Minireview

THE JOURNAL OF BIOLOGICAL CHEMISTRY
Vol. 270, No. 27, Issue of July 7, pp. 15915–15918, 1995

Excision Repair in Mammalian Cells*

Aziz Sancar‡

From the Department of Biochemistry and Biophysics, University of North Carolina School of Medicine, Chapel Hill, North Carolina 27599

There are two types of structural anomalies that lead to mutation, a permanent change in DNA sequence. The first class involves normal bases in abnormal sequence context (mismatch, bulge, loop). The second class, which is referred to as DNA damage or DNA lesion, involves abnormal nucleotides (modified, fragmented, cross-linked) in normal sequence context. DNA lesions, in addition to causing mutations, also constitute replication and transcription blocks.

Both types of structural anomalies are rectified by a series of enzymatic reactions referred to by the general term DNA repair (1–5). The repair reactions employed for correcting mismatches and lesions are similar in principle. The incorrect or damaged base is removed either as a base (base excision) or as an (oligo)nucleotide (nucleotide excision), the single-stranded gap resulting from the excision reaction is filled in by a polymerase (repair synthesis), and the newly synthesized DNA is ligated. Hence, there are two basic assays for measuring repair (6): the "incision/excision assay" and the "repair synthesis assay."

Excision Repair

In base excision repair the mismatched or damaged base is cleaved off the deoxyribose by a DNA glycosylase, and the resulting apurinic/apyrimidinic (AP)[1] deoxyribose is released by sequential actions of an AP lyase which cleaves 3′ and an AP endonuclease which cleaves 5′ to the AP site. The one-nucleotide gap is filled in and ligated (Fig. 1).

Nucleotide excision repair, conceptually, can be accomplished by two basic mechanisms. In one, a phosphodiester bond is hydrolyzed 5′ or 3′ to the mismatch (lesion), and then the incorrect base is removed by a 5′ to 3′ (or 3′ to 5′) exonuclease, which hydrolyzes DNA one nucleotide at a time starting at the nick and digesting past the lesion. This is the repair mode employed by both *Escherichia coli* and human general mismatch correction (repair) systems (1, 2). This endonuclease/exonuclease reaction pathway is not utilized for removing damaged bases from DNA. A possible explanation for this is that most base adducts eliminated from DNA by excision repair inhibit exonucleases. One way to circumvent this problem is to have an enzyme system that nicks the damaged strand on both sides of the lesion at some distance removed from the lesion. This second mechanism, indeed, is the excision repair mechanism found in all species investigated. As a matter of common practice, "excision repair" without further qualification means nucleotide excision repair of DNA damage, and hence it will be used as such in this review.

In excision repair, both procaryotes and eucaryotes hydrolyze the 3rd to 5th phosphodiester bond 3′ to the lesion; on the 5′ side the procaryotes hydrolyze the 8th (4) and the eucaryotes hydrolyze the 21st to 25th phosphodiester bond (7, 8). Thus procaryotes excise damage in 12–13-nt-long oligomers and eucaryotes excise 27–29-nt-long fragments. This dual incision activity is referred to as excision nuclease (excinuclease). The single-stranded gap generated by either type of excision is filled in by DNA polymerases and sealed by ligase.

Genetics of Excision Repair

The excision repair genes (*uvrA*, *uvrB*, and *uvrC*) of *E. coli* show no homology to the human excision repair genes (1). In contrast, the sequences of excision repair genes in mammalian cells and yeast are highly homologous, and the enzymology of excision repair in these two systems is very similar (1, 3). Only mammalian excision repair will be covered in this review. Three human diseases are caused by a defect in excision repair (9): xeroderma pigmentosum, Cockayne's syndrome, and trichothiodystrophy.

Xeroderma pigmentosum patients suffer from photosensitivity, photodermatoses including skin cancers, and in some cases from neurological abnormalities. XP patients are defective in excision repair. Mutations in 7 genes, *XPA* through *XPG*, cause XP. In addition, there is a group of patients with classic symptoms of XP but with normal excision repair. These are called XP variants (XP-V). Cells from XP-V patients are moderately sensitive to UV light but excise UV photoproducts at a normal rate and are defective in a biochemically ill defined phenomenon called postreplication repair (10).

Cockayne's syndrome patients suffer from growth failure, mental and neurological abnormalities, cataracts, dental caries, and photosensitivity and related dermatoses. Mutations in two groups of genes appear to cause Cockayne's syndrome. The CS-A and CS-B (ERCC-6) mutants exhibit classical CS symptoms without an increased rate of skin cancer. Cells from these patients have near normal UV sensitivity. A second group of patients manifest XP symptoms in addition to CS symptoms. Patients in this group have mutations in the *XPB*, *XPD*, or *XPG* genes.

Trichothiodystrophy (TTD) patients have ichthyosis and brittle hair and suffer from photosensitivity, skeletal abnormalities, and mental retardation. The patients may or may not have an increased rate of skin cancer. Mutations in three genes are associated with TTD. In the XP/TTD overlapping syndrome, the mutation is in either *XPB* or *XPD*. In classical TTD (TTD-A), the mutation is presumably in one of the other subunits of TFIIH (1).

In addition to the 9 genes identified by human diseases to be involved in excision repair, many rodent excision repair mutants have been isolated and characterized in order to define the entire set of excision repair genes (11, 12). The rodent mutants fall into 11 complementation groups, and the majority of these correspond to human XP and CS complementation groups as indicated. In fact, some of the human XP genes were cloned by virtue of complementing rodent mutant cell lines and hence are also referred to as excision repair cross complementing (ERCC) genes. Of these genes, *XPE* and *ERCC6* through *ERCC11* are not required for the basal excision reaction (13).

Structure and Function of Excision Repair Proteins

Table I summarizes some of the properties of excision repair proteins. Most of these proteins are in complexes *in vivo*, and hence the activity associated with a solitary protein *in vitro* may or may not be relevant to its function in excision repair. Human excision nuclease has been reconstituted in a defined system by mixing six highly purified polypeptides or polypeptide complexes (13).

XPA—This protein of 31 kDa has a zinc finger and is involved in damage recognition (14). It also interacts with several other components of excision repair and hence may function as a nucleation factor for excinuclease. XPA interacts through its N-terminal domain with the ERCC1-XPF heterodimer (6) to form a relatively stable complex (15, 16); it also binds to TFIIH through its C-terminal domain (17). Finally, RPA (HSSB) binds to XPA and increases its specificity for damaged DNA (18). In addition to XPA,

* This minireview will be reprinted in the 1995 Minireview Compendium, which will be available in December, 1995.

‡ To whom correspondence should be addressed: Dept. of Biochemistry and Biophysics, CB# 7260, University of North Carolina School of Medicine, Chapel Hill, NC 27599-7260. Tel.: 919-962-0115; Fax: 919-966-2852.

[1] The abbreviations used are: AP, apurinic/apyrimidinic; nt, nucleotide(s); XP, xeroderma pigmentosum; CS, Cockayne's syndrome; TTD, trichothiodystrophy; ERCC, excision repair cross-complementing; RPA, replication protein A; HSSB, human single-stranded binding protein; TFIIH, transcription factor IIH; Pol, polymerase; PCNA, proliferating cell nuclear antigen.

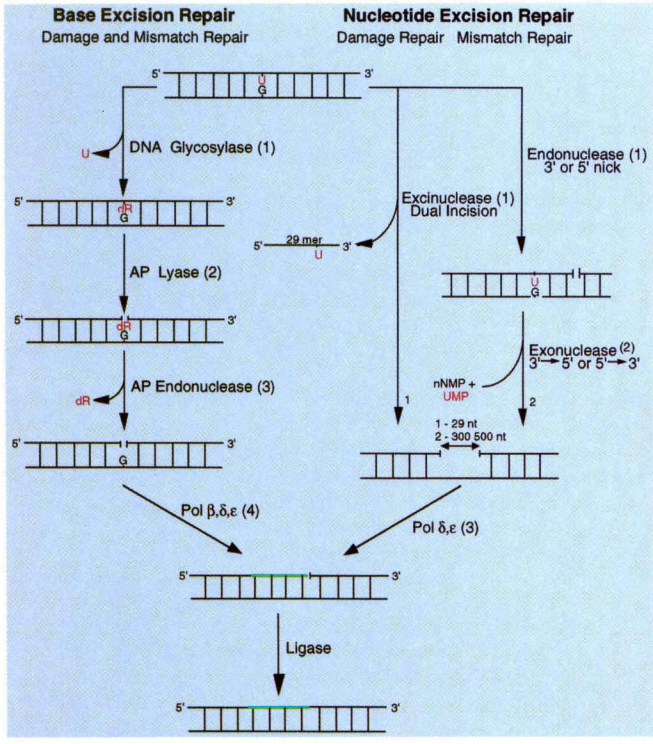

FIG. 1. **Mismatch and damage excision repair.** For simplicity a deaminated C is taken as an example of both mismatch and damage. The repair of mismatch and lesions by base excision follows the same pathway. Removal of damage by nucleotide excision occurs by dual incision, whereas removal of mismatches by nucleotide excision occurs by endonuclease/exonuclease action. The size of repair patches are 1–4 nt for base excision (66, 67), 27–29 nt for damage repair by nucleotide excision (7), and 300–500 nt for mismatch repair by the nucleotide (general) mismatch repair system (2).

other proteins that specifically bind to damaged DNA have been identified. One of these, the DDB protein, is absent in some XPE patients (19–22). However, this protein is not required for excision repair (13), and its relation to *XPE* gene is unclear at present. Another class of proteins that bind to certain types of damaged DNA have the HMG (high mobility group) domain (23, 24); however, these proteins inhibit excision repair (25).

RPA(HSSB)—This trimer of $(p70)_1(p34)_1(p11)_1$ is essential for DNA replication (26, 27) and for repair synthesis (28). It is also absolutely required for the dual incision step of excision repair (13). It binds to damaged DNA with moderate affinity and makes a complex with XPA that binds to lesions with higher affinity than either component alone (18).

TFIIH—This is a multiprotein (p89, p80, p62, p44, p41, p38, p34) complex that contains XPB (p89) and XPD (p80). TFIIH was initially identified as one of the seven general transcription factors required for basal transcription by RNA polymerase II (29). The accidental discovery that its p89 subunit is identical to XPB (30) and the unexpected finding of failure of XP-B and XP-D mutant cell-free extracts to complement in excision assay (6) led to the eventual realization that the entire TFIIH complex is a repair factor (31, 32). XPB and XPD proteins are DNA-dependent ATPases, have the so-called helicase motifs, and they, as well as TFIIH itself (29), can dissociate short fragments annealed to single-stranded DNA (1, 3). This modest helix unwinding activity is referred to as helicase by some investigators.

XPC—The sequence of the gene predicts a protein of 125 kDa. This polypeptide co-purifies with a protein of 58 kDa, which is the human homolog of the yeast Rad23 protein (HHR23B). Thus, the functional form of XPC is a $(p125)_1(p58)_1$ heterodimer (33). XPC heterodimer binds to TFIIH loosely (31) and binds very tightly to single-stranded DNA (33).

ERCC1-XPF Complex—This is a very stable complex such that a heterodimer formed with a mutant protein does not exchange subunits *in vitro* and, as a result, cell-free extracts from XP-F and ERCC-1 do not complement for excinuclease activity (6). XPF (120 kDa) and ERCC1 (33 kDa) make a complex with $(p112)_1(p33)_1$ stoichiometry (13) and bind to XPA through the N-terminal half of ERCC1 (15). The ERCC1-XPF complex is an endonuclease specific for single-stranded DNA.[2]

XPG—This protein has a single-stranded specific endonuclease activity (34–36). It also acts as a double-stranded specific exonuclease (34). It binds loosely to TFIIH (13) and to RPA (18) and is apparently recruited by these components to the excision nuclease complex.

Mechanism of Excision Repair

The three formal steps of excision repair are damage recognition, dual incision (excision), and repair synthesis and ligation.

Damage Recognition—Excision repair was first identified by the failure of UV-sensitive *E. coli* and human cells to remove thymine dimers from DNA. However, this repair system is not specific for UV damage as it excises all covalent DNA lesions tested (37–39). With regard to substrate recognition and preference, three interrelated questions must be addressed. Does the enzyme system recognize only DNA with damaged bases, how does the enzyme "know" which strand should be cut, and finally, what is the molecular basis for recognition?

First, damaged bases are not the sole substrate for the enzyme. Human excinuclease excises mismatched bases and 1–3-nt loops as well (38). However, in contrast to the true mismatch repair system, the excinuclease apparently has no way of discriminating the correct and incorrect strands and as a consequence excises the mismatch from either strand.

Regarding the problem of identifying the damaged strand from the undamaged one, the example of mismatch repair by excinuclease shows that the enzyme may not always be able to discriminate the damaged and undamaged strands. This point has not been investigated in detail. However, with thymine cyclobutane dimer there was no excision of the undamaged strand at a rate of 5% of the damaged strand (the detection limit of the assay). Thus, clearly with damage as opposed to mismatch, the enzyme has a mechanism of discriminating the right and wrong strands.[3]

This fact leads to the third question that was raised with regard to substrate recognition: what is the molecular basis of damage recognition? The simple answer at present is: we don't know. The following facts are of relevance in searching for an answer for this question. (i) Although lesions that cause gross helical deformity are repaired, those that do not are also repaired, and there is no linear relationship between the specificity coefficient (k_{cat}/k_m) of the excinuclease and the degree of helical deformity (39, 40). (ii) Recognition involves a protein complex that has a preference for damaged DNA (XPA-RPA) and a complex (TFIIH) with ATP-dependent local unwinding activity that is recruited to the damage site and, based on the precedent in *E. coli*, unwinds DNA and makes the ultimate damaged DNA-protein preincision complex. (iii) Recently, it has been found that three repair enzymes with rather narrow substrate specificity, namely DNA photolyase (pyrimidine dimers), uracil glycosylase (uracil in DNA), and exonuclease III (AP site), flip out the lesion from the duplex into a "hole" within the enzyme to bring the active site cofactor or residues in close contact with the target bonds (40–42). Whether the excinuclease system flips out the damaged nucleotide(s) or the entire excised fragment remains to be seen (43).

Dual Incision/Excision—The molecular details of mammalian excision repair are now known in considerable detail. Sixteen polypeptides are necessary and sufficient for excinuclease activity (13) as shown in Fig. 2.

The XPA-RPA complex binds to the damage site; then XPA recruits TFIIH, which makes a preincision complex in an ATP hydrolysis-dependent manner. XPC helps stabilize the precincision complex. The ATP-dependent unwinding of the DNA by TFIIH primes it for nuclease attack by the two XP proteins known to have nuclease activity. XPG is recruited by TFIIH and incises on the 3′ side (13, 44), and ERCC1-XPF, which is recruited by XPA, incises on the 5′ (44) side of the damage. The dual incision is absolutely dependent on ATP hydrolysis (8).

The major sites of incision are relatively precise and are at the

[2] C.-H. Park and A. Sancar, unpublished observation.
[3] A. Kazantsev and A. Sancar, unpublished observation.

TABLE I
The 16 polypeptides required for excision repair in mammalian cells

Fraction	No.	Proteins (M_r)	Activity	Role in repair
I. XPA	1	XPA (p31)	DNA binding	Damage recognition
II. RPA	2	p70	DNA binding	Damage recognition
	3	p34		
	4	p11		
III. TFIIH	5	XPB/ERCC3 (p89)	(*a*) DNA-dependent ATPase	(*a*) Formation of preincision complex
	6	XPD/ERCC2 (p80)	(*b*) Local unwinding	(*b*) Transcription repair coupling
	7	p62	(*c*) Transcription factor	
	8	p44	(*d*) Cdk-activating kinase	
	9	Cdk7 (p41)		
	10	CycH (p38)		
	11	p34		
IV. XPC	12	XPC (p125)	DNA binding	
	13	HHR23B (p58)		
V. XPF	14	XPF/ERCC4 (p112)	Nuclease	5′-Incision
	15	ERCC1 (p33)		
VI. XPG	16	XPG/ERCC5 (p135)	Nuclease	3′-Incision

5th phosphodiester bond 3′ and the 24th phosphodiester bond 5′ to the lesion (7, 8). However, the incision sites show some variability. The site of 3′ incision extends from the 3rd through the 8th phosphodiester bond (7, 8), and the site of 5′ incision extends from the 20th through the 26th phosphodiester bond (8). The combination of these incision patterns usually results in excision of fragments 24–32 nt in length; however, 27–29-nt fragments are the dominant species. The sites of incision are influenced by several factors, including the type of lesion (38) and the sequence context (37, 39). The same incision pattern has been observed *in vivo* in *Xenopus* eggs (8) and in cell-free extracts from *Schizosaccharomyces pombe*[4] and is considered to be the universal incision pattern for eucaryotes (4).

Repair Synthesis—In contrast to the excision reaction we know less about the details of the repair synthesis step. It is known that repair synthesis is PCNA-dependent and hence must be carried out by Polδ and Polϵ (45, 46), and, since PCNA is the polymerase clamp loaded onto template-primer by RFC replication factor, RFC may also be required. In a study with cell-free extract Polδ antibodies specifically inhibited repair synthesis (47), and in a highly purified *in vitro* system for repair synthesis it was found that Polϵ and even Klenow fragment of PolI performed repair synthesis pointing to the difficulty of assigning repair polymerase from *in vitro* reconstitution systems (48). Most likely, both Polδ and Polϵ participate in the repair synthesis step of excision repair (49).

Transcription-Repair Coupling

Transcribed sequences and in particular the template strand within a transcribed sequence are repaired at a higher rate than non-transcribed sequences (50). Cells from CS patients are defective in strand-specific repair (51). In *E. coli*, a transcription-repair coupling factor encoded by the *mfd* gene displaces stalled RNA polymerase and releases the stalled complex while recruiting the damage recognition complex of excinuclease (52). However, at present there is no *in vitro* system for transcription-repair coupling in mammalian cells. The *CSB* gene encodes a protein of 160 kDa, which contains the so-called helicase motifs and is likely to function in a manner analogous to the *E. coli* Mfd protein (50). Thus, a simple model for strand-specific repair based on behavior of CS-A and CS-B mutants and of the proteins is as follows.

RNA polymerase II stalled at a lesion is recognized by the CSA-CSB complex, which causes the polymerase to back off the lesion without disrupting the ternary complex. The CSA-CSB complex also recruits XPA and TFIIH to the lesion site and thus helps in the assembly of the excinuclease. The lesion is excised and the excision gap is filled in. The backed off RNA polymerase elongates the truncated transcript (53).

Regulation of Excision Repair

It appears that mammalian cells do not possess an SOS response like that in *E. coli* where DNA damage by bulky agents increases the transcription of excision repair genes (54). Similarly, damage-induced post-translational modification of repair proteins (55, 56) does not affect the activity of human excinuclease (57).

The connection between the p53 tumor suppressor protein and DNA repair has been the source of much speculation and debate because the p53 protein is stabilized by DNA damage and it is a transcriptional regulator. It has been reported that p53 protein binds to XPB (58) and RPA (59), both of which are essential for basal excision repair. However, p53(−/−) cells excise the two major UV photoproducts, pyrimidine dimers, and 6–4 photoproducts at the same rate as wild type cells and are equally resistant to UV

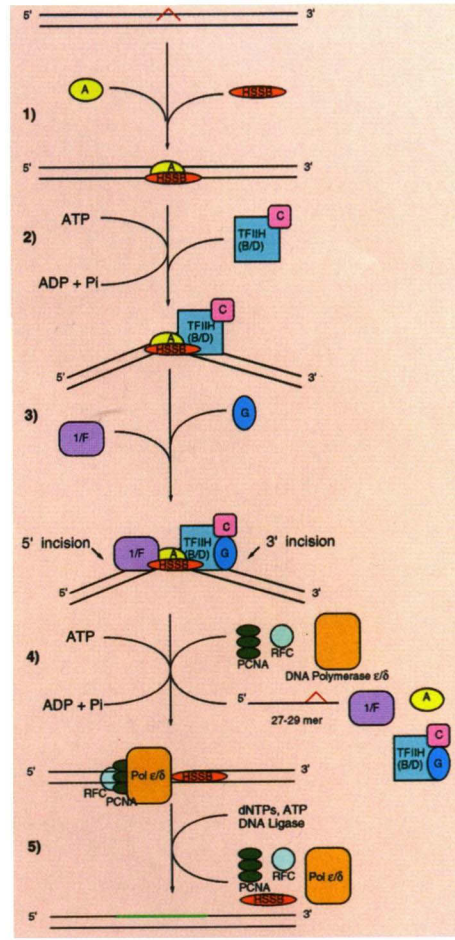

FIG. 2. **Model for mammalian excision repair.** Step *1*, ATP-independent damage recognition. Step *2*, ATP-dependent formation of preincision complex. It is quite likely that only a subset of the proteins shown is present in the actual preincision complex. Some may act as molecular matchmakers and dissociate after formation of the preincision complex. Step *3*, dual incision. The two incisions occur in random order. Step *4*, replacement of the excision proteins by repair synthesis proteins. Step *5*, repair synthesis and ligation.

[4] J. C. Huang and A. Sancar, unpublished observation.

(60). Similarly, p53 protein at nearly micromolar concentrations has no effect on excision repair in a defined system.[3] Finally, the report that the p53-induced Gadd45 protein stimulates excision repair (61) has not been confirmed.[3] Thus, existing data are consistent with the notion that p53 does not modulate excision repair either positively or negatively.

In contrast, the recent discovery that Cdk7 and cyclin H, which make up the Cdk-activating kinase, are constituents of TFIIH (62, 63) raises interesting possibilities regarding cell cycle regulation and DNA repair. Excision repair capability of the cell does not change during the cell cycle (64). However, replication and repair may be coordinated by differential effects of p21(Cip/WAF) on replicative and repair DNA synthesis (65). Future research is likely to uncover interesting interconnections between DNA repair, replication, cell cycle, and apoptosis.

REFERENCES

1. Friedberg, E. C., Walker, G. C., and Siede, W. (1995) *DNA Repair and Mutagenesis*, ASM Press, Washington, D. C.
2. Modrich, P. (1994) *Science* **266,** 1959–1960
3. Prakash, S., Sung, P., and Prakash, L. (1993) *Annu. Rev. Genet.* **27,** 33–70
4. Sancar, A. (1994) *Science* **266,** 1954–1956
5. Sancar, A. (1995) *Annu. Rev. Genet.* **29,** in press
6. Reardon, J. T., Thompson, L. H., and Sancar, A. (1993) *Cold Spring Harbor Symp. Quant. Biol.* **58,** 605–617
7. Huang, J. C., Svoboda, D. L., Reardon, J. T., and Sancar, A. (1992) *Proc. Natl. Acad. Sci. U. S. A.* **89,** 3664–3668
8. Svoboda, D. L., Taylor, J.-S., Hearst, J. E., and Sancar, A. (1993) *J. Biol. Chem.* **268,** 1931–1936
9. 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. 2, pp. 2949–2971, McGraw-Hill, New York
10. Boyer, J. C., Kaufmann, W. K., Brylawski, B. P., and Cordeiro-Stone, M. (1990) *Cancer Res.* **50,** 2593–2598
11. Thompson, L. H., Busch, D. B., Brookman, K., Mooney, C. L., and Glaser, D. A. (1981) *Proc. Natl. Acad. Sci. U. S. A.* **78,** 3734–3737
12. Collins, A. R. (1993) *Mutat. Res.* **293,** 99–118
13. Mu, D., Park, C.-H., Matsunaga, T., Hsu, D. S., Reardon, J. T., and Sancar, A. (1995) *J. Biol. Chem.* **270,** 2415–2418
14. Robins, P., Jones, C. J., Biggerstaff, M., Lindahl, T., and Wood, R. D. (1991) *EMBO J.* **10,** 3913–3921
15. Li, L., Elledge, S. J., Peterson, C. A., Bales, E. S., and Legerski, R. J. (1994) *Proc. Natl. Acad. Sci. U. S. A.* **91,** 5012–5016
16. Park, C.-H., and Sancar, A. (1994) *Proc. Natl. Acad. Sci. U. S. A.* **91,** 5017–5021
17. Park, C.-H., Mu, D., Reardon, J. T., and Sancar, A. (1995) *J. Biol. Chem.* **270,** 4896–4902
18. He, Z., Henricksen, L. A., Wold, M. S., and Ingles, J. C. (1995) *Nature* **374,** 566–568
19. Chu, G. (1994) *J. Biol. Chem.* **269,** 787–790
20. Kataoka, H., and Fujiwara, Y. (1991) *Biochem. Biophys. Res. Commun.* **175,** 1139–1143
21. Keeney, S., Wein, H., and Linn, S. (1992) *Mutat. Res.* **273,** 49–56
22. Reardon, J. T., Nichols, A. F., Keeney, S., Smith, C. A., Taylor, J. S., Linn, S., and Sancar, A. (1993) *J. Biol. Chem.* **268,** 21301–21308
23. Bruhn, S. L., Pil, P. M., Essigmann, J. M., and Lippard, S. J. (1992) *Proc. Natl. Acad. Sci. U. S. A.* **89,** 2307–2311
24. Pil, P. M., and Lippard, S. J. (1992) *Science* **256,** 234–237
25. Huang, J. C., Zamble, D. B., Reardon, J. T., Lippard, S. J., and Sancar, A. (1994) *Proc. Natl. Acad. Sci. U. S. A.* **91,** 10394–10398
26. Hurwitz, J., Dean, F. B., Kwong, A. D., and Lee, S. H. (1990) *J. Biol. Chem.* **265,** 18043–18046
27. Henricksen, L. A., and Wold, M. S. (1994) *J. Biol. Chem.* **269,** 24203–24208
28. Coverley, D., Kenny, M. K., Munn, M., Rupp, W. D., Lane, D. P., and Wood, R. D. (1991) *Nature* **349,** 538–541
29. Drapkin, R., and Reinberg, D. (1994) *Trends Biochem. Sci.* **19,** 504–508
30. Schaeffer, L., Roy, R., Humbert, S., Moncollin, V., Vermeulen, W., Hoeijmakers, J. H. J., Chambon, P., and Egly, J.-M. (1993) *Science* **260,** 58–63
31. Drapkin, R., Reardon, J. T., Ansari, A., Huang, J. C., Zawel, L., Ahn, K., Sancar, A., and Reinberg, D. (1994) *Nature* **368,** 769–772
32. Schaeffer, L., Moncollin, V., Roy, R., Staub, A., Mezzina, M., Sarasin, A., Weeda, G., Hoeijmakers, J. H. J., and Egly, J.-M. (1994) *EMBO J.* **13,** 2388–2392
33. Masutani, C., Sugasawa, K., Yanagisawa, J., Sonoyama, T., Vi, M., Enomoto, T., Takio, K., Tanaka, K., van der Spek, P., Bootsma, D., Hoeijmakers, J. H. J., and Hanaoka, F. (1994) *EMBO J.* **13,** 1831–1843
34. Habraken, Y., Sung, P., Prakash, L., and Prakash, S. (1994) *J. Biol. Chem.* **269,** 31342–31345
35. O'Donovan, A., Scherly, D., Clarkson, S. G., and Wood, R. D. (1994) *J. Biol. Chem.* **269,** 15965–15968
36. Habraken, Y., Sung, P., Prakash, L., and Prakash, S. (1994) *Nucleic Acids Res.* **22,** 3312–3316
37. Mu, D., Bertrand-Burggraf, E., Huang, J. C., Fuchs, R. P. P., and Sancar, A. (1994) *Nucleic Acids Res.* **22,** 4869–4871
38. Huang, J. C., Hsu, D. S., Kazantsev, A., and Sancar, A. (1994) *Proc. Natl. Acad. Sci. U. S. A.* **91,** 12213–12217
39. Huang, J. C., and Sancar, A. (1994) *J. Biol. Chem.* **269,** 19034–19040
40. Park, H. W., Kim, S. T., Sancar, A., and Deisenhofer, J. (1995) *Science,* in press
41. Mol, C. D., Kuo, C. F., Thayer, M. M., Cunningham, R. P., and Tainer, J. A. (1995) *Nature* **374,** 381–386
42. Savva, R., MacAuley-Hecht, K., Brown, T., and Pearl, L. (1995) *Nature* **373,** 487–493
43. Hsu, D. S., Kim, S. T., Sun, Q., and Sancar, A. (1995) *J. Biol. Chem.* **270,** 8319–8327
44. Matsunaga, T., Mu, D., Park, C.-H., Reardon, J. T., and Sancar, A. (1995) *J. Biol. Chem.* **270,** in press
45. Nichols, A. F., and Sancar, A. (1992) *Nucleic Acids Res.* **20,** 2441–2446
46. Shivji, M. K. K., Kenny, M. K., and Wood, R. D. (1992) *Cell* **69,** 367–374
47. Zeng, X. R., Jiang, Y., Zhang, S. J., Hao, H., and Lee, M. Y. W. T. (1994) *J. Biol. Chem.* **269,** 13748–13751
48. Aboussekhra, A., Biggerstaff, M., Shivji, M. K. K., Vilpo, J. A., Moncollin, V., Podust, V. N., Protic, M., Hubscher, U., Egly, J.-M., and Wood, R. D. (1995) *Cell* **80,** 859–868
49. Budd, M. E., and Campbell, J. L. (1995) *Mol. Cell. Biol.* **15,** 2173–2179
50. Hanawalt, P. C. (1994) *Science* **266,** 1457–1458
51. Venema, J., Mullenders, L. H. F., Natarajan, A. T., van Zeeland, A. A., and Mayne, L. V. (1990) *Proc. Natl. Acad. Sci. U. S. A.* **87,** 4707–4711
52. Selby, C. P., and Sancar, A. (1993) *Science* **260,** 53–58
53. Donahue, B. A., Yin, S., Taylor, J.-S., Reines, D., and Hanawalt, P. C. (1994) *Proc. Natl. Acad. Sci. U. S. A.* **91,** 8502–8506
54. Fornace, A. J., Jr. (1992) *Annu. Rev. Genet.* **26,** 505–524
55. Liu, V. F., and Weaver, D. T. (1993) *Mol. Cell. Biol.* **13,** 7222–7231
56. Carty, M. P., Zernik-Kobak, M., McGrath, S., and Dixon, K. (1994) *EMBO J.* **13,** 2114–2123
57. Pan, Z. Q., Park, C.-H., Amin, A. A., Hurwitz, J., and Sancar, A. (1995) *Proc. Natl. Acad. Sci. U. S. A.* **91,** 4636–4640
58. Wang, X. W., Forrester, K., Yeh, H., Feitelson, M. A., Gu, J. R., and Harris, C. C. (1994) *Proc. Natl. Acad. Sci. U. S. A.* **91,** 2230–2234
59. Dutta, A., Ruppert, J. M., Aster, J. C., and Winchester, E. (1993) *Nature* **365,** 79–82
60. Ishizaki, K., Ejima, Y., Matsunaga, T., Hara, R., Sakamoto, A., Ikenaga, M., Ikawa, Y., and Aizawa, S. (1994) *Int. J. Cancer* **58,** 254–257
61. Smith, M. L., Chen, I. T., Zhan, Q., Bae, I., Chen, C. Y., Gilmer, T. M., Kastan, M. D., O'Connor, P. M., and Fornace, A. J., Jr. (1994) *Science* **266,** 1376–1380
62. Roy, R., Adamczewski, J. P., Seroz, T., Vermeulen, W., Tassan, J. P., Schaeffer, L., Nigg, E. A., Hoeijmakers, J. H. J., and Egly, J.-M. (1994) *Cell* **79,** 1093–1101
63. Shiekhattar, R., Mermelstein, F., Fisher, R., Drapkin, R., Dynlacht, B., Wessling, H. C., Morgan, D. O., and Reinberg, D. (1995) *Nature* **374,** 283–287
64. Lommel, L., Carswell-Crumpton, C., and Hanawalt, P. C. (1995) *Mutat. Res.* **336,** 181–192
65. Li, R., Waga, S., Hannon, G. J., Beach, D., and Stillman, B. (1994) *Nature* **371,** 534–537
66. Singhal, R. K., Prasad, R., and Wilson, S. H. (1995) *J. Biol. Chem.* **270,** 949–957
67. Demple, B., and Harrison, L. (1994) *Annu. Rev. Biochem.* **63,** 915–948