Nucleotide excision repair II: from yeast to mammals

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An intricate network of repair systems safeguards the integrity of genetic material, by eliminating DNA lesions induced by numerous environmental and endogenous genotoxic agents. Nucleotide excision repair (NER) is one of the most versatile DNA repair systems. Deficiencies in this process give rise to the classical human DNA repair disorders xeroderma pigmentosum (XP) and Cockayne's syndrome (CS), and to a recently recognized disease called PIBIDS, a photosensitive form of the brittle hair disorder trichothiodystrophy. This is the second of a two-part review on NER. Part I (in the previous issue of TIG) concentrated on the main characteristics of the NER pathway of E. coli and yeast. Part II compares the mammalian and yeast systems, and attempts to integrate current knowledge on the eukaryotic pathway to suggest an outline for the reaction mechanism.

All living organisms have an intricate network of systems whose role is to repair damage to DNA. One of the most important of these, nucleotide excision repair (NER), is a five-step pathway that eliminates a variety of structurally unrelated lesions, including UV-induced cyclobutane pyrimidine dimers (CPD) and (6–4) photoproducts, many types of chemical adducts and DNA crosslinks. As summarized in part I of this review[1], the mechanism of NER is best understood in the bacterium *E. coli*. In part II, I focus on the more complex pathway in eukaryotes, about which much less is known. I shall discuss the main features and biological impact of NER in mammals, and attempt to put these into an evolutionary and mechanistic perspective by comparing mammalian NER with the yeast system. For a comprehensive review on DNA repair in general, see Ref. 2.

General characteristics of mammalian NER

Each mammalian nucleus contains approximately two metres of DNA and repair systems face a formidable task in surveying this for the presence of lesions. This logistic problem seems to be reduced to some extent by the preferential (i.e. more rapid and complete) repair of transcribed sequences, a process that is carried out by a special NER subpathway also found in *E. coli* and yeast[3]. Apparently, high priority is given to rapid resumption of transcription when this vital process is blocked by lesions in the template. The initial recognition and signalling of DNA injury in this subpathway is probably performed by RNA polymerase, whereas in the more slow and incomplete 'overall genome' NER subpathway, lesions are thought to be detected by repair complexes scanning the DNA. The screening for conformational abnormalities by RNA polymerase II may be more rigorous and this may explain why some lesions, such as CPDs, are more efficiently removed from transcribed strands than from the rest of the genome[3]. Other lesions, such as 6–4 photoproducts, are already very efficiently recognized by the overall genome repair system. Their rate of removal from the bulk of DNA is almost the same as that achieved by transcription-coupled repair.

Human NER-deficient syndromes

The consequences of deficient excision repair are apparent from the clinical symptoms of the human repair disorders xeroderma pigmentosum (XP), Cockayne's syndrome (CS) and PIBIDS, a special form of trichothiodystrophy. Patients suffering from one of these rare autosomal recessive diseases are very sensitive to sun (UV) light. XP patients show pigmentation abnormalities and numerous premalignant lesions in sun-exposed skin, as well as a predisposition to skin cancer and, often, accelerated neurodegeneration. Neurological dysfunction is also a hallmark of CS, although the underlying cause, demyelination of neurons, is different. Growth is retarded in all CS patients, and in a subset of XP patients. Remarkably, CS patients do not have an elevated incidence of (skin) cancer. (For reviews on the clinical features of XP and CS, see Refs 4 and 5, respectively.)

PIBIDS is an acronym for a complex syndrome that comprises photosensitivity, ichthyosis (scaling of the

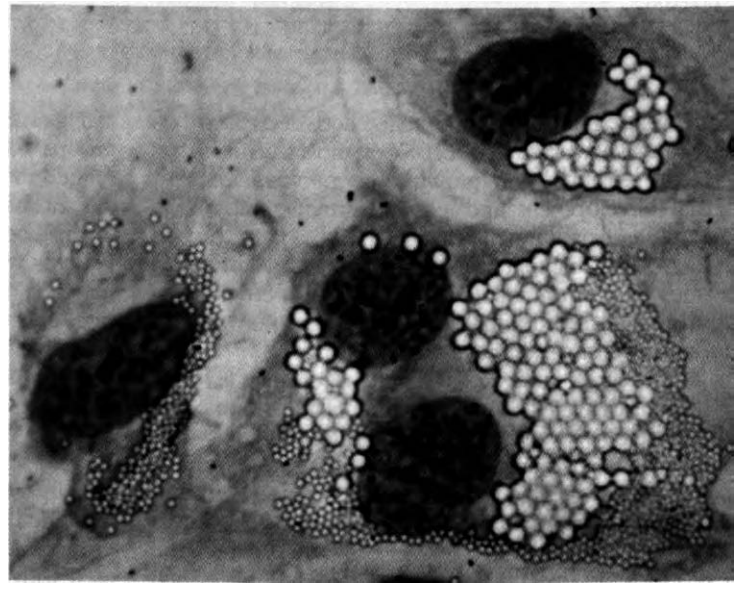

FIG 1

Micrograph showing complementation of the DNA-repair defect in XP. Fibroblasts from two XP patients were labelled with latex beads of different diameter and fused using inactivated Sendai virus. Cells were then UV-irradiated and subsequently incubated in the presence of ^{3}HTdR. Unscheduled DNA repair synthesis (UDS) was visualized using *in situ* autoradiography. The number of autoradiographic grains over each nucleus reflects the repair capacity of the cell. The nonfused monokaryons (of complementation group C and G) show UDS that is greatly reduced (XP-C) or completely absent (XP-G). The heterodikaryon, which contains both types of latex beads, has a normal level of UDS.

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TABLE 1. Properties of XP, CS and PIBIDS complementation groups

	Clinical features			Repair characteristics		
Group	Skin cancer	Neurological abnormalities	Relative frequency of occurrence	UV-sensitivity	Residual UDS[a]	Remarks
XP-A	+	++	high	+++	<5	Different from rodent groups 1–7, 11
XP-B	+/–	+++/+	very rare	++	<10	Combined XP/CS Identical to rodent group 3
XP-C selective	+	–	high	+	15–30	Deficient in 'global genome' repair Normal preferential strand-selective repair
XP-D	+	++/–	intermediate	++	15–50	Includes patients with PIBIDS and patients with XP/CS
XP/CS						Identical to rodent group 2
XP-E	+/–	–	rare	±	>50	
XP-F	+/–	–	rare/intermediate	+	15–30	Repair slow but prolonged
XP-G	+/–	+++/+	rare	++	<10	Includes patients with CS
XP-V	+	–	high	+	100	Defective in post-replication repair Normal NER
CS-A normal	–	++	rare	+	100	Defective in preferential strand-selective repair 'Global genome' repair normal
CS-B normal	–	++	high	+	100	Defective in preferential strand-selective repair 'Global genome' repair normal Identical to rodent group 6
TTD1BR	–	+	very rare	+	15	PIBIDS

[a]Unscheduled DNA synthesis as a percentage of wild-type activity.

skin), brittle hair, impaired intelligence, decreased fertility, and short stature. PIBIDS resembles CS in many aspects: its effects on growth, the nervous system[7], sexual development and photosensitivity, and in its lack of association with cancer. Brittle hair, caused by a reduced content of cysteine-rich matrix proteins, is the most prominent characteristic of trichothiodystrophy, a disorder that also affects patients who are not photosensitive (reviewed in Ref. 6).

NER deficiency is reflected at the cellular level as hypersensitivity to UV and to agents that mimic the effect of UV; in most XP and PIBIDS patients, UV-induced unscheduled DNA synthesis (UDS) is also slower or completely absent[4]. The NER defect in classical CS is limited to the subpathway of preferential repair of (the transcribed strand of) active genes; the less efficient 'overall genome' repair system is still functional[8]. Since preferential repair makes a relatively small contribution to the total repair synthesis, CS fibroblasts show near-normal levels of UDS. However, the preferential repair defect prevents the rapid recovery of RNA synthesis after UV exposure and this probably causes the increased UV sensitivity.

Complementation analysis shows that all three NER disorders are genetically heterogeneous: fusion of cells from different patients can complement each repair defect. An example of XP complementation is shown in Fig. 1. Seven excision-deficient XP complementation groups (designated XP-A to XP-G) have been catalogued to date[9] (Table 1). An eighth group, called XP-variant, has normal NER but is thought to be impaired in the poorly defined postreplication repair pathway[10]. Patients who have CS only fall into one of two complementation groups[6], CS-A or CS-B, whereas a number of very rare individuals with combined manifestations of XP and CS fall into XP groups B, D and G (Ref. 9 and our unpublished results; Table 1). At least two complementation groups can be distinguished for PIBIDS. Most patients have been assigned to XP group D (Ref. 11), further extending the clinical heterogeneity of this form of XP (Ref. 12). One recently identified PIBIDS patient constitutes an entirely new group[13]. The finding that a second NER gene is associated with the clinical symptoms of PIBIDS underscores the pleiotropic and unexpected clinical effects associated with mutations in NER genes, such as the occurrence of sulfur-deficient brittle hair.

Repair deficiency is most severe in XP groups A, B and G, and affects both overall genome and preferential repair. In XP-C the excision defect is limited to the overall genome pathway[14], thus XP-C is the biochemical opposite of CS-A and CS-B. Since the efficiency of overall genome repair has a strong impact on mutagenesis, this may explain the high incidence of skin

TABLE 2. Properties of rodent NER complementation groups

Group	Representative mutant	Parental cell line	Sensitivity of mutant[a]		Incision deficient	Correcting gene cloned	XP/CS equivalent
			UV	Mitomycin C			
1	UV20 43-3B	CHO	++	+++	yes	yes	none
2	UV5 VH-1	CHO V79	++	+	yes	yes	XP-D
3	UV24 27-1	CHO	++	+	yes	yes	XP-B
4	UV41	CHO	++	+++	yes		
5	UV135	CHO	+(+)	±	yes	yes	XP-G
6	UV61	CHO	+	+	partially	yes	CS-B
7	VB11	V79	+	±	partially		
8	US31	Mouse lymphoma	+	+			
9	CHO4PV	CHO	+	+	partially		
10	CHO7PV	CHO	+	+	partially		
11	UVS1	CHO	+/++	+	yes		

[a]The number of plus signs indicates the sensitivity of the mutant relative to wild-type cells: +, 2–5 times greater; ++, 5–10 times greater; +++, more than 10 times greater than wild-type sensitivity.

cancer associated with XP-C, and the lower risk for CS. As mentioned above, XP-D is a very heterogeneous group that includes XP, XP/CS and PIBIDS patients[12]. NER is least affected in XP-E. Finally, repair in the mild XP group F appears to be slow, but ultimately quite complete.

In all XP complementation groups, the defects in repair of CPD lesions can be bypassed by introducing the prokaryotic CPD-specific endonucleases of bacteriophage T4 and *Micrococcus luteus* (Ref. 15, and references therein). Apparently, when incision of the damaged strand has been carried out by exogenous enzymes, the cellular repair machinery is capable of completing the task. This suggests – but does not necessarily prove – that all XP defects reside in NER steps preceding incision or affecting incision itself, and implies that the first stage of the reaction is quite complex.

Rodent NER mutants

A second important category of mammalian mutants are the laboratory-induced, UV-sensitive rodent cell lines. These are mainly derived from Chinese hamster ovary (CHO) cell lines, and there are currently 11 NER complementation groups in this class of mutants[16]. Their main features are summarized in Table 2 (reviewed in Ref. 17). Mutants that belong to the first five groups are extremely sensitive to UV and bulky adducts and in that respect resemble the XP groups A, B, D and G. Repair in the few representatives of the remaining groups appears to be only partially disturbed, as in CS-A and CS-B and in XP groups C, E and F. A unique characteristic of groups 1 and 4 is their extraordinary sensitivity to cross-linking agents. This suggests that the NER genes affected in these mutants act in additional systems that repair or respond to cross-link damage in DNA. As shown below, there is considerable overlap between the Chinese hamster mutants and the human NER syndromes.

Human NER genes

So far, most mammalian NER genes have been isolated by transfection of genomic DNA into UV-sensitive rodent repair mutants[18], followed by selection of UV-resistant transformants and retrieval of the correcting sequence. Recently, however, the use of cDNA expression libraries in extrachromosomally replicating vectors based on the Epstein-Barr virus[19] has circumvented many of the problems that previously limited the use of human cells for transfection.

The human genes correcting rodent repair defects are called *ERCC* genes, for excision repair cross-complementing rodent repair deficiency genes. The number refers to the rodent group that is corrected. Table 3 lists the human NER genes cloned thus far and summarizes their main properties (reviewed in Ref. 20). Some general aspects are discussed below.

Expression

The cloned mammalian NER genes are weakly and constitutively expressed in various cells and tissues. No significant UV-inducibility has been observed for *XPAC*, *ERCC1* and *ERCC3*.

Overlap between human repair syndromes and rodent mutants

Introduction of the *ERCC2*, *ERCC3* and *ERCC6* genes into human NER-deficient cell lines alleviated specific defects in cells from groups XP-D, XP-B and CS-B respectively[21–24]. The correspondence between *ERCC6* and CS-B identifies ERCC6 as the first eukaryotic NER

TABLE 3. Properties of cloned human NER genes

Gene	Chromosomal location	Gene size (kb)	No. of amino acids in protein	Homologous gene in *S. cerevisiae*	% identity/ similarity to *S. cerevisiae* gene	Properties of protein[a]
XPAC	9q34	~25	273	*RAD14*	27/50	Zn^{2+} finger Binds ss and UV-irradiated dsDNA
XPBC/ ERCC3	2q21	~45	782	*RAD25/SSL2*	55/72	DNA binding helicase Chromatin binding? Role in transcription
XPCC			823	*RAD4?*		Homology to RAD4 limited to one segment of the protein
XPDC/ ERCC2	19q13.2	~20	760	*RAD3*	52/72	DNA binding? DNA helicase? Essential function?
CSBC/ ERCC6	10q11–21	~85	1493	unknown		DNA helicase? Chromatin binding? Additional NTP-binding? Nonessential function
ERCC1	19q13.2	15–17	297	*RAD10*	26/39	DNA binding? Carboxy terminus has homology to segments of UvrA and UvrC Involved in recombination?
XPGC/ ERCC5	13q32–33	~32	1186	*RAD2*	24/39	Complexed with ERCC4, ERCC11, XPFC

[a]Question marks indicate characteristics inferred on the basis of the predicted amino acid sequences of the proteins.

protein known to be specifically involved in the preferential repair of active genes. The *ERCC1* gene did not alleviate the NER defect in cell lines of any XP, CS or PIBIDS complementation groups (Ref. 25 and our unpublished results). Hence *ERCC1* is a repair gene not yet revealed by the known NER disorders. Recently, the *ERCC5* and the *XPGC* (XP-G-correcting) gene products were found to be identical[26,27]. Transfection experiments have shown that the XP-A-correcting (*XPAC*) gene is not implicated in rodent groups 1–7 or 11 (our unpublished results). It has yet to be established whether XP-C has a corresponding rodent mutant. The extensive overlap between human syndromes and rodent mutants stresses the value of the latter class for understanding the molecular basis of repair defects in humans.

Overlap between mammalian and yeast genes

Except for *ERCC6* and possibly *XPCC*, all human genes have identified counterparts in the yeast system[26,28–33] (Table 3), with the level of sequence identity between corresponding yeast and mammalian proteins ranging from 25% to over 50%. *XPCC* may be equivalent to *RAD4*, but the region of similarity comprises only one quarter of the protein[19]. Furthermore, the NER defects of XP-C (preferential repair unaffected) and *rad4* (total NER deficiency) appear to differ. The ERCC1 gene product shows a remarkable pattern of homology with RAD10. The first 214 amino acids align with the entire 210 amino acid RAD10 polypeptide[29]; of the remaining 83 residues, the first part shows some homology with a segment of the *E. coli* NER protein UvrA, while the 60 carboxy-terminal residues strongly resemble the carboxy terminus of UvrC.

Encoded functions

XPAC. The purified XPAC protein has an affinity for single-stranded (ss) DNA as well as UV-irradiated double-stranded (ds) DNA[34,35] and contains a predicted DNA-binding zinc-finger domain[36]. Its preference for binding to UV-induced lesions[34] may implicate XPAC in damage recognition. From the nature of the XP-A repair defect as measured in the *in vitro* NER assay (see below), the protein is expected to function in a preincision step of NER (Ref. 37). In a number of XP-A patients, the XPAC gene contains aberrant splicing signals and nonsense codons, many of which are expected to completely inactivate it (Ref. 38 and references therein). In general, there is a good correlation between the severity of the mutation and the severity of the clinical features.

XPCC. Unfortunately, the predicted 823 amino acid sequence of XPCC does not provide interpretable clues to its function. The absence of *XPCC* mRNA in many XP-C patients suggests that complete inactivation of the gene is not lethal[19].

ERCC1. Deletion analysis of *ERCC1* indicates that the five carboxy-terminal amino acids of the protein residing in a region that has significant homology with the carboxyl terminus of Uvr C, are indispensable for its repair function (our unpublished observations). The corresponding part of Uvr C is similarly essential[39]. Another parallel between ERCC1 and Uvr C is that absence of the entire amino-terminal region appears not to have a drastic effect on the repair function of the proteins. There is recent evidence that ERCC1 resides in a complex with several other NER proteins: the products of the as yet uncloned *ERCC4*, *ERCC11*

and *XPFC* genes (our unpublished results). Since group 1 and 4 mutants, unlike other rodent NER mutants, are extremely sensitive to crosslinking agents, the ERCC1 complex may also play a role in the repair of (a subset of) DNA cross links. One of the partners of ERCC1 in this complex could be the human counterpart of RAD1: the yeast protein is tightly associated with the ERCC1 homologue, RAD10 (Ref. 1). The role of these proteins in mitotic recombination, and the presumed ability of RAD1 to remove regions of non-homology from the 3' end of recombining DNA molecules[1], are compatible with the idea that this complex may be responsible for, or associated with, incision, and (when required for the elimination of interstrand cross links) with an additional recombination step.

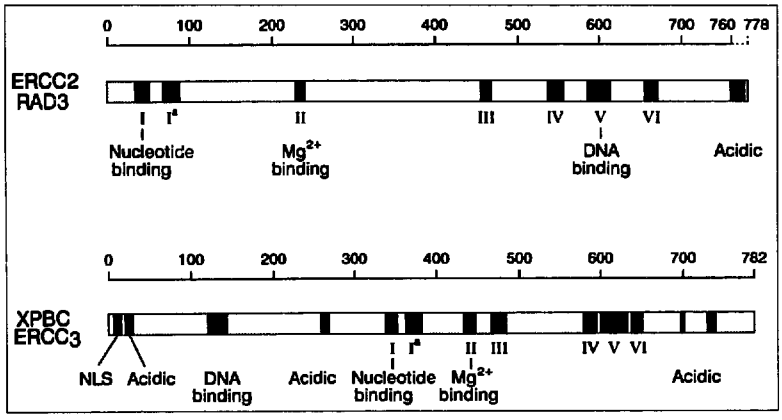

FIG 2

Comparison of the ERCC2/RAD3 and XPBC/ERCC3 proteins. Both proteins are schematically represented with the predicted functional domains shown as black boxes. Motifs I and VI comprise seven consecutive sequence elements that match domains conserved between superfamilies of DNA and RNA helicases. The scale corresponds to the number of amino acids in the protein. NLS, nuclear location signal.

ERCC2 and ERCC3. The primary amino acid sequences of ERCC2 and ERCC3 suggest that they are helicases[23,30]. Helicases are known to operate in a wide variety of cellular processes including replication, recombination, transcription, splicing and translation (reviewed in Ref. 40). Two helicases have already been demonstrated in the *E. coli* NER reaction: the $UvrA_2B$ complex involved in scanning for lesions and possibly in attachment of UvrB at the site of the damage, and UvrD, involved in releasing the damaged oligonucleotide after incision[1]. ERCC2 and ERCC3 could play similar roles in mammalian NER, or could even function in steps that do not exist, or have not been discovered, in *E. coli*. It is interesting to note that there are intriguing parallels between ERCC2 and ERCC3 (Ref. 23):

(1) *ERCC2* and *ERCC3* mutants are very similar;

(2) The proteins have a similar degree of sequence conservation with their yeast cognates RAD3 and RAD25/SSL2 (Refs 30–32).

(3) The proteins are of similar size and their seven 'helicase' motifs suggest a DNA-unwinding function (Fig. 2). Very recently, evidence for helicase activity of ERCC3 has been obtained[41]. The *ERCC3* gene product was identified by Egly and co-workers[41] as one of the components of the human TFIIH/BTF2 transcription factor, which is required for initiation of transcription of genes by RNA polymerase II. Highly purified fractions of TFIIH have an ATP-dependent helicase activity strongly associated with the ERCC3 subunit of the complex[41]. Other evidence for a role for ERCC3 in gene expression has come from the yeast gene *RAD25/SSL2* (Ref. 1) and from the work of Mounkes *et al.*[42], who have identified the *Drosophila* homologue of *ERCC3* as the gene mutated in *haywire* mutants. These mutants show various defects including male-sterility, which is thought to be caused by reduced expression of the *B2t* tubulin gene required for normal spermatogenesis[42].

A role for ERCC3 in transcription (and subtle defects in this process caused by mild mutations in the gene) may explain some of the clinical symptoms of XP-B that are not easily accounted for by the NER defect. These include the severe growth defect and the dysmyelination of neurons. The latter phenotype may be related to the expression level of the myelin basic protein that, at least in mice, critically determines the degree of CNS myelination[43]. This suggests that defects in group XP-B represent, at least in part, a transcription syndrome.

An important question remains: how can ERCC3 be involved in both transcription and nucleotide excision? Two options can be envisaged. The simplest interpretation is that ERCC3 catalyses a DNA unwinding step both in transcription initiation and in NER. A second possibility is that ERCC3 functions only in transcription initiation, and that some mutations in the protein have an adverse effect on the transcription of one or more DNA repair genes, indirectly resulting in a NER defect[31]. One would then have to assume that the strict dependence of such a repair gene on optimal functioning of ERCC3 has been preserved in eukaryotic evolution from yeast to *Drosophila* and to humans.

Considering the remarkable similarities between ERCC2 and ERCC3, it is tempting to speculate that these proteins act together in the same step of transcription initiation and the NER reaction, perhaps forming a helicase complex required for local melting of the double helix, to allow entry of RNA polymerase or NER proteins, and/or their translocation along the DNA template[24]. Evidence that supports the latter function for RAD3 has been reported recently[44]. As schematically depicted in Fig. 3, the XPAC protein and/or the protein mutated in XP-E (Ref. 45) might also constitute part of such a complex. It is also possible that ERCC2 and ERCC3 are required for release of the damage-containing oligonucleotide after incision, and turnover of bound NER proteins.

ERCC5. Homology searches of the 1186 amino acid ERCC5 (XPGC) sequence revealed an overall similarity with the RAD2 protein. In addition, two regions of

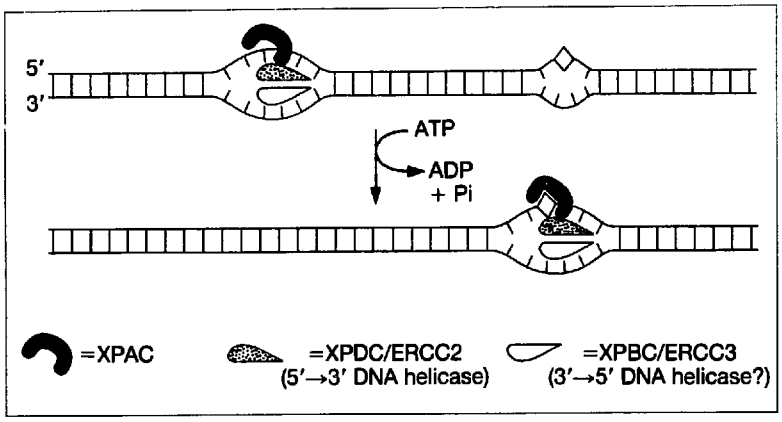

FIG 3

Speculative model for the concerted action of the presumed ERCC2 and ERCC3 helicases and the postulated damage recognition protein XPAC in scanning DNA for structural distortions. The XP-E protein might also participate in this complex, as it also has damage-specific DNA binding activity [45].

100 and 140 amino acid residues showed a high degree of homology with an open reading frame on chromosome XI of *S. cerevisiae*, the function of which is not known[26,27]. Unfortunately, the primary sequences of these RAD2 family members yield few clues to their possible function in NER.

ERCC6. The predicted sequence of the 1493 amino acid protein ERCC6, which belongs to the RAD16 subfamily, again reveals putative helicase domains[24]. The anticipated nucleic acid unwinding activity of ERCC6 should fit into the mechanism of the strand-selective repair of active genes that is defective in CS-B. At least two possibilities (or a combination of these) can be envisaged. First, the protein may be involved in scanning the transcribed strand for a blocked RNA polymerase, thus guiding the NER machinery to lesions that thwart transcription. Second, the DNA or DNA/RNA unwinding activity may be involved in unwinding the RNA–DNA duplex closely behind the transcription complex, thus dissociating it from the template and removing steric hindrance to the lesion. These speculative models can be tested by biochemical experiments using the purified proteins and a bona fide *in vitro* repair assay system.

Mammalian NER *in vitro*

An *in vitro* NER assay using cell-free extracts promises to help resolve the reaction mechanism of mammalian NER (Refs 46, 47). This system permits the use of defined, damaged DNA substrates and purified proteins or antibodies to dissect the reaction into discrete steps and to determine the components involved. Fractionation of cell extracts has revealed that many factors, including the XP-A protein and human single-stranded binding protein (HSSB), are required for the generation of incised intermediates[37]. Recent analysis of the products of incision has demonstrated that, as in *E. coli*, an asymmetric dual incision is made in a damaged template[48]. The 5' incision in human NER is made further upstream, and one or two nucleotides more 3' of the injury than in *E. coli*, generating a 29 bp lesion-containing oligonucleotide[48]. After incision, DNA synthesis is apparently carried out by DNA polymerase δ or ε, since this reaction is dependent on the proliferating cell nuclear antigen[37] (PCNA). DNA polymerase δ is normally implicated in leading strand synthesis of semi-conservative DNA replication. These findings therefore reveal that part of the replication machinery is also used in repair reactions, and illustrate that there is considerable overlap between these fundamental processes that metabolize DNA.

Concluding remarks

The known or postulated properties of the eukaryotic NER genes, and analogy with the main steps of the *E. coli* pathway, suggest the following scenario for NER in mammals:

(1) The ERCC2/ERCC3/XPAC and possibly XPEC proteins are involved in detection of lesions, with the helicases scanning the DNA helix, and XPAC and XPEC recognizing the lesion. ERCC2 may also be implicated in this step.

(2) Upon encountering a lesion, the complex locally denatures the DNA; this specific denatured conformation is recognized by the ERCC1/ERCC4/ERCC11/XPFC complex, which performs the dual incision. The Uvr C-like carboxy terminus of ERCC1 could play an important role in this reaction.

(3) HSSB, PCNA and DNA polymerase are involved in removal of the damage-containing oligonucleotide, turn over of the incision complex and resynthesis of DNA.

Future research will undoubtedly reveal whether this speculative scenario bears any relation to the actual situation within the cell. Although complete elucidation of the eukaryotic NER reaction mechanism may still seem far away, the contours of the systems are beginning to emerge from the pieces of the puzzle that have already been identified; the yeast model is expected to be of great importance because of its versatility and relative simplicity. Furthermore, valuable tools are available in the form of *in vitro* repair assay systems.

Finally, we should soon see the NER genes that have already been cloned being used to generate repair-deficient transgenic mice by targeted gene inactivation. Such mouse models may yield valuable insight into how the molecular defect is translated into clinical features, such as predisposition to cancer, and into the origin of the clinical heterogeneity observed in human disorders. They may also prove very important for studies related to ageing, neurodegeneration and assessment of the genotoxicity of mutagenic agents.

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References

1 Hoeijmakers, J.H.J. (1993) *Trends Genet.* 9, 173–177
2 Friedberg, E.C. (1985) *DNA Repair*, Freeman
3 Bohr, V.A. (1991) *Carcinogenesis* 12, 1983–1992
4 Cleaver, J.E. and Kraemer, K.H. (1989) in *The Metabolic Basis of Inherited Disease* (Scriver, C.R., Beaudet, A.L., Sly, W.S. and Valle, D., eds) (Vol. II), pp. 2949–2971, McGraw Hill
5 Nance, M.A. and Berry, S.A. (1992) *Am. J. Med. Genet.* 42, 68–84
6 Lehmann, A.R. (1987) *Cancer Rev.* 7, 82–103
7 Peserico, A., Battistella, P.A. and Bertoli, P. (1992) *Neuroradiology* 34, 316–317
8 Venema, J. *et al.* (1990) *Proc. Natl Acad. Sci. USA* 87, 4707–4711
9 Vermeulen, W. *et al.* (1991) *Mutat. Res.* 255, 201–208
10 Lehmann, A.R. *et al.* (1975) *Proc. Natl Acad. Sci. USA* 72, 219–223
11 Stefanini, M. *et al.* (1992) *Mutat. Res.* 273, 119–125
12 Johnson, R.T. and Squires, S. (1992) *Mutat. Res.* 273, 97–118
13 Stefanini, M. *et al. Am. J. Hum. Genet.* (in press)
14 Venema, J. *et al.* (1991) *Mol. Cell Biol.* 11, 4128–4134
15 de Jonge, A.J.R. *et al.* (1985) *Mutat. Res.* 150, 99–105
16 Riboni, R. *et al.* (1992) *Cancer Res.* 52, 6690–6691
17 Collins, A.R. (1993) *Mutat. Res.* 293, 99–118
18 Hoeijmakers, J.H.J., Odijk, H. and Westerveld, A. (1987) *Exp. Cell Res.* 169, 111–119
19 Legerski, R. and Peterson, C. (1992) *Nature* 359, 70–73
20 Hoeijmakers, J.H.J. and Bootsma, D. (1990) *Cancer Cells* 2, 311–320
21 Lehmann, A. *et al.* (1992) *Mutat. Res.* 273, 1–28
22 Fletjer, W.L. *et al.* (1992) *Proc. Natl Acad. Sci. USA* 89, 261–265
23 Weeda, G. *et al.* (1990) *Cell* 62, 777–791
24 Troelstra, C. *et al.* (1992) *Cell* 71, 939–953
25 van Duin, M. *et al.* (1989) *Mutat. Res.* 217, 83–92
26 Scherly, D. *et al. Nature* (in press)
27 O'Donnovan, A. and Wood, R.D. *Nature* (in press)
28 Bankmann, M., Prakash, L. and Prakash, S. (1992) *Nature* 355, 555–558
29 van Duin, M. *et al.* (1986) *Cell* 44, 913–923
30 Weber, C.A., Salazar, E.P., Stewart, S.A. and Thompson, L.H. (1990) *EMBO J.* 9, 1437–1447
31 Gulyas, K.D. and Donahue, T.F. (1992) *Cell* 69, 1031–1042
32 Park, E. *et al.* (1992) *Proc. Natl Acad. Sci. USA* 89, 11416–11420
33 McKay, M. and Hanawalt, P. (1992) *Mutat. Res.* 274, 157–161
34 Robins, P. *et al.* (1991) *EMBO J.* 10, 3913–3921
35 Eker, A.P.M. *et al.* (1992) *Mutat. Res.* 274, 211–224
36 Tanaka, K. *et al.* (1990) *Nature* 348, 73–76
37 Shivji, M.K.K., Kenny, M.K. and Wood, R.D. (1992) *Cell* 69, 367–374
38 Satokata, I., Tanaka, K., Yuba, S. and Okada, Y. (1992) *Mutat. Res.* 273, 203–212
39 Liu, J.J. and Sancar, A. (1991) *Proc. Natl Acad. Sci. USA* 88, 6824–6828
40 Matson, S.W. and Kaiser-Rogers, K.A. (1990) *Annu. Rev. Biochem.* 59, 289–329
41 Shaeffer, L. *et al.* (1993) *Science* 260, 58–63
42 Mounkes, L.C. *et al.* (1992) *Cell* 71, 925–937
43 Popko, P. *et al.* (1987) *Cell* 48, 713–721
44 Naegeli, H., Bardwell, L. and Friedberg, E.C. (1993) *Biochemistry* 32, 613–621
45 Chu, G. and Chang, E. (1988) *Science* 242, 564–567
46 Wood, R.D., Robins, P. and Lindahl, T. (1988) *Cell* 53, 97–106
47 Sibghat-Ullah, Husain, I., Carlton, W. and Sancar, A. (1989) *Nucleic Acids Res.* 17, 4471–4484
48 Huang, J-C., Svoboda, D.L., Reardon, J.T. and Sancar, A. (1992) *Proc. Natl Acad. Sci. USA* 89, 3664–3668

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