Nascent DNA processing by RecJ favors lesion repair over translesion synthesis at arrested replication forks in *Escherichia coli*

Charmain T. Courcelle*†, Kin-Hoe Chow‡, Andrew Casey*, and Justin Courcelle*

*Department of Biology, Portland State University, Box 751, Portland, OR 97207-0751; and ‡Huntsman Cancer Institute, University of Utah, Salt Lake City, UT 84112

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DNA lesions that arrest replication can lead to rearrangements, mutations, or lethality when not processed accurately. After UV-induced DNA damage in *Escherichia coli*, RecA and several *recF* pathway proteins are thought to process arrested replication forks and ensure that replication resumes accurately. Here, we show that the RecJ nuclease and RecQ helicase, which partially degrade the nascent DNA at blocked replication forks, are required for the rapid recovery of DNA synthesis and prevent the potentially mutagenic bypass of UV lesions. In the absence of RecJ, or to a lesser extent RecQ, the recovery of replication is significantly delayed, and both the recovery and cell survival become dependent on translesion synthesis by polymerase V. The RecJ-mediated processing is proposed to restore the region containing the lesion to a form that allows repair enzymes to remove the blocking lesion and DNA synthesis to resume. In the absence of nascent DNA processing, polymerase V can synthesize past the lesion to prevent lethality, although this occurs with slower kinetics and a higher frequency of mutagenesis.

mutagenesis | nucleotide excision repair

Irradiation of cells with UV light (254 nm) induces DNA lesions that can arrest replication forks (1). Nucleotide excision repair and translesion DNA synthesis are two processes that operate at arrested replication forks to reduce the frequency of recombination and promote cell survival after UV-induced DNA damage. Although nucleotide excision repair is generally considered to be error free, the processes of translesion synthesis and recombination can be associated with mutagenesis or rearrangements, making it important to identify the order and conditions that determine when each process is employed at the arrested fork. In *Escherichia coli*, the robust recovery of DNA replication after UV-induced arrest largely depends on lesion removal by the nucleotide excision repair enzymes (1–4). Cells mutated in any of these gene products are unable to remove lesions from the genome and the recovery of DNA synthesis is severely impaired, resulting in elevated levels of recombination, mutagenesis, and lethality (1, 3–5).

Several studies suggest that translesion synthesis by polymerase (Pol) V can also contribute to the recovery at UV-arrested forks. *E. coli* have three damage-inducible DNA polymerases, Pol II (*polB*), Pol IV (*dinB*), and Pol V (*umuD* and *umuC*), that have multiple homologues in both prokaryotes and eukaryotes (6). These polymerases can incorporate nucleotides opposite to specific DNA lesions with higher efficiencies than the replicative polymerase, Pol III (7–9). After UV-induced damage, Pol V, but not Pol II or IV, increases cell survival and is responsible for essentially all of the UV-induced mutagenesis that occurs after irradiation (2, 7, 10, 11). Additionally, after higher doses of UV irradiation that begin to reduce the survival of wild-type cells, Pol V contributes to the rate that DNA synthesis recovers and that nascent-strand gaps are joined, indicating that Pol V participates in the recovery after UV-induced damage (2, 12).

Although the events that determine whether repair, translesion synthesis, or recombination occurs at the arrested fork are not known, several enzymes have been characterized that are known to process arrested replication forks before the resumption of DNA synthesis (2–4, 13–17). After arrest by UV-induced damage, the nascent DNA at the replication fork is partially degraded by the combined action of RecJ, a 5′–3′ single-strand exonuclease, and RecQ, a 3′-5′ helicase, which appear to preferentially target the nascent lagging strand (4, 15, 18, 19). Although the absence of RecJ or RecQ has not been reported to render cells hypersensitive to DNA damage, these enzymes do impair the specificity and frequency of recombination in some assays (20–23). In addition, mutations in RecQ homologues from other organisms can result in elevated levels of strand exchange, chromosomal rearrangements, and genomic instability (24–28). Taken together, these observations suggest that RecJ and RecQ may play a role in determining how arresting DNA lesions are repaired or processed. We examined that possibility directly and found that RecJ, and to a lesser extent RecQ, is required for the efficient recovery of DNA synthesis after arrest. Additionally, we found that in the absence of the nascent DNA processing, the recovery and survival of the cell become dependent on translesion synthesis by Pol V.

Results and Discussion

Either RecJ or Translesion Synthesis by Pol V Is Essential for DNA Synthesis to Recover After Arrest by UV-Induced Damage. To examine whether RecJ or RecQ affect the mechanism by which replication recovers, we monitored the time at which DNA synthesis resumed in *recJ* and *recQ* mutants after arrest by UV-induced DNA damage. To this end, duplicate aliquots of [^{14}C]thymine-labeled cultures were pulse-labeled for 2 min with [^{3}H]thymidine at various times after 27 J/m^2 UV irradiation. In this way, both the average speed of the replication forks (^{3}H incorporation per 2 min) and the overall DNA accumulation (^{14}C incorporation) could be simultaneously followed at specific times after treatment. All experiments included a mock-irradiated control that allowed us to directly compare irradiated and unirradiated cultures and ensure that any observed differences in the rate of DNA synthesis were due to UV treatment, and not the effect of thymine addition or differences in growth phase.

Under our conditions, a dose of 27 J/m^2 of UV irradiation generates an average of one cyclobutane–pyrimidine dimer per 9-kb single-strand DNA as measured by T4 endonuclease V-sensitive sites in the DNA, but does not significantly reduce the survival of wild-type cells (4, 29). This dose initially reduces the

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Abbreviation: Pol, polymerase.

†To whom correspondence should be addressed. E-mail: charmc@pdx.edu.

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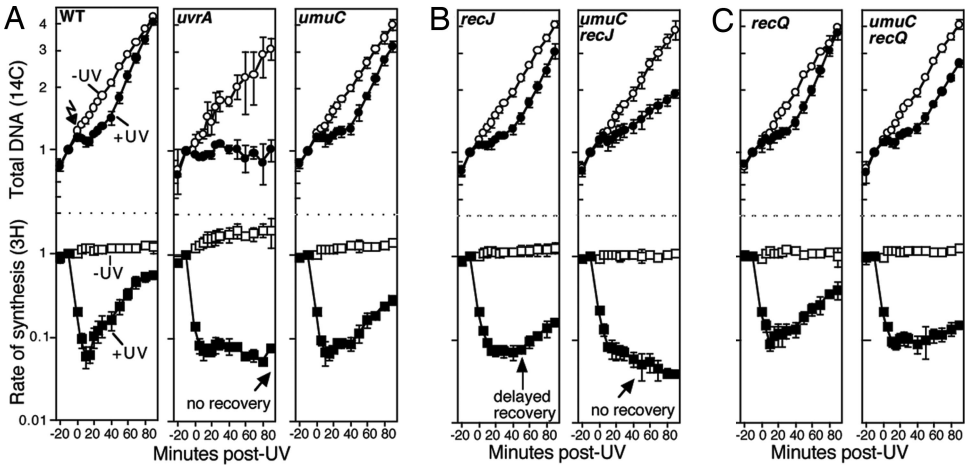

Fig. 1. RecJ-mediated processing of arrested replication forks allows DNA synthesis to resume without translesion synthesis by Pol V. Duplicate aliquots of [^{14}C]thymine-labeled cultures were pulse-labeled for 2 min with [^{3}H]thymidine at various times after UV irradiation with 27 J/m^2, a dose that inhibits replication but does not significantly reduce survival of wild-type cultures (2). The rate of DNA synthesis could then be monitored relative to the total amount of DNA present at specific times after treatment. [^{3}H]Thymidine was added to [^{14}C]thymine-prelabeled cultures for 2 min at the indicated times after either mock irradiation (open symbols) or UV irradiation with 27 J/m^2 (filled symbols) at time 0. The amounts of ^{3}H and ^{14}C are plotted relative to amounts found 10 min before mock- or UV irradiation. ^{14}C-labeled DNA accumulation (open circles) and ^{3}H-labeled DNA synthesis per 2 min (open squares) are shown. Each graph represents an average of at least three independent experiments. Error bars represent one standard deviation.

rate of DNA synthesis by >90%, before the rate of synthesis begins to recover ≈15 min after irradiation. As demonstrated previously and shown in Fig. 1*B* for the purpose of controls, nucleotide excision repair and translesion synthesis differentially affect the rate of recovery (2). In UV-irradiated *uvrA* mutants, which are unable to remove UV-induced lesions, the rate of DNA synthesis does not recover and little further DNA accumulation is observed. In contrast, in *umuC* mutants, which are unable to carry out Pol V-mediated translesion synthesis, the rate of synthesis begins to recover at a time similar to that of wild-type cells, although the kinetics of the recovery are modestly reduced as compared to wild-type cells (Fig. 1*A* and ref. 2). Thus, in an otherwise wild-type background, Pol V contributes to recovery but is not essential for replication to resume after UV irradiation. Taken together, we interpret the lack of [^{3}H]thymidine incorporation immediately after UV irradiation to reflect arrest of essentially all replication in the cell. The recovery in rate that occurs at ≈15 min coincides with when the majority of lesions in the genome are repaired (4, 29), and is likely to reflect replication forks resuming on lesion-free templates. Although replication forks may be restored before this time, these forks would likely rearrest upon encountering lesions again within a relatively short distance.

When we examined *recJ* mutants by this assay, no recovery of DNA synthesis occurred for a period of ≈50 min after UV irradiation (Fig. 1*B*), indicating that RecJ processing is essential for the rapid recovery of DNA synthesis in the cell. The impaired recovery in the absence of RecJ was surprising because *recJ* mutants have not been reported to be sensitive to UV irradiation. The survival of *recJ* mutants implies that a secondary or late-acting pathway must exist in these cells that is sufficient for survival.

To further investigate the mechanism by which the late-acting recovery occurs, we initially considered the process of translesion synthesis, particularly that catalyzed by Pol V for several reasons. Although Pol V does not affect the time that DNA synthesis resumes, at higher doses of UV irradiation, it does contribute to the survival, mutagenesis, and kinetics of postirradiation DNA synthesis, indicating that Pol V is active during the recovery period (2, 7, 10, 11, 30). In addition, UmuD undergoes posttranslational processing that delays the functional expression of Pol V after damage (30). When we examined *recJ* mutants that also lacked Pol V, we observed no recovery in the rate of synthesis throughout the time course of the experiment, similar to that seen in *uvrA* mutants (Fig. 1*B*). Curiously, despite similar deficiencies in recovering DNA synthesis, *umuC recJ* mutants accumulated more DNA than did *uvrA* mutants over the time course. The additional accumulation seen in *umuC recJ* mutants could partly reflect less DNA degradation that occurs in the absence of the RecJ nuclease (see Fig. 6, which is published as supporting information on the PNAS web site). Alternatively, the accumulation may represent higher levels of uncoupled DNA synthesis that can occur in the repair-proficient *umuC recJ* mutants, as compared to *uvrA* mutants. However, if this result were due to uncoupled DNA synthesis, one might expect to observe some recovery in the rate of synthesis in the *umuC recJ* strain, and this was not detected. Consistent with previous work showing that Pol V, but not Pol II or IV, contributes to the recovery after UV-induced damage (2), no further delay was observed in *recJ* mutants that also lacked Pol II or Pol IV (data not shown).

In UV-irradiated *recQ* mutants, the recovery of DNA synthesis was also modestly impaired and, similar to *recJ* mutants, this effect was exacerbated in the absence of Pol V (Fig. 1*C*). However, the impaired recovery exhibited by *recQ* mutants was less severe than that observed in *recJ* mutants, suggesting that RecQ's helicase activity enhances, but is not essential, for RecJ-promoted recovery.

The above observations imply that the RecJ-mediated processing is essential for a predominant, early-acting mechanism that promotes the resumption of DNA synthesis after arrest. If true, one prediction would be that the defect in *recJ* mutants would be exhibited even after low doses of DNA damage, where the number of blocks to replication are less likely to exceed the capacity of other mechanisms that may operate at early times. Therefore, to ask whether other pathways could promote recovery at early times, we assessed the rate that DNA synthesis recovered after a low dose of UV irradiation (5 J/m^2) in *recJ* mutants using the assay described above. At 5 J/m^2, the recovery exhibited by wild-type, *uvrA*, and *umuC* cultures was similar to that observed at the higher 27 J/m^2 dose except that the rate was initially inhibited by only 50% rather than 90% (Fig. 2). An

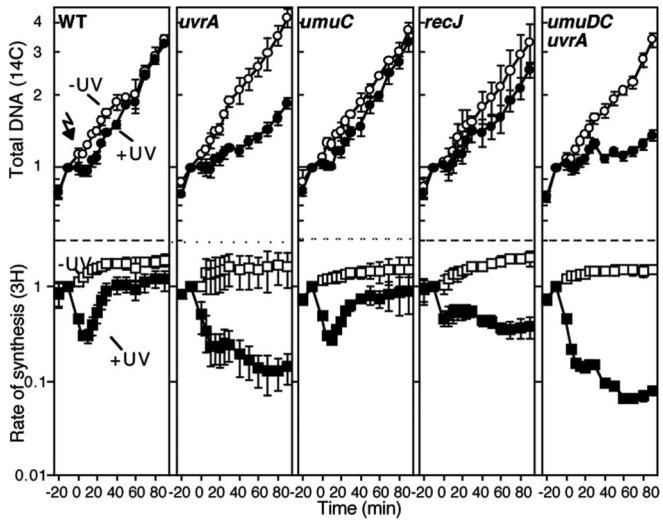

Fig. 2. Nascent DNA processing by RecJ is required to restore DNA synthesis at early times after low doses (5 J/m^2) of UV irradiation. Data were obtained and plotted as in Fig. 1. ^{14}C-labeled DNA accumulation (open circle); ^{3}H-labeled DNA synthesis per 2 min (open square). Each graph represents an average of at least three independent experiments. Error bars represent one standard deviation.

additional difference at the low dose was that more DNA accumulated in the *uvrA* mutant, despite the fact that the rate of synthesis did not recover during the experiment. However, when we examined *recJ* mutants, we observed that the rate of DNA synthesis failed to recover in a timely manner even at a UV dose of only 5 J/m^2 (Fig. 2), indicating that RecJ processing is required at early times for DNA synthesis to resume.

In the Absence of RecJ-Mediated Processing, Survival Becomes Dependent on Translesion Synthesis by Pol V and Results in Higher Frequencies of Mutagenesis. The idea that Pol V can promote recovery when the predominant mechanism cannot occur was also supported by the survival of these mutants after exposure to UV. The absence of either RecJ or Pol V does not render cells severely sensitive to UV irradiation. However, we observed that in the absence of RecJ, Pol V became critical to cell survival (Fig. 3). Mutants lacking both *recJ* and *umuC* were approximately as hypersensitive to UV irradiation as *recF* mutants, which are known to be defective in recovering replication after UV-induced arrest (14). The absence of RecQ also reduced the survival of *umuC* mutants, although, as seen in the previous assays, the effect was less severe than that of RecJ (Fig. 3). No effect on survival was observed in *recJ* mutants that lacked either Pol II or Pol IV (Fig. 3*A*), consistent with several studies, both *in vitro* and *in vivo*, that suggest Pol V, but not Pol II or Pol IV, is able to function at sites of UV-induced damage (2, 7, 11, 30, 31). One study did observe a delay in the recovery of the *polB* strain, STL1336, after UV-irradiation (32). However, previous studies with this strain observed no Pol II-mediated translesion synthesis on UV-damaged templates (31) and a propensity of the strain to accumulate suppressor mutations that affect its response to DNA damage (33).

It is interesting to note that the survival curve of *recJ* mutants was distinct from that of wild-type cultures. *recJ* mutants were modestly sensitive to low doses of UV, whereas at higher doses, they were more resistant than wild-type cultures (Fig. 3 *B* and *C*). The hypersensitivity to low doses would be consistent with the idea that RecJ is required during the initial response to DNA damage. The resistance of *recJ* mutants to high doses may indicate that the delayed recovery is beneficial when high levels of DNA damage are present. Previous studies have shown that inhibiting replication by placing the culture in "liquid holding" media that lacks a carbon source, similarly increases cell survival after DNA damage (34).

The survival of RecJ at higher doses also suggests that translesion synthesis by Pol V is capable of promoting near wild-type levels of survival when required to function in this role. By contrast, *umuC* mutants were only hypersensitive at the higher doses of UV irradiation (Fig. 3*B*), consistent with the interpretation that Pol V becomes important either when lesions are not repaired in a timely manner, or when lesions, due to their chemical nature or sequence context, may be resistant to processing by repair enzymes.

The data are consistent with a model in which RecJ-mediated processing serves to restore the lesion-containing site to a form that is accessible to nucleotide excision repair enzymes, which require double-stranded DNA to function (Fig. 4). In the absence of the nascent DNA degradation by RecJ, the block to replication remains until translesion synthesis by Pol V can synthesize past the arresting lesion. A prediction of this model is that in the absence of RecJ, the frequency of mutagenesis might increase, when the recovery depends on translesion synthesis by Pol V. To examine this possibility, we determined the frequency

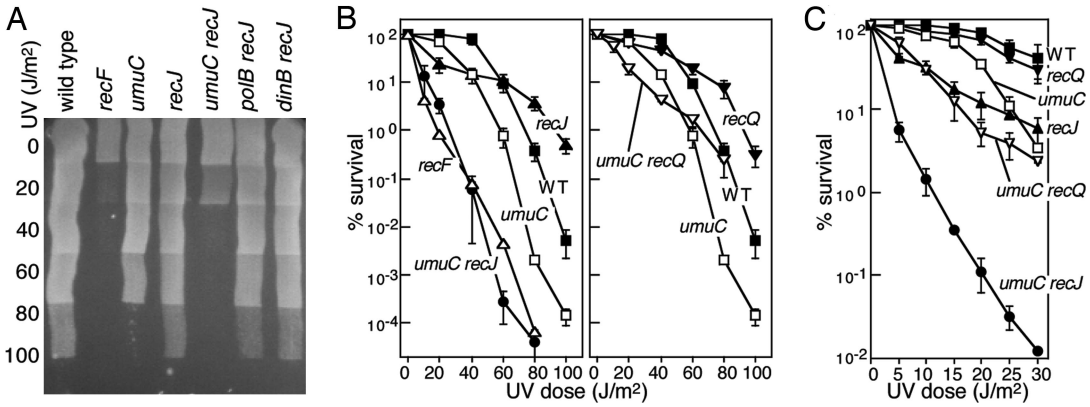

Fig. 3. In the absence of RecJ, survival after UV-induced damage depends on translesion synthesis by Pol V. (*A*) Survival of parental (WT), *recF*, *umuC*, *recJ*, *umuC recJ*, *polB recJ*, and *dinB recJ* strains after UV irradiation with the indicated dose. (*B*) The survival of parental (filled square), *recJ* (filled triangle), *umuC* (open square), *umuC recJ* (filled circle), *recF* (open triangle), *recQ* (inverted filled triangle), and *umuC recQ* (inverted open triangle) cultures are shown after UV irradiation at the indicated doses. (*C*) The survival of parental (filled square), *recJ* (filled triangle), *umuC* (open square), *umuC recJ* (filled circle), *recQ* (inverted filled triangle), and *umuC recQ* (open inverted triangle) cultures are shown after UV irradiation between 0 and 30 J/m^2.

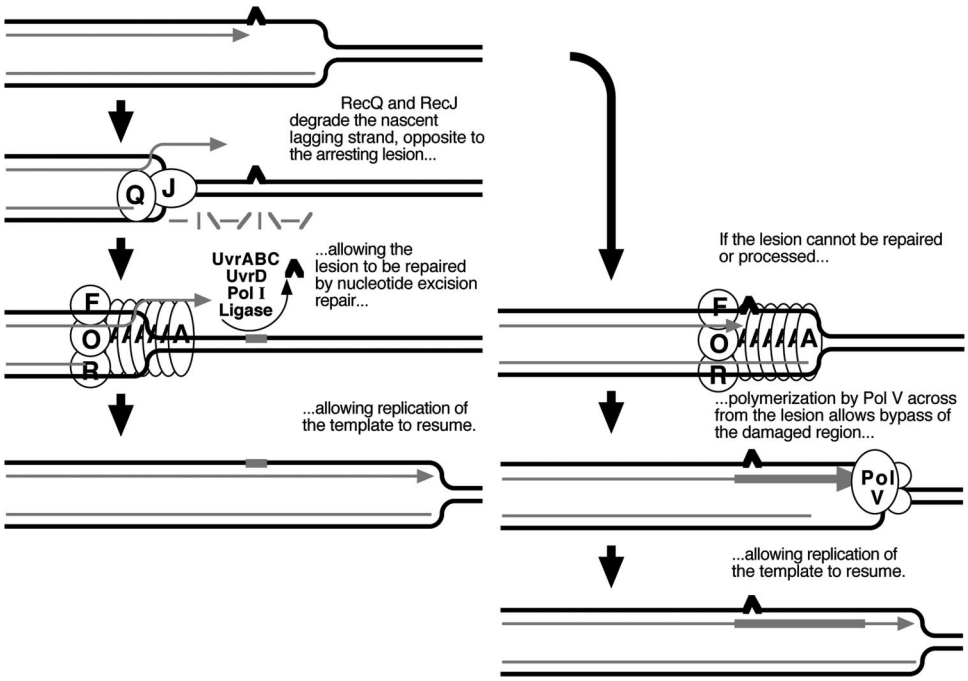

Fig. 4. Model for the recovery of replication in the presence and absence of RecJ. Previous studies have demonstrated that RecF-O-R and RecA (depicted as F, O, R, and A) are required to protect and stabilize replication forks after arrest (4, 14) and are shown in the model as functioning in this role.

that rifampin-resistant mutants arose in UV-irradiated cultures. We found that the absence of RecJ increased the frequency of Rif-resistant mutants 2-fold in cultures exposed to a moderate 10 J/m^2 dose of UV, and ≈3-fold in cultures irradiated at 30 J/m^2 (Fig. 5*A*). A similar increase in rifampin-resistant mutants was observed in UV-irradiated *recQ* cultures, consistent with the idea that Pol V is used more frequently in the absence of RecJ or RecQ. We also observed a modest increase in the frequency at which spontaneous mutants appeared in *recJ* cells compared to wild-type cells (Fig. 5*B*), suggesting the possibility that translesion synthesis may occur more frequently at other endogenous lesions in the absence of RecJ or RecQ as well.

Although Pol V is not essential for replication to resume, it does contribute to the mutagenesis and nascent-strand gap joining that occurs after UV-induced damage. These observations suggest that the primary function of Pol V is not that of a backup pathway to restore DNA synthesis at arrested forks (2, 7, 10, 11, 30). Several plasmid-based studies have suggested that lesions in the lagging-strand template do not arrest the replication machinery, but instead produce gaps in the nascent DNA (35, 36). The contribution of Pol V to nascent-strand gap joining may suggest that Pol V preferentially targets these substrates (2). Alternatively, PolV has also been shown to contribute to nontargeted mutagenesis at nondamaged sites, suggesting that it may function as a component of the holoenzyme at times after the active UmuD′ subunit of Pol V has been up-regulated (37, 38). It should also be pointed out that UV irradiation induces predominantly single-stranded lesions that can be processed by nucleotide excision repair or translesion DNA synthesis. In situations where strand breaks are induced or generated at the replication fork, these pathways would likely be insuf-

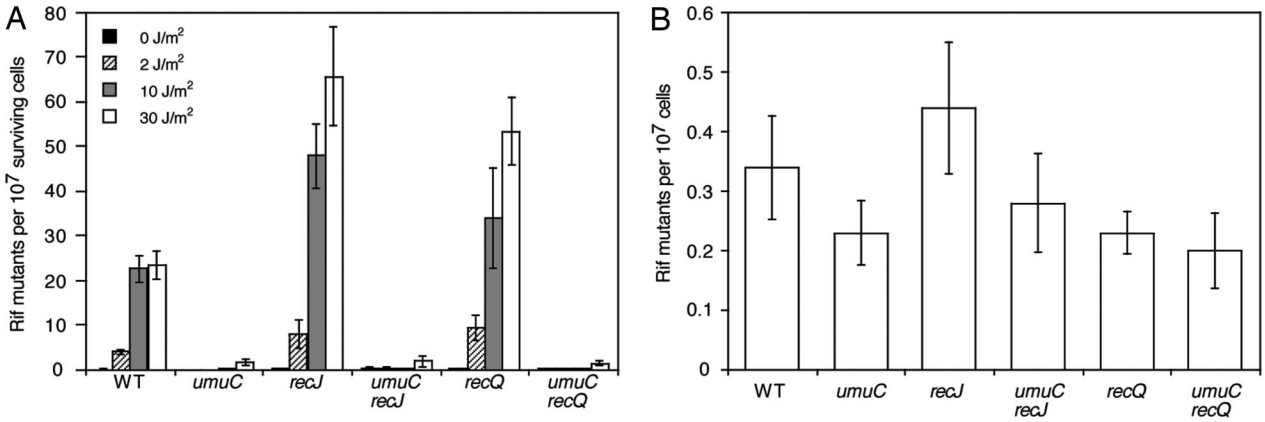

Fig. 5. The presence of RecJ reduces the frequency of UV-induced mutagenesis. (*A*) Cultures were UV irradiated at the indicated doses and examined for the number of rifampin (Rif)-resistant colonies that appeared after an overnight incubation. The number of Rif-resistant colonies per 10^7 surviving cells is plotted. Graphs represent an average of at least three independent experiments ± SEM. (*B*) Cultures were examined for the number of spontaneous Rif-resistant colonies appearing after an overnight incubation. The number of Rif-resistant colonies that appeared per 10^7 cells is plotted. Graphs represent an average of 30 independent cultures ± SEM.

ficient, and recombinational mechanisms may play a more important role (39).

The absence of RecQ impaired recovery, reduced survival, and increased mutagenesis after UV irradiation less severely than the absence of RecJ in these assays, suggesting that RecQ's helicase activity contributes to, but is not essential for, RecJ-promoted recovery. Other studies have also noted that, in mutants that depend on the RecF pathway for recombination or survival, RecJ plays a more critical role than RecQ (40). With respect to their activity at replication forks, the absence of either gene product diminishes the nascent DNA degradation that can be detected at the arrested replication fork (4, 15). Considering that *in vitro*, the RecJ exonuclease specifically acts on single-stranded DNA, we initially proposed that RecQ would first be required to unwind the double-stranded DNA near the arrested replication fork before any RecJ degradation could occur (4, 15, 18, 19). However, these results are more consistent with the idea that, *in vivo*, RecQ enhances the RecJ degradation, and that some nascent strand degradation occurs independently of RecQ. After the arrest of replication forks on plasmid substrates, it has been shown that the nascent DNA is partially displaced spontaneously when the hyperwound DNA ahead of the replication fork recoils, potentially providing a substrate for RecJ degradation (41). The presence of RecQ is clearly required for much more extensive degradation to occur at the arrested replication fork and may serve a larger role in maintaining fork stability and suppressing illegitimate recombination events (20, 21). Nevertheless, the presence of the RecQ helicase clearly enhanced the RecJ-mediated recovery in each case, consistent with the idea that these enzymes are acting cooperatively.

Related models to those presented in Fig. 4 for how DNA synthesis resumes after disruption suggest that replication of the leading and lagging strands become uncoupled and is reestablished downstream from the site of disruption rather than at the disrupting lesion (42, 43). Although the experiments presented here could be consistent with either model, the functional requirement for RecJ-mediated processing would essentially remain the same in each case. If disruption leads to reassembly downstream of the arresting lesion, it is clear from this data that RecJ-mediated processing is required before the efficient reassembly of the replication machinery can occur on the template. In the case of translesion synthesis, it is well established that Pol V can efficiently synthesize past the UV-induced lesion itself (7, 9). Thus, the observation that Pol V can restore DNA synthesis suggests that, at least in this situation, replication resumes from the original site of the disruption.

Materials and Methods

Bacterial Strains. All bacterial strains are in a SR108 background, a *thyA36 deoC2* derivative of W3110. SR108, HL946 (SR108 *recF332*::Tn*3*), HL944 (SR108 *recQ1803*::Tn*3*), HL924 (SR108 *recJ284*::Tn*10*), HL952 (SR108 *uvrA*::Tn*10*), CL579 (SR108 *recF6206*::*tet*^{r}), CL575 (SR108 *umuC122*::Tn*5*), and CL632 (SR108 *umuDC595*::*cat*) have been described (2–4, 15). CL740 (SR108 *umuDC595*::*cat uvrA*::Tn*10*) was constructed by P1 transduction of the *uvrA*::Tn*10* allele from HL952 into CL632. CL596 (SR108 *umuC122*::Tn*5* *recQ6215*::*cam*) and CL766 (SR108 *umuC122*::Tn*5* *recJ284*::Tn*10*) were constructed by P1 transduction of the *recQ6215*::*cam* and *recJ284*::Tn*10* alleles from TP648 (44) and HL924, respectively, into CL575. CL779 (SR108 *dinB*::*kan*^{r} *recJ284*::Tn*10*) and CL773 (SR108 *polB*::Ω Sm-Sp *recJ284*::Tn*10*) were made by P1 transduction of *recJ284*::Tn*10* from HL924 into CL634 (2) and CL636 (2), respectively. Phenotypes were confirmed by antibiotic resistance and, when appropriate, UV hypersensitivity. A complete list of strains used in this study is also shown in Table 1, which is published as supporting information on the PNAS web site.

Recovery of DNA Synthesis. This approach is modified from Khidhir *et al.* (45). Fresh overnight cultures were diluted 1:100 and grown in DGCthy media supplemented with 0.1 μCi/ml of [^{14}C]thymine to an OD_{600} of precisely 0.3, at which point half of the culture received an incident dose of 5 or 27 J/m^2, whereas the other half of the culture was mock irradiated. At the times indicated, duplicate 0.5-ml aliquots of culture were pulse labeled with 1 μCi/ml [^{3}H]thymidine for 2 min at 37°C. The cells were then lysed, the DNA was precipitated in cold 5% trichloroacetic acid (TCA) and filtered onto Millipore glass fiber filters, and the amount of ^{3}H and ^{14}C in each sample determined by liquid scintillation counting.

UV Survival Studies. Sylvania 15-watt germicidal lamp (254 nm) at an incident dose of 0.9 J/m^2 per s (0.2 J/m^2 per s for doses $<$20 J/m^2) was used for irradiations. Cells were grown in Davis medium supplemented with 0.4% glucose, 0.2% casamino acids, and 10 μg/ml thymine (DGCthy media). Cultures were inoculated from fresh overnight cultures and grown to an OD_{600} between 0.4 and 0.5. Serial dilutions of each culture were plated in triplicate on Luria-Bertani plates supplemented with 10 μg/ml thymine and UV irradiated at the indicated doses. Plates were incubated overnight at 37°C, and colonies were counted the next day.

UV-Induced Mutagenesis. Mutagenesis induced by UV was measured by the appearance of rifampin-resistant colonies as a result of UV exposure. At least 69 base substitutions within the *rpoB* gene have been identified that confer resistance to rifampin, allowing one to monitor numerous UV-induced mutation sites in different sequence contexts (46). Overnight cultures were diluted 1:100 and grown in DGCthy media to an OD_{600} of 0.4, at which point the culture was split into four equal fractions and irradiated with an incident dose of 0, 2, 10, or 30 J/m^2 UV. After overnight incubation at 37°C, the cultures were plated on Luria-Bertani plates containing 10 μg/ml thymine and 100 μg/ml rifampin. The number of cells surviving after UV treatment was also determined at this time by plating three 10-μl aliquots of serial 10-fold dilutions on Luria–Bertani plates containing 10 μg/ml thymine. Rifampin-resistant colonies and surviving cells were counted after overnight incubation at 37°C.

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