COMMENTARY

# How relevant is the *Escherichia coli* UvrABC model for excision repair in eukaryotes?

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## Summary

**Knowledge about the DNA excision repair system is increasing rapidly. A detailed model for this process in *Escherichia coli* has emerged in which a lesion in the DNA is first recognized by the $UvrA_2B$ helicase complex. Subsequently, UvrC mediates incision on both sites of the DNA injury. Finally, the concerted action of helicase II (UvrD), polymerase and ligase takes care of removal of the damage-containing oligonucleotide, DNA resynthesis and sealing of the residual nick.**

**In the eukaryotes, yeast and mammals a total of 10 excision repair genes have been analysed thus far. However, little is still known about the molecular mechanism of this repair reaction. Amino acid sequence comparison suggests that at least three DNA helicases operate in eukaryotic nucleotide excision. In addition, a striking sequence conservation is noted between human and yeast repair proteins. But no eukaryotic homologs of the UvrABC proteins have been identified. In this Commentary the parallels and differences between the prokaryotic and eukaryotic excision repair pathways are weighed in an attempt to assess the relevance of the *E. coli* model for the eukaryotic system.**

## Introduction

Although DNA serves as a very efficient and versatile structure for storage, duplication and use of genetic information, we cannot ignore the fact that this molecule is not an absolutely stable and safe compound. Radiation (e.g. UV light, X-rays) and numerous chemical (mainly electrophilic) agents can damage its structure and hence interfere with its proper functioning. Apart from the direct hampering effect on vital processes such as transcription and replication, DNA lesions may also give rise to mutations leading to inborn defects, carcinogenesis and cell death. To avoid these deleterious consequences, all living organisms have equipped themselves with a sophisticated network of DNA repair systems (for a comprehensive review on DNA repair in general, see Friedberg, 1985). One of the major and general repair pathways is the nucleotide excision repair process. It consists of five basic steps: detection of the damage, incision, excision, synthesis of new DNA and ligation. This system deals with a remarkably diverse array of lesions including various UV-induced photoproducts such as cyclobutane pyrimidine dimers (CPD) chemical adducts and cross-links.

The biological impact of this process is underscored by two rare, hereditary disorders in which this repair pathway is impaired: xeroderma pigmentosum (XP) and Cockayne's syndrome (CS). Individuals suffering from XP present with various cutaneous abnormalities, notably extreme sun sensitivity, abnormal pigmentation and a >2000-fold increased risk of skin cancer. In addition, many patients exhibit mental retardation (see Cleaver and Kraemer, 1989, for an extensive review on XP). CS is also characterized by UV intolerance, developmental problems and neurological degeneration. However, in this disorder tumor incidence is not dramatically elevated (for a review see Lehmann, 1987).

Cell fusion studies have revealed an extensive genetic heterogeneity within each disease: in XP a total of eight complementation groups has been identified of which seven (XP groups A–G)* are disturbed in nucleotide excision; in CS three groups (CS A–C) have been defined (of which CS-C is identical to XP-B). CS groups A and B carry defects in a sub-pathway of the excision repair system responsible for the preferential repair of UV-induced CPDs from the transcribed strand of active genes (Venema *et al.* 1990*a*, for a review on preferential repair, see e.g. Smith and Mellon, 1990). The subpathway dealing with the slower and less-complete removal of lesions from the genome overall is still intact. The opposite is found for XP group C (Venema *et al.* 1990*b*). XP-A, -B and -G, on the other hand, appear to be largely deficient in both processes. In addition, a proportion of the patients belonging to the heterogeneous XP-D group may belong to this category. These findings point to a considerable biochemical complexity underlying the excision repair process.

Besides the respectable number of complementation groups in human patients there is also substantial genetic heterogeneity within the collection of UV-sensitive rodent mutant cell lines, generated in the laboratory. To date at least eight but probably more than 10 complementation

Key words: DNA excision repair, evolutionary conservation, DNA repair genes.

*The sole patient comprising XP group H has recently been reassigned to XP-D (see Vermeulen *et al.* 1991, and references therein).

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groups have been identified (for a review see Busch *et al.* 1989). Although only proven for one case (Weeda *et al.* 1990) and ruled out for another (van Duin *et al.* 1989), it is likely that there is significant overlap between the human and rodent classes of mutants (see below).

The genetic and biochemical complexity of the excision repair system is also apparent from the analysis of mutants in lower organisms. In *Saccharomyces cerevisiae* the class of excision-deficient mutants, collectively designated the *RAD3* epistasis group, points to the existence of a minimum of 10 genetic loci involved in nucleotide excision (for a review see Friedberg, 1988). On statistical grounds it is, however, likely that the yeast genome is far from saturated with mutations in this type of gene. In *E. coli* three main excision-defective mutants defining the UvrABC functions have been extensively characterized. In addition, several other genes, *uvrD, polA, recA* and *phr*, have been shown to affect, directly or indirectly, nucleotide excision repair *in vivo* (see below).

## The molecular mechanism of excision repair in *E. coli*

The *in vitro* reaction of *E. coli* nucleotide excision has been unravelled in detail (for a recent review see van Houten, 1990). The main properties of the most important gene products involved are summarized in Table 1. Three key proteins UvrA, -B, and -C carry out the crucial steps of detection and recognition of the DNA injury and incision of the damaged template. First, a $UvrA_2B$ complex interacts with DNA, because of the DNA binding properties of UvrA. This complex translocates along the template at the expense of ATP, thereby partly unwinding the double strand as a result of the helicase activity of the UvrB protein. It is envisaged that the complex in this fashion scans the DNA and 'feels' structural abnormalities. UvrB alone (Orren and Sancar, 1989) or $UvrA_2B$ together (Grossman and Yeung, 1990) then wait for the arrival of the UvrC protein, after which a dual cut is introduced into the damaged strand: one positioned 7 nucleotides upstream of the lesion and the other 3 or 4 nucleotides downstream. The UvrD helicase, in concerted action with DNA polymerase I, releases the damage-containing 12- or 13-base oligonucleotide as well as the bound Uvr proteins. The resulting gap in the DNA template is filled in by DNA polymerase I and sealed by DNA ligase. As discussed below it is likely that within the bacterium additional factors are implicated that have modulating effects on the *in vivo* process such as the photoreactivating enzyme (Sancar and Smith, 1989). Finally, nucleotide excision in *E. coli* is under the control of the SOS response mediated by the *lexA-recA* regulon, permitting a low, constitutive level of expression and strong induction under SOS conditions.

Since the *E. coli* system has been characterized in detail and little is still known about the process in eukaryotes, it is relevant to consider to what extent the *E. coli* model might be valid for the eukaryotic excision repair mechanism. In the next paragraphs the present knowledge about the proteins involved in the best-studied eukaryotic systems, yeast and mammals, will be summarized and compared with the *E. coli* paradigm.

## Main properties of the eukaryotic excision repair proteins

Most of the genes correcting the existing members of the yeast *RAD3* epistasis group have now been cloned. The list of cloned human excision repair genes is steadily growing. Particularly, the class of rodent mutants has proven to be a valuable tool for the isolation of human *E*xcision *R*epair *C*ross *C*omplementing rodent repair deficiency (*ERCC*) genes. The principle features of the proteins encoded by the excision repair genes of *Saccharomyces cerevisiae* and man are summarized in Tables 2 and 3, respectively (for a recent review see Hoeijmakers and Bootsma, 1990). Several interesting implications emerge from these data.

(1) The amino acid sequences of the ERCC-2, -3 and -6 gene products suggest that at least three DNA helicases are involved in mammalian excision repair (Weber *et al.* 1990; Weeda *et al.* 1990; C. Troelstra, unpublished results). The infered helicase functions are based on the identification of seven consecutive sequence elements in these proteins that are homologous to motifs conserved between two superfamilies of DNA and RNA helicases. The occurrence of so many domains in the correct order and within the expected intervals is highly significant. In the case of ERCC-2 the evidence is further strengthened by the fact that this protein is the human homolog of yeast RAD3 that has been shown to possess a $5'\rightarrow3'$ DNA helicase activity (Sung *et al.* 1987). It is possible that, in addition to unwinding DNA, some of these proteins have a role in stripping off bound polypeptides from the DNA in the course of the excision reaction.

**Table 1.** *Properties of* E. coli *proteins involved in excision repair**

| Protein | Size (aa)† | No. of molec./cell‡ | Protein functions (binding sites/affinity for) | Activity |
|---|---|---|---|---|
| UvrA | 940 | 20 (200) | 2 NTPs, 2 $Zn^{2+}$, UvrB ds UV-DNA>ds DNA§ | Can dimerize§ and complex with UvrB |
| UvrB | 672 | 200 (1000) | 1 NTP, UvrA no DNA binding¶ | $5'\rightarrow3'$ DNA helicase as $UvrA_2B$ complex |
| UvrC | 588 (610)‖ | 10 | ssDNA | Together with UvrB: endonuclease |
| UvrD (helicase II) | 720 | 3000 (4500) | 1 NTP, dsDNA, RNA/DNA | $3'\rightarrow5'$ DNA or RNA/DNA ssDNA helicase |
| Photolyase | 471 | 10–20 | $FADH_2$, pterin (chromophores) dsUV-DNA>dsDNA | Photoreactivation of CPD, stimulation of excision repair |

* DNA polymerase I and DNA ligase are not included.
† aa, amino acids.
‡ The number of molecules per cell after SOS induction are given in parenthesis.
§ DNA binding and dimerization are stimulated by ATP. UvrA has 2 $Zn^{2+}$ fingers and one putative helix-turn-helix motif for DNA binding. ds, double-stranded; ss, single-stranded.
¶ UvrB has no DNA binding activity by itself: however, a $UvrA_2B$ complex binds DNA and puts UvrB onto a lesion.
‖ When a GTG triplet is the actual translation initiation codon.

**Table 2.** *Properties of* S. cerevisiae *proteins involved in excision repair**

| Protein | Size† (aa) | Human homolog | Functional properties‡ |
|---|---|---|---|
| RAD1 | 1100 | Unknown | Histone binding?, involved in recombination |
| RAD2 | 1031 | Unknown | Transcription is induced by UV |
| RAD3 | 778 | ERCC-2 | ssDNA-dependent ATPase, 5′–3′ DNA helicase histone binding?, additional helicase-independent vital function |
| RAD4 | 754 | Unknown | DNA binding?, histone binding? |
| RAD7§ | 565 | Unknown | Histone binding?, membrane association, transcription induced by UV |
| RAD10 | 210 | ERCC-1 | DNA binding?, involved in recombination |

* Only from genes with published nucleotide sequences.
† Predicted from the DNA sequence (aa, amino acids).
‡ ? Denotes a function postulated on the basis of amino acid sequence homology to functional domains in other proteins; direct proof at the level of the protein is lacking.
§ Excision repair only partially dependent on RAD7.

**Table 3.** *Properties of human proteins involved in excision repair**

| Protein | Size† (aa) | Human homolog | Functional properties‡ |
|---|---|---|---|
| XPAC | 273 | ? | ss/dsDNA binding, $Zn^{2+}$ and histone binding? |
| XPBC/ERCC-3 | 782 | ERCC-$3^{sc}$ | NTP, DNA and histone binding?, DNA helicase? additional vital function? |
| ERCC-1§ | 297 | RAD10 | DNA binding?, C terminus has homology to parts of UvrA and UvrC, involved in recombination?, not involved in XP or CS |
| ERCC-2 | 760 | RAD3 | NTP and DNA binding (?), 5′–3′ helicase (?), additional vital function(?), probably XPDC |
| ERCC-6¶ | ~1500 | Unknown | 2-NTP and histone binding?, DNA helicase? |

* Only from genes for which nucleotide sequence information is available.
† Predicted from the DNA sequence (aa, amino acid).
‡ ? Denotes a function postulated on the basis of amino acid sequence homology to functional domains in other proteins; direct proof at the level of the protein is lacking.
§ Corresponding rodent mutants (group 1) display an extreme sensitivity to cross-linking agents, in addition to a hypersensitivity to UV light (which is shared with other excision-deficient mutants, the genes of which are listed here).
¶ Corresponding mutant only moderately sensitive to UV, but this may be due to a leaky mutation (sequence information from C. Troelstra, unpublished results).

Unfortunately, the predicted amino acid sequence of the other cloned mammalian repair genes does not hint at any specific enzymatic activity. The clearest functional feature that is apparent from the primary amino acid sequence of these genes is the putative Zn finger found in the XPAC gene product, suggesting that it binds DNA (Tanaka *et al.* 1990). This proposition is confirmed by the finding that the protein correcting the XP-A defect after microinjection into fibroblasts indeed binds single-stranded as well as double-stranded DNA (Hoeijmakers *et al.* 1990). Other functional domains infered from the deduced amino acid sequences are summarized in Table 3. These functions have not yet been proven at the protein level.

(2) A considerable number of the proteins listed in Table 2 and 3 appear to have additional functions beyond their implication in excision repair. RAD1 and 10 (and perhaps by analogy also ERCC-1) are involved in mitotic recombination (Schiestl and Prakash, 1988, 1990). RAD3 (and probably its human counterpart ERCC-2) has an undefined vital function (Higgins *et al.* 1983; Naumovski and Friedberg 1983; Busch *et al.* 1989). As discussed below the same may hold for the XPBC/ERCC-3 protein and its yeast homolog ERCC-$3^{sc}$. The finding that so many polypeptides have dual involvements indicates that eukaryotic repair pathways are tightly interwoven with other cellular processes.

(3) The *ERCC-3* gene presents the first example of overlap between human and rodent mutants. This gene was cloned on the basis of its ability to correct UV-sensitive CHO mutants of group 3 but appeared at the same time capable of complementing cells from the rare XP group B, a group that combines the clinical symptoms of XP and CS (Weeda *et al.* 1990). It is likely that more such cases will be identified (see below).

**Table 4.** *Amino acid sequence conservation of excision repair proteins*

| Protein | Homology with human protein (% similarity/identity) | | Yeast homolog |
|---|---|---|---|
| | Mouse | *S. cerevisiae* | |
| ERCC-1* | 92/86 | 39/26.5 | RAD10 |
| ERCC-2 | ? | 72/52 | RAD3 |
| XPBC/ERCC-3† | 96/94 | >70/>50 | ERCC-$3^{sc}$ |
| XPAC | 94/85 | ?‡ | ?‡ |

* Additional homology with parts of UvrA and -C.
† G. Weeda and M. H. M. Koken (Rotterdam; unpublished results).
‡ Yeast homolog expected, on basis of the degree of sequence conservation between man and mouse, which is similar to that between human and murine ERCC-1.

(4) One of the most striking features emerging from the analysis of the genes listed above is the strong amino acid sequence conservation between the human and yeast repair proteins. Quantitative information on the degree of sequence homology is presented in Table 4. The mammalian ERCC-1 gene product displays an intriguing pattern of homology: for the first part (214 amino acids), it harbours significant kinship with the RAD10 protein (210 amino acids). The remaining C terminus of ERCC-1, which

notably is missing in RAD10, bears for the first ~40 amino acids some similarity to part of UvrA and for the last ~60 amino acids there is a striking resemblance with the C terminus of UvrC (van Duin *et al.* 1988, and references therein). Thus this gene seems to be composed of (or parts of) repair genes of lower organisms. When comparing the degree of similarity between the human and mouse ERCC-1 protein with that between the XPAC protein of man and mouse one can extrapolate and predict that a yeast XPAC counterpart exists with roughly the same level of homology as is found between ERCC-1 and RAD10.

(5) Finally, interesting parallels can be drawn between the *ERCC-2* (and *RAD3*) gene and the *XPBC/ERCC-3* gene (and its yeast homolog). As shown in Tables 2 and 3 both genes encode (presumed) DNA helicases with similar $M_r$ values and mutations in these genes cause very similar phenotypes in rodent cells. Furthermore, very recently it was discovered that *ERCC-2* confers wild-type UV resistance on XP group D cells (C. A. Weber and L. H. Thompson, Livermore, personal communication). Hence, the *ERCC-2* gene is most probably, like *ERCC-3*, also an XP gene. XP group D also encompasses patients with combined XP and CS clinical symptoms, since the recent reassignment of the XP/CS group H patient to XP-D (Vermeulen *et al.* 1991).

In addition, both human genes have yeast cognates with approximately the same degree of sequence homology at the amino acid level (Table 4). (In fact the strong sequence conservation of the *ERCC-3* gene permitted the cloning of the yeast homolog by cross-hybridization using the human cDNA as a probe. The *ERCC-3*$^{sc}$ gene was not known as a mutant before; thus demonstrating that the yeast mutant collection is indeed, incomplete.) Finally, preliminary results from gene-disruption experiments suggest that *ERCC-3*$^{sc}$, like *RAD3*, has an additional vital function (unpublished results in collaboration with S. and L. Prakash, Rochester). The strong lines of correspondence between *ERCC-2* and *-3* suggest that they have a comparable, non-overlapping function or are involved in a common step in the excision pathway. A possibility is that the XPBC/ERCC-3 protein has a 3′→5′ DNA helicase activity (the opposite from RAD3 and ERCC-2) and that both work together in unwinding the DNA in search of lesions (cf. $UvrA_2B$) or in releasing the damage-containing oligonucleotide after incision has taken place (cf. UvrD).

From the foregoing it is evident that knowledge about the human and yeast systems is rapidly increasing. However, we are still far from understanding the molecular intricacies of nucleotide excision in eukaryotes. The high sequence conservation noted above for several important components supports the idea that the process as a whole is strongly conserved at least between yeast and man. In this light it is useful to consider whether this conservation extends to *E. coli*.

## Comparison of the *E. coli* and eukaryotic excision repair systems

The idea that *E. coli* serves as a good model for eukaryotic excision repair is based on a number of observations.

(1) The basic steps of the pathway: damage recognition, incision, excision, repair synthesis and ligation have been shown to occur in both kingdoms. The recent discovery, that in *E. coli* as well as in eukaryotes several DNA helicases are involved, strengthens this point.

(2) As far as can be inferred from the sensitivity of mutants to damaging agents it appears that the substrate repertoire of both pathways is quite similar. However, from recent studies employing the purified UvrA, B and C proteins and defined lesions it becomes evident that the *E. coli* enzymes are capable of removing a much broader range of lesions than originally deduced from the spectrum of sensitivities of the corresponding mutants (van Houten, 1990). This is due to the fact that there is certain degree of redundancy in repair systems, resulting in overlap in the removal of some lesions between different repair pathways. The same may be true for the eukaryotic system; however, at present this remains a matter for speculation. If this is the case, it implies that the mechanisms for damage recognition are likely to be similar.

(3) Preferential repair of CPDs in the transcribed strand of active genes has been reported for mammalian cells, yeast and *E. coli* (Mellon *et al.* 1987; Smerdon and Thoma, 1990; Mellon and Hanawalt, 1989). This suggests that this subpathway of the excision repair system is conserved across the prokaryotic–eukaryotic border. The specific components involved have, however, not been characterized in any species.

These findings suggest that in eukaryotes there is a repair system similar to that in *E. coli*; however, there are also substantial differences, some of which have become clear only recently.

(1) The number of excision-deficient mutants in *E. coli* and in eukaryotes (and consequently the number of distinct genes) differs considerably. The incomplete set of excision-deficient yeast mutants encompasses already 11 or more mutants, i.e. significantly higher than the number in *E. coli*.

(2) Mutants with a similar repair defect to that found in XP-C and CS have not (yet) been reported for *E. coli*.

(3) With the exception of the carboxyl terminus of ERCC-1, none of the known and strongly conserved eukaryotic excision repair proteins bears significant 'overall' amino acid sequence homology to *E. coli* repair proteins. This means that at present no functional homologs can be unequivocally assigned across the eukaryotic–prokaryotic border.

Several hypotheses can be put forward to account for these contrasting observations.

(a) The excision repair genes that encode the UvrABC function in eukaryotes have not yet been isolated and the same holds for the bacterial equivalents of the eukaryotic repair genes that have been cloned to date. It is certain that many important factors in the eukaryotic system are unidentified and it is possible that even the well-characterized *E. coli* process involves a number of components that are still unknown. Examples of these are proteins engaged in preferential removal of CPD from the transcribed strand of active genes in *E. coli* (Mellon and Hanawalt, 1989), or factors similar to the photoreactivating enzyme that has recently been shown to stimulate excision repair (Sancar and Smith, 1989); i.e. components with a subtle, modulating function. However, it is clear that when such proteins are missing in *E. coli*, excision repair can still be accomplished, at least *in vitro*, whereas most of the eukaryotic genes isolated to date do have such an essential function.

(b) It is also possible that the eukaryotic proteins recently identified do not have bacterial counterparts that are intimately involved in the *E. coli* excision process. This would mean that the eukaryotic pathway involves many

extra components or has subpathways that do not exist in prokaryotes.

(c) A third possibility is that the UvrABCD-like functions in eukaryotes are so different that no significant 'overall' homology can be recognized any longer at the protein level.

Regardless of which of the above-mentioned explanations turns out to be true, it seems likely from present knowledge that considerable differences exist between bacterial and eukaryotic excision repair pathways. These may be located at least in part in (pre)incision steps and related to the fundamental differences in chromatin structure. This may also provide one possible explanation for the observation that the UvrABC(D) gene products appear to be non-functional in living mammalian cells (Zwetsloot *et al.* 1986), but are functional in 'cell-free' extracts containing purified, damaged plasmid DNA as substrate (Hansson *et al.* 1990). Undoubtedly, future research will resolve these issues.

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