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recA-Dependent DNA Repair Processes

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Summary

UV-radiation-induced lesions in DNA result in the formation of: (1) excision gaps (i.e. a lesion is excised, leaving a gap), (2) daughter-strand gaps (i.e. a lesion can be skipped during replication, leaving a gap), and (3) double-strand breaks (i.e. the DNA strand opposite a gap can be cut). In Escherichia coli, *the* recA *gene product is involved in repairs of all three types of lesions – repair of daughter-strand gaps (2) and double-strand breaks (3) constitutes post-replication repair. The evidence suggests, furthermore, that* recA*-dependent repair of excision gaps* (1) *produced in DNA replicated prior to UV irradiation (pre-replication repair) appears to occur by similar mechanisms.*

Introduction

The RecA protein of *Escherichia coli* has many functions: it binds to single- and double-stranded DNA, and it is an ATPase, a protease and a recombinase.[1,2] The RecA protein is essential for homologous recombination, an enzymatic process whereby two homologous DNA molecules pair and exchange sections of their DNA. The protease function of 'activated' RecA protein catalyses the cleavage of the LexA protein, the repressor for a set of 18 or so 'SOS' genes that are induced in irradiated cells.[2] RecA protein also cleaves the UmuD protein[3-5] (one of the SOS gene products) to activate it for its role (in combination with the UmuC protein) in mutagenesis. A mutation in the *recA* gene sensitizes cells to killing by UV irradiation (and other agents), suggesting that *recA*-dependent processes are very important to the survival of cells with damaged DNA.

In *E. coli*, pyrimidine dimers (primary lesions formed when two adjacent pyrimidines in the same DNA strand become bonded together) produced by UV irradiation can be repaired by two different nucleotide-excision-repair processes; one process is *recA*-independent and one process is *recA*-dependent (reviews in ref. 6). If these primary lesions are not excised, the DNA replication complex can proceed past them, forming DNA daughter-strand gaps (secondary lesions),[7] which are repaired efficiently by several *recA*-dependent processes.[8,9] Finally, an unrepaired daughter-strand gap can be converted to a double-strand break (tertiary lesion) by the enzymatic cutting of the DNA strand opposite the gap. These double-strand breaks can also be repaired by *recA*-dependent recombinational processes.[10,11] Therefore, depending upon the physiological state and the genetic background of a cell, the primary lesion produced by UV irradiation (or any other agent) may not be the actual lesion that the cell must ultimately cope with in order to survive (see upper part of Fig. 1). The repair of daughter-strand gaps, and of the double-strand breaks that can arise at these gaps, constitute the processes of post-replication repair.

In this brief review we will summarize the current understanding of the molecular mechanisms for the multiple pathways of post-replication repair and of *recA*-dependent nucleotide-excision repair in *E. coli*, and suggest directions for future research.

Repair of DNA Daughter-Strand Gaps

Formation of Gaps

When DNA replication proceeds along a damaged template, synthesis apparently halts at the site of a non-coding lesion, and then resumes downstream from the lesion, thereby producing a daughter-strand gap.[7] Daughter-strand gaps have been estimated to be 1000–40,000 nucleotides long (reviewed in ref. 12). Since DNA replication is presumed to be semi-discontinuous, and the size of the DNA that is synthesized discontinuously (i.e. an Okazaki fragment) in the lagging strand is about 1000 nucleotides long,[13] the maximum size of a daughter strand gap produced in the lagging strand should be about 1000 nucleotides long. If daughter-strand gaps are formed in the leading strand, one would suspect that these gaps should be much larger than those formed in the lagging strand, since only a few initiation sites on the template for leading-strand synthesis are known.[14]

Pathways for the Repair of Gaps

Daughter strand gaps are repaired by efficient recombinational processes that are *recA*-dependent,[8,9] and about half of the gaps are repaired by a process that is *recF*-dependent (Fig. 1 B).[10,15-17] Although little is known about the molecular mechanisms for this gap-filling repair process, the involvement of the *recF* gene suggests that the RecF pathway of homologous recombination may be involved.[18]

The fact that a *uvrB recF* strain is not as deficient in the repair of daughter-

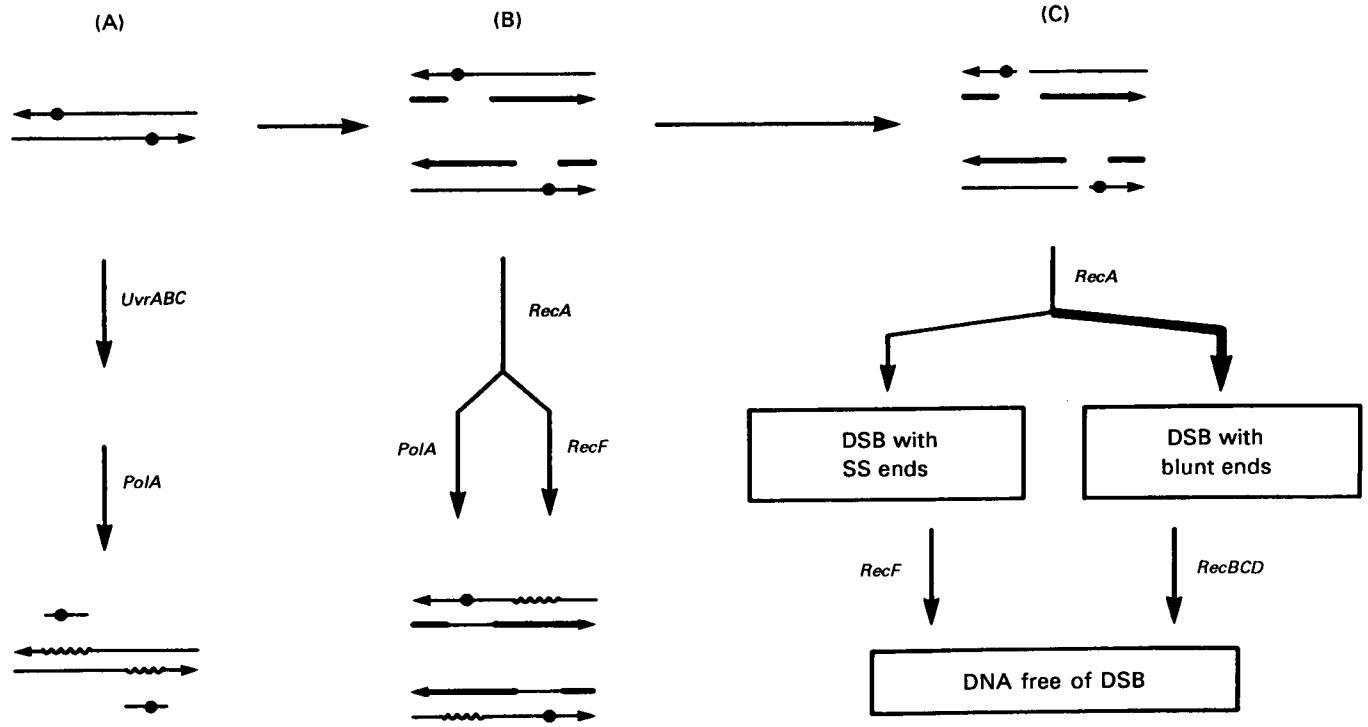

Fig. 1. *The formation of primary, secondary and tertiary lesions in DNA, and their subsequent repair in UV-irradiated E. coli. (A) Primary lesions (e.g. cyclobutane-type pyrimidine dimers) are repaired by a pathway of uvrABC-dependent nucleotide excision repair that is polA-dependent. If pyrimidine 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. 3). (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 polA-dependent.*[20] *Additionally, a few of the daughter-strand gaps are repaired by a process that is umuC-dependent,*[21] *and may define the mutagenic pathway of post-replication repair. (C) Unrepaired DNA daughter-strand gaps can be converted to double-strand breaks (DSBs; 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 (Modified from ref.* 12.)

strand gaps as is a *uvrB recA* strain suggested that a second pathway must exist for the repair of these gaps.[10] This second pathway (*recF*-independent) is also independent of the *recBC* genes and is constitutive.[19] Recent studies using different *polA* mutants indicate that DNA polymerase I (especially its $5' \rightarrow 3'$ exonuclease activity) plays a major role in the *recF*-independent repair of daughter-strand gaps.[20] Since the *polA* gene is involved in short-patch excision repair and the *recF* gene is involved in long-patch excision repair (see below), it raises the possibility that *polA* in involved in the repair of the shorter daughter-strand gaps while *recF* is involved in the repair of the longer daughter-strand gaps.

Since a *uvrA ΔpolA recF* strain is not quite as deficient in the repair of daughter-strand gaps as is a *uvrA recA* strain,[20] it suggests that additional pathway(s) may exist for the repair of these gaps. Consistent with this idea, a small fraction of the repair of daughter-strand gaps is dependent on the *umuC* gene,[21] which is also required for UV-radiation mutagenesis.[2] This *umuC*-dependent repair is independent of the *recF* gene, and may define an error-prone (i.e. mutagenic) pathway of post-replication repair.[21]

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.[22] However, it would seem unlikely that the UmuDC proteins facilitate DNA synthesis past *every* non-coding lesion, since this would result in a very high mutation rate. An alternative hypothesis is that the UmuDC proteins are involved in the repair of rare lesions such as overlapping daughter-strand gaps (Fig. 2), perhaps facilitating a trans-lesion-type of DNA synthesis (i.e. potentially mutagenic) to repair one of the gaps, after which the other gap could be repaired by the PolA and/or the RecF pathways described above.

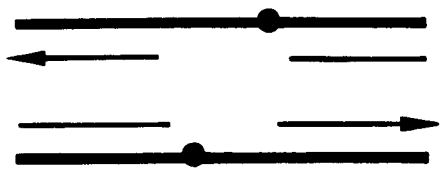

Fig. 2. *Overlapping daughter-strand gaps. When the parental strands of DNA (heavy lines) that contain closely spaced non-coding lesions (large dots) are replicated (thin lines), overlapping daughter-strand gaps may be formed. These overlapping gaps may constitute one type of mutagenic lesion.*

Other genes that have been implicated in post-replication repair are *lexA*, *lig*, *polC*, *recJ*, *recN*, *recO*, *recQ*, *ruv*, *ssb* and *uvrD*, but in most cases their involvement has not been studied extensively. The *lig* (DNA ligase) and *ssb* (DNA single-strand binding protein) genes are believed to be essential in all pathways for the repair of gaps (and breaks). The partial effect of the *lexA* gene on the repair of daughter-strand gaps is attributed to its role in the regulation of the 'SOS' genes. Although a single mutation in the *recB(C)* or *recJ* gene produced little or no effect on the repair of daughter-strand gaps, double mutants of *recB(C)* and *recJ* are grossly deficient in this repair. This raises the possibility that the repair of daughter-strand gaps may require either a functional RecJ protein or a functional RecBCD enzyme.[23]

Mechanisms for the Repair of Daughter-Strand Gaps

The repair of daghter-strand gaps is accomplished by recombinational processes that transfer parental-strand DNA to the daughter strand to fill the gaps. About 50% of the time in *E. coli*,[24] the repair of gaps results in the joining of daughter-strand DNA with

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parental DNA that contains lesions. This 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 gaps.[25] 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 daughter-strand gaps are repaired in mammalian cells by a mechanism that differs from that found in *E. coli*.

One model for post-replication repair in mammalian cells suggests that the term 'replication repair' may be more correct than 'post-replication repair.'[26] In this model, DNA synthesis stops in the leading strand upon reaching a lesion, but synthesis continues for a short time in the lagging strand. These two daughter strands then pair together, and the leading strand is extended by a few bases, using the nascent lagging strand as the template. When these daughter strands subsequently reassociate with the parental strands, they bypass the lesion in the parental strand in an error-free manner. Therefore, according to this model, a daughter-strand gap is really never produced in the leading strand.

Another model for the repair of daughter-strand gaps, derived from studies on bacteriophage T4, suggests that an RNA primer is used to bypass the lesion.[27] There is support for such a model in bacteria and mammalian cells, since DNA newly synthesized after UV irradiation shows a transient sensitivity to alkali (possibly RNA linkers).[28]

Further evidence consistent with the involvement of RNA in post-replication repair is the observation that strains of *E. coli* that overproduce ribonuclease H (RNase H), which degrades the RNA in DNA–RNA hybrids, are more sensitive to killing by UV irradiation, and show little ability to replicate UV radiation-damaged DNA and to perform post-replication repair.[29] Also consistent with these data is the observation that the expression of the *rnh* gene (the gene encoding RNase H) is inhibited during the SOS response in a $recA^+$ strain, but not in a $recA^-$ strain where the SOS response is not expressed.[30,31] Therefore, during the SOS response, *E. coli* cells *reduce* their levels of RNase H, apparetly to protect RNA–DNA hybrids that are required for survival.

It is clear that in order to better understand the processes of post-replication repair, we need a cleaner picture of the way DNA is replicated on damaged templates *in vivo*.

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 daughter-strand gaps,[10] the question arose: what type of post-replication repair process is the *recB* gene involved in? It was observed that if daughter-strand gaps are not repaired, they are converted to double-strand breaks by cutting the DNA strand opposite the gap. These double-strand breaks are then repaired by a recombinational process that requires functional *recA* and *recB* genes (Fig. 1C).[10,11] The formation and repair of double-strand breaks after UV irradiation have been observed in both normal and XPA human fibroblasts.[32] Therefore, this aspect of post-replication repair appears to be similar for *E. coli* and humans cells.

The recombination deficiency and radiation sensitivity of *recBC* strains of *E. coli* are suppressed by an additional mutation in the *sbcB* gene, which is the structural gene for exonuclease I (ExoI), a single-strand specific $3' \rightarrow 5'$ DNA exonuclease. The presence of an *sbcB* mutation also restores the proficiency of *recBC* cells to repair double-strand breaks, and this repair is dependent on the *recF* gene.[33] Since the RecBCD enzyme 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),[34] it appears that the double-strand breaks formed at daughter-strand gaps are normally processed to blunt ends by Exo I (*sbcB*) and Exo V (*recBCD*) before being repaired by the *recBCD*-dependent process. When double-strand breaks containing single-stranded tails are not degraded by Exo I and Exo V (i.e. in *sbcB recBC* cells), they become substrates for a *recF*-dependent recombination process. Therefore, depending on the structure of a double-strand break and the genetic background of the cell, a double-strand break may be repaired by the RecBCD pathway (the primary pathway in a wild-type cell) or by the RecF pathway, or both (Fig. 1C).

The formation and repair of double-strand breaks in UV-irradiated *E. coli* is very complex and poorly understood, and its complexity is best exemplified by the number of genes that appear to control this repair. With the exception of the *umuC* gene, all of the genes that have been implicated in post-replication repair are also involved, to varying degrees, in the repair of DNA double-strand breaks. While the *recF* mutation appears to affect specifically the repair of double-strand breaks in UV-irradiated *uvrA recBC sbcB* cells,[33] mutations in *recA*, *recBC*, *recN*, *ssb*, *uvrD*, *lexA* and *polA* all produce a deficiency in the repair of double-strand breaks in $sbcB^+$ cells (reviewed in ref. 12). Presumably, some of these genes are preferentially involved in either the RecF or the RecBCD pathway for the repair of double-strand breaks, 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 double-strand breaks.[35]

Nucleotide Excision Repair

Nucleotide-excision repair (i.e. *uvrABC* dependent repair) can be divided into two pathways: one is *polA*-dependent, growth medium-independent, and produces short repair patches (20–30 nucleotides long). The second pathway is *recA*- and *recF*-dependent, growth medium-dependent, and produces long repair patches (200–1500 nucleotides long).[12,36] A model for the *polA*-dependent pathway of nucleotide excision repair has been around for about 20 years (e.g. Fig. 1A), and recently minor revisions have been made in this model based upon *in vitro* studies using the purified gene products required in this reaction.[37–39] However, only recently has a model been presented to explain *recA*-dependent nucleotide-excision repair.[6]

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.[6] The greater part of this *recA*-dependent excision repair is *recF*-dependent, and a small portion is *recB*-dependent.[6] The *recF* and *recB* genes apparently function in *recA*-dependent excision repair in a manner similar to their function in post-replication repair, that is, 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. 3C–E), and the RecBCD pathway

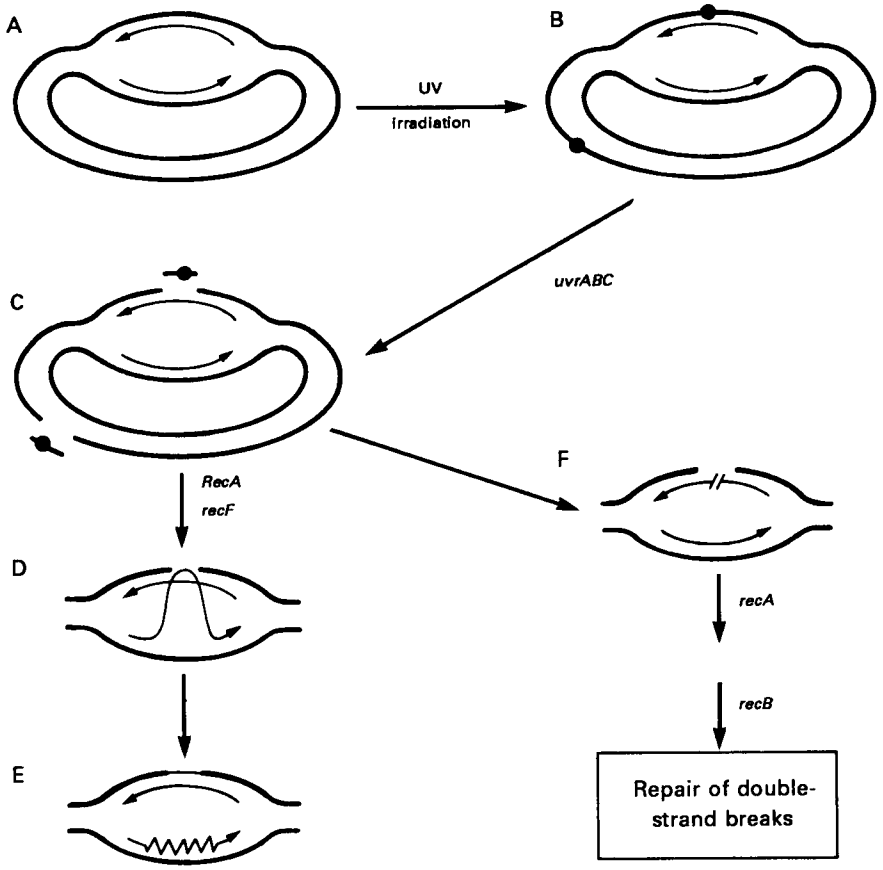

Fig. 3. *The recA-dependent repair of excision gaps in UV-irradiated E. coli. Lesions can be produced in both the replicated and unreplicated regions of the chromosome (A, B), but only the excision gaps produced in the replicated region of the chromosome (C) can be repaired by an intrachromosomal recombinational 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 an recB-dependent process. (from ref.* 6.)

repairs double-strand breaks that are formed by cutting the single-stranded DNA opposite the excision gaps (Fig. 3F).

Future Directions

Three critical questions that need to be answered are: how is DNA replicated on damaged templates? are daughter-strand gaps formed in both the leading the the lagging strands? what are the sizes of these gaps? We have recently developed an assay procedure that can distinguish and measure the sizes of gaps in the leading and lagging strands (i.e. using strand-specific single-stranded DNA probes for specific genes). The use of strand-specific probes has the potential of testing several key features of the model for post-replication repair.

Although a number of genes have been identified that affect post-replication repair, the quest for additional genes remains an important approach before one can fully understand the complex processes of post-replication repair. In this regard, several of the genes (i.e. *recO*, *recQ*, *ruv*) that affect the RecF pathway of recombination have yet to be tested directly for their role in post-replication repair.

One would like to know what additional gene products are needed in the two major gap-filling repair processes (i.e. *recF*-dependent and *polA*-dependent), and what the basis is for the existence of these two independent pathways. Could one process be involved in the repair of the larger daughter-strand gaps (specifically, RecF), while the other (namely PolA) is involved in the repair of the smaller daughter-strand gaps?

Very little is known about the formation and repair of DNA double-strand breaks. The enzyme(s) responsible for the conversion of daughter-strand gaps to double-strand breaks remain to be identified. Although a model has suggested the nature of the substrates for the *recB*-dependent (i.e. blunt-ended double-strand breaks) and *recF*-dependent (i.e. gaps or double-strand breaks with single-stranded tails) repair processes,[12,33] this model remains to be tested.

Interest in post-replication repair has waned in recent years as attention has focused on excision repair in mammalian cells. However, the opportunities are almost unlimited for applying the newer techniques of molecular biology to the study of the poorly understood *recA*-dependent repair processes in *E. coli.*

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