphenicol were diluted back 1:200 in 1X A media and grown to early log phase (Klett 15). The cultures were split, and mitomycin C was added to one group; cultures were allowed to grow for an additional 2 h (to mid-log), and the assays were performed. For each assay, two samples were taken and each experiment was performed two or more times. Unless specifically noted, the assays were performed at 37°C. The β-galactosidase results are expressed as Miller units.

**Spontaneous mutagenesis.** Single colonies were used to start overnight cultures in L broth. The overnight cultures were diluted 1:40 in L broth and grown to late log phase. The cells were concentrated by centrifugation, suspended in 0.85% saline, and plated on streptomycin-containing L plates. Total cell numbers were determined by plating appropriate dilutions on nonantibiotic L plates. All incubations were done at 37°C. Mutation frequency was measured in at least three independent cultures.

**UV survival assays.** Cultures were grown to mid-log phase (3 x 10^8 cells per ml), diluted 1:100 in 0.85% saline, and irradiated. Appropriate dilutions were plated on L plates and incubated overnight at 37°C to determine survival.

**RESULTS**

**Results of mutagenesis and genetic mapping experiments.** Approximately 40,000 colonies were screened for the Lac + phenotype after MNNG mutagenesis of strain NO64. Three mutants had the additional phenotype of UV sensitivity. Genetic crosses described below strongly suggested that the mutations in these strains are in *uvrD*. (i) By using a combination of Hfr and P1 transduction mapping, these mutations were found to be closely linked to *uvrD* at 85 min on the linkage map. (ii) A three-factor cross with the mutant *uvrD3* gave the same linkage to *fad* and *met* (Table 2). (iii) In these crosses, the SOS constitutive behavior and UV sensitivity were inseparable. (iv) As shown below, some of the defects in these mutants could be complemented by *uvrD*.

The UV sensitivity of these mutants and their map positions suggested they were alleles of *uvrD*, the gene which encodes DNA helicase II. Subsequently, the mutations were designated as *uvrD242*, *uvrD243*, and *uvrD244*.


UV sensitivity of uvrD mutants. The extent of increased UV sensitivity in the uvrD mutants is shown in Fig. 1. We constructed merodiploids of each mutant with a low-copy-number uvrD+ plasmid, pVMK35. A low-copy-number plasmid was used for the complementation studies because overproduction of wild-type UvrD protein by a high-copy-number plasmid causes increased UV sensitivity (13). The low-copy-number plasmid did not increase UV sensitivity of the wild-type strain (Fig. 1). However, uvrD+ largely complemented the UV sensitivity in the mutant strains. This result indicates that the mutations do lie in the uvrD gene and that the repair defect in these strains is recessive and can be complemented.

SOS expression in uvrD mutants. The basal level of SOS expression in the uvrD mutants is shown in Table 3. Expression of sulA was increased five- to sevenfold more than that of the wild type in these strains. For comparison, the basal levels of two previously identified uvrD alleles, uvrD3 and uvrD156 (formerly mutU4), are shown. The uvrD3 mutation did not increase the basal level of SOS expression, which indicates that it is a different class of uvrD mutation. In contrast, uvrD156 increased sulA expression approximately 10-fold, which indicates that uvrD156 shares this same property with uvrD242, uvrD243, and uvrD244.

Expression of sulA was also measured in the uvrD merodiploid strains. The newly identified uvrD alleles were only partially or not at all complemented by uvrD+, indicating that there is a dominant or codominant relationship between the alleles. This dominance or codominance for SOS expression was dramatically different from the recessive behavior for UV sensitivity in these mutants (described above). The variability in genetic properties indicates that the protein has partial function.

Since uvrD plays a major role in excision and mismatch repair, we considered the possibility that a lack of these types of repair would result in an increased level of SOS expression. A uvrA6 sulA::Mu d fusion strain which lacks the excision repair function did not appear to increase sulA expression on MacConkey lactose media. A strain defective in mismatch repair (mutL mutant) expressed sulA at wild-type levels (Table 3). Also, as noted above, sulA expression in the uvrD3 mutant is that of the wild type, although this mutant is deficient in excision repair of DNA damage and is therefore UV sensitive. Taken together, these observations suggest that a DNA repair defect is not sufficient to increase expression of the SOS response.

Additionally, we measured β-galactosidase expression in a rep-5 strain which is defective in DNA replication. Expression of sulA was elevated 2.9-fold over wild-type levels, indicating a low induction in this mutant (Table 3).

The levels of mitomycin C-induced SOS expression are

### Table 3. β-Galactosidase expression from sulA::Mu d fusion in previously isolated mutants

| E. coli K-12 strain | Relevant genotype | U of β-galactosidase (mean ± SE) in samples* |
|---------------------|------------------|---------------------------------------------|
|                     |                  | With mitomycin C | Without mitomycin C |
| NO120               | uvrD*            | 59 ± 3          | 1,630 ± 80          |
| NO139               | uvrD244          | 260 ± 13        | 2,570 ± 130         |
| NO197               | uvrD242          | 330 ± 17        | 2,520 ± 130         |
| NO198               | uvrD243          | 380 ± 19        | 2,500 ± 130         |
| NO221               | uvrD245          | 61 ± 3          | 1,160 ± 60          |
| NO265               | uvrD156          | 620 ± 31        | 2,740 ± 130         |
| NO224               | uvrD* uvrD*      | 60 ± 3          | 1,850 ± 100         |
| NO223               | uvrD244 uvrD*    | 230 ± 16        | 3,120 ± 220         |
| NO225               | uvrD242 uvrD*    | 180 ± 22        | 2,520 ± 300         |
| NO226               | uvrD243 uvrD*    | 170 ± 34        | 3,200 ± 600         |
| NO266               | mutL::Tn10       | 54 ± 2          | 1,870 ± 100         |
| NO276               | rep-5            | 170 ± 9         | 1,140 ± 60          |
| NO248               | uvrD244 lexA3    | 23 ± 1          | 25 ± 1              |
| NO249               | uvrD244 recA     | 20 ± 1          | 17 ± 1              |

* Assays were performed as described in Materials and Methods. The error was based upon the variation found in three or more determinations of each value and varied from 5 to 20%.
shown in Table 3. The uvrD mutants were further inducible by the addition of mitomycin C, demonstrating that these mutant strains can respond further to an SOS-inducing treatment. The mitomycin C-induced expression was enhanced above wild-type levels in strains bearing the new uvrD alleles. This increased expression was also observed in derivatives of the uvrD mutants bearing the uvrD\textsuperscript{+} plasmid, which indicated a lack of complementation.

**Increased SOS expression depends on LexA protein cleavage.** To determine whether the increased expression of sulA in the uvrD mutants was mediated through RecA and LexA, we blocked SOS expression by this route using mutations. Double mutants of uvrD244 were made with either ΔrecA, which eliminates RecA activation, or lexA3 (Ind\textsuperscript{−}), which makes a noncleavable repressor. Expression of sulA in these double mutants was abolished, which indicates that SOS induction in the uvrD244 strain is dependent upon recA and lexA (Table 3). When screening for sulA::Mu d fusion mutations earlier in this study, we observed that lexA3 repressed the fusion in uvrD242 and uvrD243 strains as well (judged on MacConkey lactose plates).

**Spontaneous mutagenesis in uvrD mutants.** Since some uvrD mutants have a mutator phenotype, we measured levels of spontaneous mutagenesis in uvrD242, uvrD243, and uvrD244 mutants. The new uvrD alleles had increased spontaneous mutator activity compared with that of the wild type (Table 4). The uvrD156 mutation is known to exhibit a mutator phenotype (20), again indicating that the new alleles may be similar and differ from uvrD3. Complementation studies with the newly isolated uvrD mutants showed that increased spontaneous mutagenesis was recessive to the wild-type allele, since mutagenesis was reduced to near wild-type levels. Prior work had shown that spontaneous mutability and UV sensitivity of uvrD156 mutants could be complemented by the uvrD\textsuperscript{+} allele (21).

**Increased spontaneous mutagenesis independent of LexA protein cleavage.** Since the new uvrD mutations resulted in an increase in SOS expression, we wanted to determine whether this increase was responsible for the elevated spontaneous mutation frequency. SOS mutagenesis requires the products of lexA-regulated UmuC, UmuD, and RecA proteins (19). By using the uvrD244 strains blocked for SOS induction (uvrD244 lexA3 and uvrD244 ΔrecA), we measured spontaneous mutagenesis. The spontaneous mutation frequency in the SOS-blocked uvrD244 strains was not reduced, which indicates that mutagenesis is not a result of increased SOS expression (Table 5).

**Our ability to construct the uvrD244 ΔrecA lexA3** double mutants demonstrates that the uvrD mutant is viable when SOS functions are repressed. All of the new uvrD mutant strains were viable with lexA3 when we screened for sulA fusion mutations earlier in this study, which shows that the uvrD mutants do not require SOS expression for viability. This result is in contrast to that obtained with dam mutants, which require expression of certain SOS-regulated genes for viability.

**DISCUSSION**

We have isolated three new mutations designated uvrD242, uvrD243, and uvrD244 which increase expression of the SOS response in the absence of an inducing treatment. These mutations are alleles of uvrD, the gene which encodes DNA helicase II, for the following reasons: (i) These mutants exhibit the UV sensitivity and spontaneous mutator activity characteristic of other, previously isolated, uvrD mutants. (ii) P1 transduction analysis shows that the mutations map very close to the known location of uvrD at 85 min on the standard *E. coli* linkage map. (iii) A uvrD\textsuperscript{+} allele complements the UV sensitivity and mutator activity of the mutant strains. (iv) A known uvrD mutant, uvrD156, also showed increased SOS expression to an even greater degree than did the newly isolated uvrD mutants. Increased SOS expression in uvrD242, uvrD243, and uvrD244 was dependent upon the cleavage of LexA protein. We conclude that the uvrD mutations probably act to induce the SOS system by generating an endogenous SOS-inducing signal that activates RecA protein, which leads to increased LexA repressor cleavage.

Mutations in rep and dnaAB(Ts) which encode DNA helicases or DNA-unwinding proteins also have been found to increase expression of the SOS response, perhaps by a mechanism similar to uvrD mutations. Chaudhury and Smith (5) showed that the exonuclease activity of the recBCD enzyme was not needed for SOS induction and suggested that the RecBCD DNA-unwinding activity was required. These combined results suggest that helicases are likely to be important in regulating expression of the SOS response.

The increased SOS expression in the uvrD mutants was incompletely complemented by uvrD\textsuperscript{+}, which indicates that the mutants synthesize a partially functional protein. Additional evidence for synthesis of an active gene product by these mutants came from the observation that we were able to construct a rep- uvrD244 double mutant by standard genetic crosses. Taucher-Scholz, Abdel-Monem, and Hoffmann-Berling (24) proposed that, during DNA replication, Rep and UvrD proteins act jointly on opposite strands to unwind duplex DNA. They also proposed that the two helicases could substitute for each other when one helicase is mutated and inactivated. Recent characterization of UvrD protein supports these proposals (15). Since it has been suggested that either Rep or UvrD protein must be active for DNA replication (20, 24) and since severely defective uvrD alleles are not viable in such a combination (20, 24), our experiments suggest that the UvrD244 protein may have sufficient activity to function in DNA replication.

The uvrD mutants are UV sensitive because they are deficient in excision repair of DNA damage. However, we have shown that increased SOS expression is not a result of a defect in repair. SOS expression was not increased in another well-characterized, repair-deficient mutant, uvrD3, which indicates that the two properties are separable. The repair deficiency of the uvrD242, uvrD243, and uvrD244 mutants was complemented efficiently by uvrD\textsuperscript{+}, whereas

**TABLE 4. Spontaneous mutagenesis in uvrD strains**

| E. coli K-12 strain | Relevant genotype | Mutation frequency\textsuperscript{b} (no. of mutants scored) | Avg |
|---------------------|------------------|-------------------------------------------------------------|-----|
| NO120 uvrD\textsuperscript{+} | 3 (43)\textsuperscript{c} | 3 |
| NO139 uvrD244 | 54 (140), 46 (119), 30 (128) | 41 |
| NO197 uvrD242 | 68 (150), 53 (86), 28 (162) | 41 |
| NO198 uvrD243 | 57 (109), 62 (103), 66 (158), 188 (253) | 90 |
| NO224 uvrD\textsuperscript{+} uvrD\textsuperscript{+} | 4 (27)\textsuperscript{d} | 4 |
| NO223 uvrD244 uvrD\textsuperscript{+} | 6 (49)\textsuperscript{d} | 6 |
| NO225 uvrD242 uvrD\textsuperscript{+} | 8 (48)\textsuperscript{d} | 8 |
| NO226 uvrD243 uvrD\textsuperscript{+} | 10 (52)\textsuperscript{d} | 10 |

\textsuperscript{a} Streptomycin-resistant mutation assays were performed as described in Materials and Methods.

\textsuperscript{b} Mutation frequency is shown as number of Str\textsuperscript{r} mutants per 10\textsuperscript{10} cells.

\textsuperscript{c} Averaged results of six experiments.

\textsuperscript{d} Averaged results of six experiments.

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SOS expression remained elevated under these conditions. Genetic studies have suggested that the increased spontaneous mutagenesis in uvrD mutants is due to a lack of mismatch repair directed by dam (6, 9, 10, 14). Our data show that the higher levels of spontaneous mutagenesis in uvrD mutants is not a consequence of increased expression of the SOS response, since mutagenesis remained increased in recA(Def) and lexA3(Ind+) derivatives (Table 5). Furthermore, SOS expression was not increased in the mutL mismatch repair mutant.

Based on our results and published data, we conclude that UvrD protein influences a variety of different processes, including DNA replication, excision repair, and methyl-directed mismatch repair. The complex phenotypes and genetic properties of uvrD mutants suggest that UvrD protein can be altered so as to influence one or more of these processes. We argue that the most likely reasons for increased expression of the SOS response are the effects of altered UvrD protein on DNA replication.

Current models of SOS induction support the idea that the RecA protein promotes cleavage of LexA protein after it binds to single-stranded regions of the chromosome produced by DNA damage. The availability of nucleotide cofactors then determines the rate of cleavage of LexA protein by the complex of RecA protein and DNA. Extending this model, we propose two possible modes for increased cleavage of LexA protein by an altered helicase. (i) An abnormally high degree of unwinding at replication forks exposes stretches of single-stranded DNA which serve as additional binding sites for RecA protein, activating its coexpressed function. (ii) Unwinding of DNA is impeded at replication forks, slowing the rate of chromosomal replication and generating increased amounts of one or more small signal molecules. These molecules stimulate the coprotease activity of any RecA protein that is bound to single-stranded regions of the chromosome.

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