INVITED REVIEW

recA-DEPENDENT DNA REPAIR IN UV-IRRADIATED *ESCHERICHIA COLI*

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Summary

UV-radiation-induced lesions in DNA result in the formation of excision gaps, daughter-strand gaps (DSG) and double-strand breaks (DSB), which are repaired by several different mechanisms.

Postreplication repair. The *recA* gene is a master gene that controls all of the pathways of postreplication repair. The repair of DSG proceeds by one pathway that is also *recF* dependent, and one pathway that is constitutive and independent of the *recF* and *recBC* genes. A small fraction of the *recF recB*-independent repair of DSG is dependent upon the *umuC* gene, and may define an error-prone pathway of postreplication repair. Unrepaired DSG can be converted to DSB, which are normally repaired by the RecBCD pathway. However, in the *recBC sbcB* background, these DSB are repaired by a *recF*-dependent process. The RecF pathways of postreplication repair appear to utilize DNA containing a single-stranded region (either a gap or a DSB with a single-stranded end), while the RecBCD pathway appears to utilize the blunt ends of duplex DNA to promote the recombinational repair of DSB. The *polA* gene (especially the $5' \rightarrow 3'$ exonuclease activity of DNA polymerase I) functions in pathways of postreplication repair (both for the repair of DSG and DSB) that are largely independent of the *recF* gene.

Nucleotide excision repair. The repair of excision gaps is independent of the *recA* gene in cells with unreplicated chromosomes, but is *recA* dependent in cells with partially replicated chromosomes at the time of UV irradiation. This *recA*-dependent repair of excision gaps appears to be analogous to the *recF*- and *recB*-dependent pathways of postreplication repair, *i.e.* the RecF pathway repairs DNA gaps, and the RecBCD pathway repairs the DSB that arise at unrepaired gaps.

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1. Introduction

In *Escherichia coli*, pyrimidine dimers (primary lesions) produced in DNA by UV irradiation can be repaired by two different *uvrABC*-dependent nucleotide excision repair processes; one process is *recA* independent and one process is *recA* dependent (reviewed in ref. 1).

If these primary lesions are not excised and the DNA replication complex proceeds past them, then DNA daughter-strand gaps (DSG) (secondary lesions) will be formed [2]. *E. coli* cells possess efficient, *recA*-dependent recombinational systems for the repair of DSG [3, 4]. Finally, unrepaired DSG can be converted to DNA double-strand breaks (DSB) (tertiary lesions), which can also be repaired by *recA*-dependent recombinational processes [5, 6]. Therefore, depending upon the physiological state and the genetic background of a cell, the primary lesion produced by UV irradiation may not be the actual lesion that the cell must ultimately cope with in order to survive.

A mutation in *recA* knocks out all of homologous recombination. A *recB* or *recC* mutation knocks out about 99% of this recombination; the remaining 1% is controlled by the *recF* gene [7]. Although the RecF pathway of recombination is a minor pathway in a wild-type cell, it becomes the only pathway in the presence of *recBC* and *sbcB* mutations. That is, the ability to perform recombination can be restored in a *recBC* strain by an additional *sbcB* mutation (suppressor of *recBC*) [8]. Since *recA*-dependent DNA repair also depends, to varying extents, upon the *recB* and *recF* genes (see below), one would predict that there should be analogies between the mechanisms for recombination and for *recA*-dependent DNA repair.

While all inducible, "SOS" responses are *recA* dependent in *E. coli*, not all *recA*-dependent DNA repair processes require induction. That is, the RecA protein plays both a direct role in recombinational repair (*e.g.* its recombinase function) and an indirect role, *i.e.* it controls the induction of the SOS repair genes through its protease function (reviewed in ref. 9; see also refs. 10 and 11). In most cases, however, it has not been determined precisely as to which role RecA protein plays (*i.e.* direct or indirect or both) in each of the multiple pathways of DNA repair.

In this review we summarize the current understanding of the molecular mechanisms for the multiple pathways of *recA*-dependent postreplication repair and of *recA*-dependent nucleotide excision repair.

2. Repair of DNA daughter-strand gaps

When DNA replication proceeds along a damaged template, synthesis halts at the site of a non-coding lesion, and then resumes downstream from the lesion, thereby producing a DSG [2]. These DSG have been estimated to be 1000 [12] to 40 000 [13] nucleotides long. Since DNA replication is presumed to be semidiscontinuous, and the size of the DNA that is synthe-

sized discontinuously in the lagging strand (*i.e.* an Okazaki fragment) is about 1000 nucleotides long [14], the maximum size of a DSG produced in the lagging strand should be about 1000 nucleotides long. One might imagine, however, that there may be fewer reinitiation sites available in the leading strand, and that the longer DSG that have been observed may therefore reside in the leading strand.

DSG are repaired by efficient recombinational processes that are *recA* dependent [3, 4]. About half the DSG are repaired by a *recF*-dependent process [5, 15 - 17], while the remaining DSG are repaired by a process that is independent of the *recF* and *recBC* genes, and is constitutive [18] (Fig. 1(B)). The *polA* gene (especially the $5' \rightarrow 3'$ exonuclease activity of DNA polymerase I) appears to play a role in this *recF*-independent pathway for

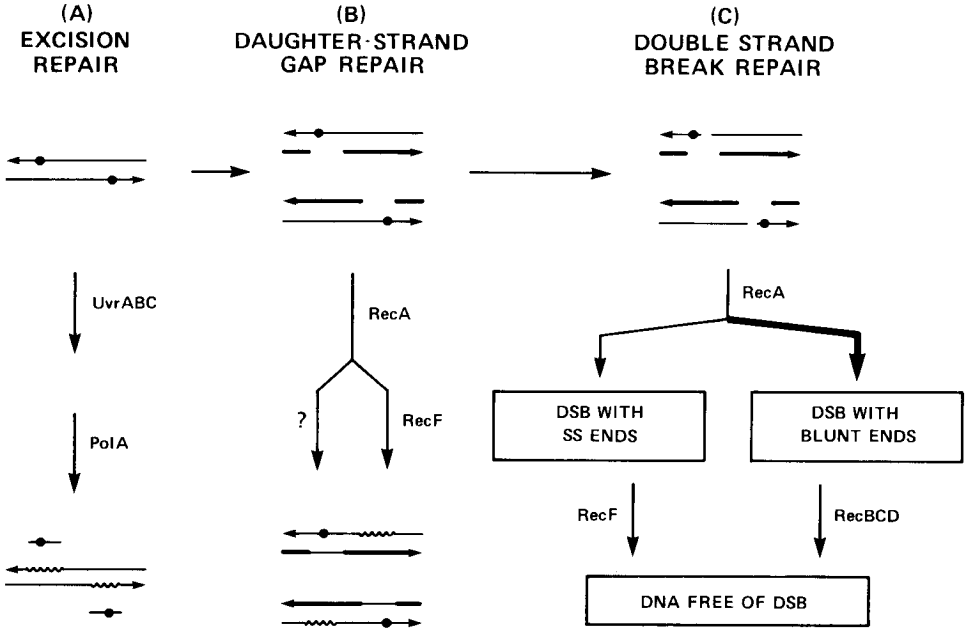

Fig. 1. The formation of primary, secondary and tertiary lesions in DNA, and their subsequent repair in UV-irradiated *E. coli*. (A) Primary lesions (*e.g.* cyclobutane-type pyrimidine dimers) are repaired by a pathway of *uvrABC*-dependent nucleotide excision repair that is *polA* dependent. If pyrimidine dimers are formed in that portion of the chromosome that was replicated prior to UV irradiation, they can be repaired by an excision repair process that is *recA* dependent (see Fig. 2). (B) If DNA replication proceeds along a damaged template, DNA daughter-strand gaps (secondary lesions) are formed. These gaps can be repaired by two *recA*-dependent processes: one that is also *recF* dependent, and one that is independent of the *recF* and *recBC* genes, but whose genetic control is not known precisely (hence the "?"). (C) Unrepaired DNA daughter-strand gaps can be converted to double-strand breaks (tertiary lesions). The major process for the repair of DNA double-strand breaks is *recBCD* dependent; however, in a *recBC sbcB* strain the repair of double-strand breaks is *recF* dependent.

the repair of DSG [19]. The *umuC* gene is involved in a minor pathway for the repair of DSG that is also independent of the *recF* and *recBC* genes [20], and may define an error-prone pathway for the repair of DSG.

Although little is known about the molecular mechanisms for these different gap-filling repair processes, the involvement of the *recF* gene suggests that the RecF pathway of homologous recombination (see ref. 8) may be involved in this repair process. According to such a hypothesis, mutations affecting the RecF pathway of recombination (*e.g. recJ* [21], *recN* [22], *recQ* [23], and *ruv* [24]) should exert some effect on the repair of DSG. Consistent with this hypothesis, a *recJ* mutation produces a marked deficiency in the repair of both DSG and DSB (see below) in *uvrA recBC sbcB* cells [25].

The *recF* gene product has been identified as a 40 kDa protein [26], but its biochemical function is unknown. One approach to understanding the function of the *recF* gene in DNA repair has been to isolate and identify suppressor mutations for *recF*. Suppressor mutations (*srfA*) for *recF* have been found to map in the *recA* gene [27, 28]. Studies on the mechanism by which these *recA*(Srf) mutations suppress the *recF*-deficiency in postreplication repair have led to the conclusion that the RecF protein plays an indirect role in postreplication repair by modulating the recombinase activity of the RecA protein such that it can participate in *recF*-dependent recombination and repair in the absence of the RecF protein [28]. A further elucidation of the site of the *recA*(Srf) mutations in the *recA* gene and the identification of the amino acid changes as well as any functional changes in the RecA protein from *recA*(Srf) cells should help to define the domain of the RecA protein that is putatively involved in the RecF pathway of recombination, and should help to delineate the biochemical function of the RecF protein. Such studies are currently underway in our laboratory and that of A. J. Clark (Berkeley).

The fact that a *uvrB recF* strain is not as deficient in the repair of DSG as is a *uvrB recA* strain suggested that a second pathway must exist for the repair of DSG [5]. This conclusion was supported by studies using an insertion mutation of *recF* (*recF332*::Tn*3*) to ensure that the earlier results were not due to leakiness in the original *recF143* mutation [18]. This second pathway (*recF* independent) is also independent of the *recBC* genes and is constitutive [18]. Recent studies, using Δ*polA* mutants, indicate that the *polA* gene plays a major role in the *recF*-independent repair of DSG [19]. Studies on different *polA* mutants (*i.e. polA1*, *polAex2*, Δ*polA* etc.) suggest that it is the $5' \rightarrow 3'$ exonuclease activity of DNA polymerase I that plays a major role in the repair of DSG. Since a DSG is likely to contain an RNA primer that is needed to reinitiate DNA synthesis downstream of a dimer, and since an RNase H activity is known to be associated with the $5' \rightarrow 3'$ exonuclease activity of DNA polymerase I, it is tempting to speculate that the role of DNA polymerase I in the repair of DSG may be due to its RNase H activity. Furthermore, since DNA polymerase I is known to be involved in the joining of Okazaki fragments synthesized in the lagging strand of

unirradiated cells, this raises the possibility that the DSG formed in the lagging strand of UV irradiated cells may be selectively repaired by the *polA*-dependent pathway, while the DSG formed in the leading strand (*i.e.* the presumably longer gaps; see above) may be repaired by the *recF*-dependent pathway.

Since a *uvrA ΔpolA recF* strain is not quite as deficient in the repair of DSG as is a *uvrA recA* strain [19], it suggests that a third pathway may exist for the repair of DSG. Consistent with this observation, a small fraction of the repair of DSG is dependent on the *umuC* gene [20]. This *umuC*-dependent repair is independent of the *recF* and *recBC* genes, and may define an error-prone pathway of postreplication repair. A *uvrA ΔpolA recF umuC* strain has not yet been tested to see if it is as deficient as a *uvrA recA* strain in the repair of DSG.

The *umuC* gene has been cloned and its product has been identified as a 45 kDa protein, but its biochemical function remains unknown [29]. (Note that both the UmuC protein and the 16 kDa UmuD protein are required for UV radiation mutagenesis; in fact, strains deficient in either protein have similar phenotypes [29].) Based upon delayed photoreactivation experiments, it has been suggested that the UmuDC proteins facilitate an error-prone type of DNA replication that can synthesize past a non-coding lesion [30]. However, it would seem unlikely that the UmuDC proteins facilitate DNA synthesis past *every* non-coding lesion, since a *uvrB umuC* strain shows DNA synthesis kinetics that are similar to a *uvrB* strain when UV irradiated with 2 J m^{-2} (unpublished data). An alternate hypothesis is that the UmuCD proteins are involved in the repair of rare lesions such as overlapping DSG, perhaps facilitating a translesion-type of DNA synthesis to repair one of the DSG, after which the other DSG could be repaired by the pathways described above. Since overlapping DSG cannot be repaired by the usual recombinational mechanisms for postreplication repair, it was proposed some years ago that the unusual challenge that an overlapping DSG presents to a cell might be a signal for the induction of the SOS repair system [31].

The repair of DSG by the *recF*-dependent or the *recF*-independent process appears to be accompanied by the transfer of DNA lesions from the parental strand to the daughter strand [32, 33]. This occurs about 50% of the time in *E. coli* [32], and appears to be due to the random resolution of the Holliday junction, an intermediate in recombination. This situation contrasts with the case for mammalian cells, where very few lesions are transferred to the daughter strands during the repair of DSG [34]. It is not clear whether this means that Holliday junctions are only resolved in one way in mammalian cells (*i.e.* to yield lesion-free daughter strands), or that DSG are repaired in mammalian cells by a mechanism that differs from that found in *E. coli.*

3. Repair of DNA double-strand breaks

Since a *uvrB recB* strain has about the same UV-radiation sensitivity as a *uvrB recF* strain, and the *recB* gene appears to play little or no role in the repair of DSG [5], the question arose as to what type of postreplication repair process is the *recB* gene involved in. It was observed that if DSG are not repaired, they can be converted to DSB. These DSB are then repaired by a recombinational process that requires functional *recA* and *recB* genes [5, 6].

The recombination deficiency and radiation sensitivity of *recBC* strains are suppressed by an additional mutation in the *sbcB* gene, which is the structural gene for exonuclease I, a single-strand specific $3' \rightarrow 5'$ DNA exonuclease [35]. The presence of an *sbcB* mutation also restores the proficiency of *recBC* cells to repair DSB, and this repair is dependent on the *recF* [36] and *recJ* [25] genes. Since the RecBCD enzyme [37] has a DNA helicase activity that requires blunt or nearly blunt ends of DNA duplexes (*i.e.* it will not unwind DNA that has a long single-stranded tail [38]), it seems that the DSB that are formed at DSG are normally processed to blunt ends by Exo I (*sbcB*) and Exo V (*recBCD*) before being repaired by the *recBCD*-dependent process. When DSB containing single-stranded tails are not degraded by Exo I and Exo V (*i.e.* in *recBC sbcB* cells), they become substrates for a *recF*-dependent recombination process. Therefore, depending on the structure of a DSB and the genetic background of the cell, a DSB may be repaired by the RecBCD pathway (the primary pathway in a wild-type cell) or by the RecF pathway, or both (Fig. 1(C)).

The formation and repair of DSB in UV-irradiated *E. coli* is very complex and poorly understood. Its complexity is best exemplified by the number of genes that appear to control the repair of DSB. With the exception of the *umuC* gene, practically all of the genes that have been implicated in postreplication repair are also involved, to varying degrees, in the repair of DSB. While the *recF* [36] and *recJ* [25] mutations appear to affect specifically the repair of DSB in UV-irradiated *uvrA recBC sbcB* cells, mutations in *recA*, *recBC*, *recN*, *radB*, *ssb*, *uvrD*, *lexA* and *polA* [5, 19, 25, 39 - 41] all produce a deficiency in the repair of DSB in $sbcB^+$ cells. Presumably, some of these genes are preferentially involved in either the RecF or the RecBCD pathway for the repair of DSB, and some may be involved in both pathways. A similar set of genes has also been observed to control the repair of X-ray-induced DSB; however, in this case there is a requirement for the *recF* and *recJ* gene products even in wild-type cells [42]. This suggests that additional types of DSB may be formed by X irradiation.

The formation and repair of DSB after UV irradiation have been observed in both normal and XPA human fibroblasts [43]. Therefore, this aspect of postreplication repair appears to be similar for *E. coli* and human cells.

4. Nucleotide excision repair

Nucleotide excision repair (*i.e. uvrABC* dependent) can be divided into two pathways: one is *polA* dependent, growth medium independent, and produces short repair patches. The second pathway is *recA* dependent, growth medium dependent, and produces long repair patches. A model for the *polA*-dependent pathway of nucleotide excision repair has been around for about 20 years (*e.g.* see ref. 44) and recently minor revisions have been made in this model based upon *in vitro* studies using the purified gene products required in this reaction [45 - 48]. However, only recently has a model been presented to explain *recA*-dependent nucleotide excision repair [1].

The observations for the requirement of the *recA* gene product in nucleotide excision repair came from two experimental approaches. In studies where the capacity to repair excision gaps was measured, the major pathway for this process was found to be *polA* dependent, and it was able to proceed in the absence of growth medium. However, a small portion of excision repair required that the cells be in complete growth medium, and this repair was inhibited by mutations in the *recA*, *recB*, *lexA* [49] and *recF* [1] genes. This repair was also inhibited by chloramphenicol [49], which inhibits protein synthesis. These results for *lexA* and chloramphenicol can be interpreted as indicating that *recA*-dependent excision repair is largely inducible.

In a second approach, it was observed that short repair patches (20 - 30 nucleotides long) were produced by a *polA*-dependent excision repair process, while long repair patches (200 - 1500 nucleotides long) were produced by a *recA*-dependent process [50]. This long patch repair system was also shown to be *recF* dependent [51] and inducible [52], but not *recBC* dependent [53].

The factors or conditions that determine where long repair patches are inserted into DNA are not known. However, it has been shown recently that the *recA*-dependent repair of excision gaps only functions in the portion of the chromosome that was replicated prior to UV irradiation (*i.e.* where sister duplexes exist and where intrachromosomal recombination can occur); the repair of excision gaps that occurred in cells with unreplicated chromosomes was *recA* independent [1]. The majority of this *recA* dependent excision repair is *recF* dependent, and a small portion is *recB* dependent [1]. The *recF* and *recB* genes are suggested to function in *recA*-dependent excision repair in a manner similar to their function in postreplication repair, *i.e.* in the portion of a chromosome that was replicated prior to UV irradiation, the RecF pathway repairs excision gaps by a recombinational process that results in the formation of long repair patches (Fig. 2(C) - 2(E)), and the RecBCD pathway repairs DSB that are formed either by overlapping excision gaps [54, 55], or by nicking the single-stranded DNA opposite the excision gaps (Fig. 2(F)).

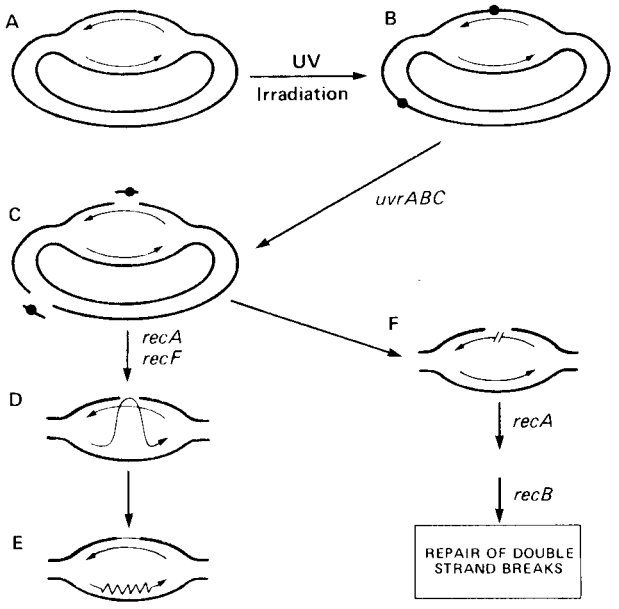

Fig. 2. The *recA*-dependent repair of excision gaps in UV-irradiated *E. coli*. Lesions can be produced in both the replicated and unreplicated regions of the chromosome (A, B), but only the excision gaps produced in the replicated region of the chromosome (C) can be repaired by an intrachromosomal recombinational process that is *recF* dependent (D). This process leaves a gap in the homologous sister duplex that can be filled by long patch repair replication (wavy line), using the parental strand opposite the gap as a template (E). If the DNA strand opposite the excision gap is cut (—//—; (F)), the resulting double-strand break is repaired primarily by a *recB*-dependent process. (From ref. 1.)

In summary, the *recA*-dependent repair of excision gaps only occurs in that portion of the chromosome that was replicated prior to UV irradiation. The *recF*-dependent and *recB*-dependent pathways of nucleotide excision repair appear to be analogous to the *recF*- and *recB*-dependent processes of postreplication repair, *i.e.* in the replicated portion of the chromosome, the RecF pathway repairs gaps and the RecBCD pathway repairs the DSB that arise at unrepaired gaps.

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