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REVIEW

Xeroderma pigmentosum genes: functions inside and outside DNA repair

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Xeroderma pigmentosum (XP) is an autosomal recessive disease, which is characterized by susceptibility to ultraviolet light (UV)-induced skin cancer. Among eight genes so far identified as responsible for XP, *XPA* through *XPG* are involved in nucleotide excision repair of DNA damage induced by UV as well as various chemical carcinogens. Since this repair system removes a major UV photoproduct, the cyclobutane pyrimidine dimer, quite slowly from the global genome, this lesion must be accurately bypassed during replication by DNA polymerase η, encoded by the *XPV* gene. Recent studies have revealed that each of these XP genes possesses additional functions, some of which are concerned with other DNA repair pathways and/or cellular DNA damage responses. Such differential functions not only explain clinical heterogeneity among different genetic complementation groups but also have implications for the promotion of carcinogenic processes in XP patients.

Introduction

Genomic DNA is highly susceptible to damage caused by its intrinsic instability, endogenously produced reactive oxygen species and a wide variety of environmental agents such as radiations and chemicals. Some lesions, like double strand breaks, can directly lead to chromosome aberrations (e.g. deletion, translocation, etc.), whereas structural changes in the bases often interfere with DNA replication in S-phase. When replicating DNA polymerases are blocked by base lesions on the template strand, the replication forks may collapse, thereby resulting in double strand breaks. In addition, depending on the type of lesions, certain DNA polymerases are capable of elongating DNA strands across damaged sites, and this translesion DNA synthesis (TLS) is frequently associated with replication errors, giving rise to mutations. To cope with such deleterious effects of DNA damage promoting carcinogenesis, organisms are equipped with multiple DNA repair systems (1,2).

Nucleotide excision repair (NER) is a versatile DNA repair system that eliminates a broad spectrum of base lesions generated on one strand, including ultraviolet light (UV)-induced cyclobutane pyrimidine dimer (CPD) and pyrimidine (6-4) pyrimidone photoproduct (6-4PP), as well as other bulky base adducts that can be induced by numerous chemical compounds (1,3). Although these lesions do not share common chemical structures, they are supposed to induce more or less distortion of the DNA helical structure (4). It is known that defects in NER are associated with several human autosomal recessive hereditary disorders, such as xeroderma pigmentosum (XP). Patients suffering from XP exhibit extreme sensitivity to sun exposure and a marked predisposition to skin cancer. Classical complementation analyses using cell fusion have identified eight genetic complementation groups in XP, for which the genes responsible are already cloned (5) (Table I). Seven of these groups, XP-A through XP-G, are associated with defective NER, while the remaining group, a variant form of XP (XP-V), is proficient in NER but deficient in a specialized DNA polymerase η (pol η) involved in TLS. This article overviews how these XP gene products function in DNA repair and prevent carcinogenesis.

Abbreviations: ATR, ataxia telangiectasia mutated and Rad3 related; BER, base excision repair; CPD, cyclobutane pyrimidine dimer; CS, Cockayne syndrome; GGR, global genome repair; ICLs, interstrand crosslink lesions; NER, nucleotide excision repair; PCNA, proliferating cell nuclear antigen; pol η, DNA polymerase η; 6-4PP, pyrimidine (6-4) pyrimidone photoproduct; RPA, replication protein A; TCR, transcription-coupled repair; TDG, thymine DNA glycosylase; TFIIH, transcription factor IIH; TLS, translesion DNA synthesis; TTD, trichothiodystrophy; UV, ultraviolet light; UV-DDB, UV-damaged DNA-binding protein; XP, xeroderma pigmentosum.

Roles for XP gene products in NER mechanism

DNA damage recognition by XPC. As the first step of NER, base lesions are sensed and located, for which at least two distinct mechanisms operate in parallel (1,3) (Figure 1). One of these NER subpathways, so called global genome repair (GGR), can operate anywhere in the genome, whereas the other, transcription-coupled repair (TCR), is specialized to eliminate lesions from the transcribed strand of active genes.

The GGR subpathway is relevant as it can reduce probabilities of DNA replication forks encountering lesions, thereby preventing chromosomal aberrations and mutations. One of the XP genes, *XPC*, encodes a basic protein (6,7) that is essential for damage recognition in GGR (8–10). XPC protein exists as a heterotrimeric complex containing one of the two human orthologs of *Saccharomyces cerevisiae* Rad23p (designated RAD23A and RAD23B) and centrin 2, which is known as a centrosomal protein belonging to the calmodulin superfamily (11,12). The yeast Rad23p and its mammalian homologs interact with both the 26S proteasome (13–15) and multiubiquitin chains (16–19), and the presence of this subunit significantly stabilizes the XPC protein *in vivo* (20,21) and *in vitro* (8,11,22,23). On the other hand, centrin 2 has been shown to potentiate the damage recognition function of the XPC complex (12,22).

The XPC complex exhibits DNA binding activity with preference for a branched DNA structure containing a junction between double- and single-stranded regions (24). Thus, the DNA helical distortion associated with local unwinding is a crucial factor for recognition by XPC and the NER machinery (25,26), so that DNA damage is even unnecessary for binding by XPC if the DNA contains some artificial structure like a bubble (27). Recent biochemical studies have revealed that XPC actually recognizes single-stranded configurations in the undamaged strand opposite a lesion (28), and this notion has been strongly supported by a structural analysis of the *S. cerevisiae* XPC ortholog, Rad4p, bound to damaged DNA (29). These biochemical properties seem to provide an important molecular basis by which GGR can handle various, structurally diverse base lesions. This also explains why GGR efficiency can vary depending on types of lesions: for instance, UV-induced CPDs that induce only a small helical distortion (30,31) are poorly recognized by XPC (8,27,32) and are removed much more slowly by GGR than 6-4PPs (33,34) that are much more distorting and easily recognized by XPC.

UV-DDB/XPE promotes the damage recognition process in GGR. Mammalian cells express another damage recognition factor

Table I. XP genes and functions of protein products

Gene	Protein size[a]	Protein product and its complex formation	Function	
XPE/DDB2	428 (48 kDa)	UV-DDB (DDBI–DDB2)	GGR	DNA damage recognition associates with cullin 4A ubiquitin ligase
XPC	940 (106 kDa)	XPC–RAD23–centrin 2	GGR	DNA damage recognition
XPB/ERCC3	782 (89 kDa)	TFIIH complex	GGR and TCR	DNA unwinding (helicases) damage verification?
XPD/ERCC2	760 (87 kDa)	XPB–XPD–p62–p52–p44–p34–p8–cdk7–cyclin H–MAT1	Transcription	Pre-incision complex assembly promoter opening RNA pol II phosphorylation
XPG/ERCC5	1186 (133 kDa)	XPG	GGR and TCR	Pre-incision complex assembly associates with TFIIH 3′-endonuclease
XPA	273 (31 kDa)	XPA	GGR and TCR	Pre-incision complex assembly damaged (kinked) DNA binding
XPF/ERCC4	905 (103 kDa)	ERCC1–XPF	GGR and TCR	5′-Endonuclease
XPV/POLH	713 (78 kDa)	Pol η	TLS	Replication bypass of CPDs

[a]Number of amino acids (calculated molecular weight).

that is specifically involved in GGR. UV-damaged DNA-binding protein (UV-DDB) was initially identified as a heterodimer consisting of DDB1 and DDB2 subunits, the latter of which corresponds to the *XPE* gene product (35–38). UV-DDB exhibits much higher binding affinity and specificity than XPC for certain types of lesions, particularly UV-induced photolesions (8,39). This is relevant for repair of CPD, since XPC poorly detects CPD by itself. In fact, CPD repair is severely impaired in fibroblast cells isolated from XP-E patients, while the same cells appear to remove 6-4PPs quite efficiently (40,41). It should be noted that UV-DDB never substitutes for the functions of XPC. XP-C fibroblasts totally lack GGR activity regardless of lesion types albeit the presence of functional UV-DDB (34,40). Furthermore, XPC is absolutely required for reconstitution of *in vitro* NER reactions, whereas UV-DDB is dispensable (42–44). XPC and UV-DDB physically interact (39) and, by using local UV irradiation technique, it was shown that UV-DDB promotes recruitment of XPC to UV-damaged sites *in vivo* (45–48). In addition to UV lesions, UV-DDB exhibits affinity for some chemical adducts, abasic sites and bubble-like structures (49–51), although the biological meanings of such binding remain to be understood.

Recently, it was shown that UV-DDB further associates *in vivo* with cullin 4A, Roc1 and the COP9 signalosome, which are known components of ubiquitin ligase (52). Ubiquitin ligase seems to be activated upon UV treatment of cells and, in turn, ubiquitylates XPC (39,53); and *in vitro*, DDB2 and cullin 4A also were found to be polyubiquitylated in addition to XPC. The reported degradation of DDB2 induced by UV irradiation is probably due to this autoubiquitylation (45,54,55), whereas ubiquitylation of XPC *in vivo* appears to be reversible (39). When DDB2 is polyubiquitylated *in vitro*, UV-DDB loses its damaged DNA-binding activity, whereas ubiquitylated XPC still retains its DNA-binding capacity. Based on these findings, we propose that ubiquitylation may assist UV-DDB to dissociate from the lesion, thereby promoting the lesion transfer from UV-DDB to XPC and the subsequent initiation of NER (39). Ubiquitin ligase associated with UV-DDB also induces ubiquitylation of histones, suggesting its roles in chromatin remodeling around the sites where repair occurs (56,57).

Alternative transcription-dependent damage recognition pathway. In the TCR subpathway, unlike GGR, the presence of damage is thought to be sensed as a blockage of translocation by elongating RNA polymerase II (58–60). This process requires neither XPC nor UV-DDB, so that TCR is normal in XP-C and XP-E cells (41,61). Conversely, Cockayne syndrome (CS) patients belonging to genetic complementation groups A and B are deficient in TCR, but not in GGR (62). They often manifest cutaneous photosensitivity but, unlike those with XP, no obvious susceptibility to skin cancer has been reported for CS-A and CS-B patients (2,63). However, it was also documented that both *Csa* and *Csb* knockout mice are actually predisposed to skin cancer if exposed to UV (64,65). Although the precise molecular mechanism underlying TCR still remains to be understood, this pathway ensures a rapid recovery of transcriptional activity and seems to prevent apoptosis induction (66–68).

Roles for XPB and XPD helicases in demarcation and verification of damage. Except for XPC and XPE (DDB2) which are specifically involved in GGR, the other NER-related XP groups (XP-A, B, D, F and G) show defects in both subpathways, indicating that the later steps of GGR and TCR are conducted by a common mechanism. After damage recognition specific for each subpathway, DNA duplex must be unwound around the lesion, a process that is accomplished by the basal transcription factor IIH (TFIIH). TFIIH is a multifunctional complex composed of 10 subunits (69), including the *XPB* and *XPD* gene products, both of which share seven conserved motifs with ATP-dependent DNA helicases (70,71). In GGR, TFIIH is probably recruited through a direct interaction with XPC, for which XPB and the 62-kDa subunit (p62) in TFIIH are responsible (10,72–76). TFIIH interacts also with RNA polymerase II, CSA, and CSB, which may be important for recruitment of TFIIH to the sites where TCR occurs (77–79).

XPB protein has a 3' to 5' helicase activity, whereas XPD helicase has an opposite directionality (5' to 3') (80–82). Both helicase activities are essential for NER (83,84). It was shown that XPD helicase is robustly stimulated by an interaction with the p44 subunit of TFIIH, and several mutations identified in some XP-D patients compromise this interaction (85). Biochemical studies revealed that translocation on single-stranded DNA by the *S. cerevisiae* XPD homolog, Rad3p, can be blocked by the presence of a lesion (86–88), implying that helicases could play some role in a damage recognition process. Although XPC can recognize and bind to artificial DNA structures like a bubble, the *in vitro* NER system never incises DNA unless there is a damaged base indeed present (27). This indicates that the presence of damage needs to be verified after the binding of XPC (26,27,89), and TFIIH helicases have been suggested to be involved in such a verification process (4,90,91). It has been proposed that the XPB and XPD helicases may scan individual DNA strands by moving in the same direction. According to this model, either of the two helicases may encounter a lesion, a mechanism that would allow direct discrimination between the damaged and undamaged strands. However, it has not yet been excluded experimentally that the two helicases may bind to the same strand and move in opposite directions to further open the DNA duplex.

Pre-incision complex assembly. Following the initial unwinding of DNA duplex by the TFIIH helicases, additional protein factors are assembled to form a complex containing fully opened DNA, called 'pre-incision' complex (75,92–94). One such factor is the *XPG* gene product, which belongs to a family of structure-specific

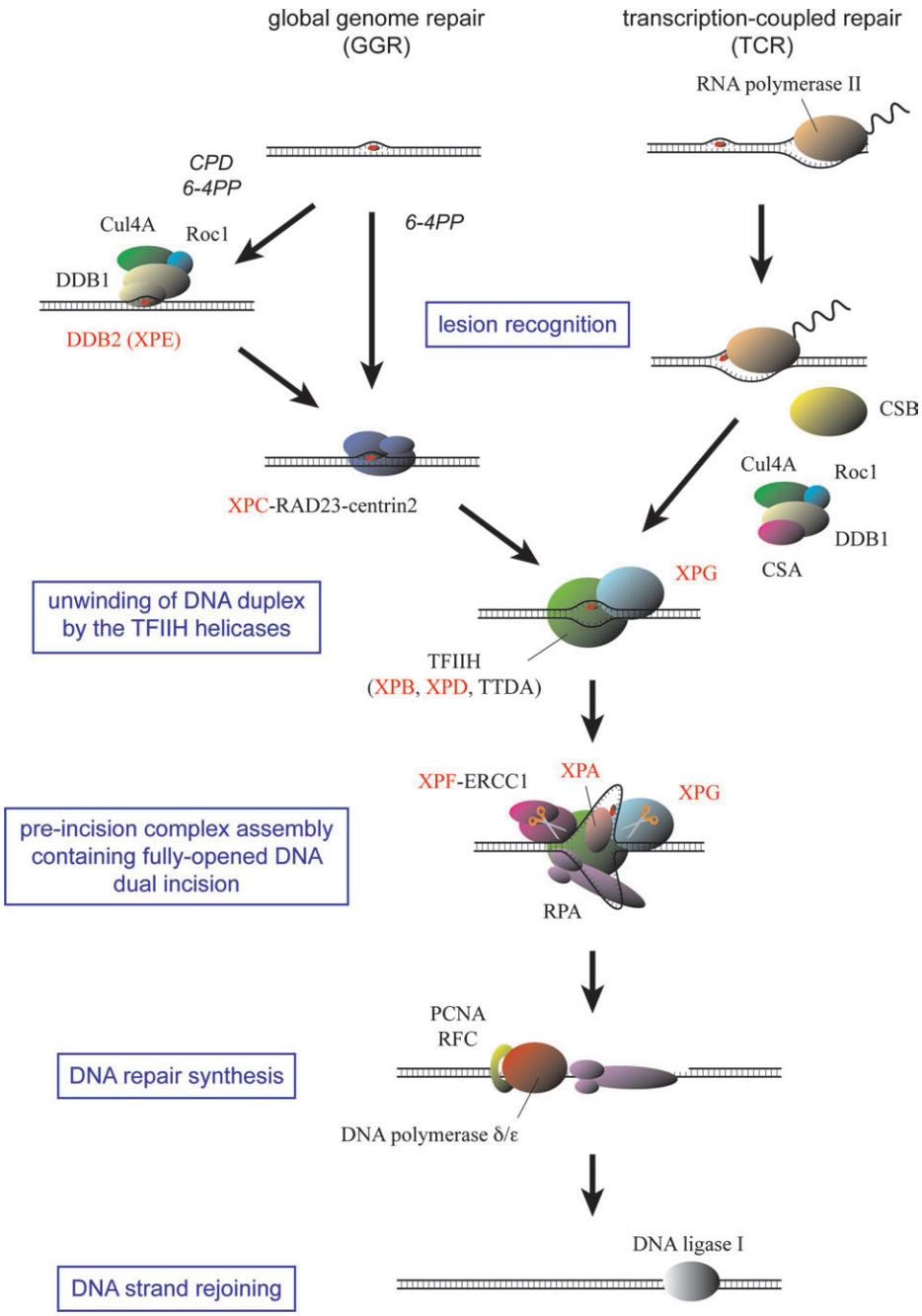

Fig. 1. Model of the human NER mechanism. XP gene products are highlighted in red. UV-DDB may facilitate recruitment of XPC, not only to CPD sites but also to 6-4PP sites, particularly when only a small number of lesions occur (32). See text for detail.

endonucleases involving flap endonuclease-1 (95). Although XPG protein functions as one of two endonucleases making dual incisions in a later step of NER (96,97), it is required structurally for formation of the fully opened DNA conformation apart from its catalytic function (98,99). A quite strong physical interaction has been demonstrated between XPG and TFIIH, and impairment of this interaction destabilizes the TFIIH complex, dissociating XPD and cdk-activating protein kinase subcomplex (containing cdk7, cyclin H and MAT1 subunits) (72,100). Although these findings raise the possibility that XPG may be recruited to damaged sites as a pre-assembled complex with TFIIH, sequential assembly models have been proposed from *in vivo* (10) and *in vitro* studies (75).

XPA protein is another XP gene product essential for assembly of the pre-incision complex. XPA contains a zinc-finger domain and exhibits a damaged DNA binding activity (101–104), but structural studies revealed that this zinc-finger domain is also involved in a protein–protein interaction with replication protein A (RPA) (105). RPA is an evolutionarily conserved, heterotrimeric protein complex that binds and stabilizes single-stranded DNA regions (106). Not only XPA but also RPA bind to damaged DNA with some specificity (107–109), which is significantly enhanced by the interaction between them (110). Although the XPA–RPA complex was originally thought to be responsible for primary damage recognition, accumulated *in vivo* and *in vitro* evidence shows that recruitment of XPA to lesion sites occurs later than TFIIH recruitment (10,75). Although precise roles for damaged DNA binding by XPA–RPA still remain to be understood, it was reported that purified XPA protein exhibits specific binding affinities for some kinked DNA substrates, including a three-way or four-way junction (111). This suggests that XPA may recognize a certain intermediate conformation of DNA that could

emerge during action of TFIIH helicases. In concert with such DNA binding, reported protein–protein interactions may facilitate recruitment and assembly of XPA and RPA into the pre-incision complex (74,112–114).

Dual incision by structure-specific endonucleases. After assembly of a pre-incision complex containing fully opened DNA, two single-strand breaks are introduced to the damaged strand by the ERCC1–XPF complex and XPG, releasing an oligonucleotide containing the damaged base(s). Among the factors required for dual incision, ERCC1–XPF is the last one assembled into the complex (10,75,115), and an interaction between ERCC1 and XPA seems to be crucial for its recruitment (116–118). Although both ERCC1–XPF and XPG are structure-specific endonucleases that cut DNA at a junction between double-stranded and single-stranded regions, they have different polarities: ERCC1–XPF cleaves DNA at the 5' boundary of a bubble structure (96,119), whereas XPG makes an incision at the 3' boundary (96,97,120). Positions of the two incision sites can vary significantly depending on types of lesions, but length of the excised oligonucleotide is almost constant, ranging between 24 and 32 nucleotides (96,121,122).

Theoretically, ERCC1–XPF and XPG can make incisions in both DNA strands of a bubble substrate, so that preceding discrimination of the damaged strand must be important to avoid erroneous cleavage of the undamaged strand. This might be accomplished through damage verification by TFIIH helicases (and, presumably, XPA–RPA), which may subsequently direct assembly of the pre-incision complex in the correct orientation. Within this complex, RPA probably binds to the undamaged strand and may guide the two endonucleases to their proper positions (112,123).

DNA repair synthesis. After excision of the damage-containing oligonucleotide, the resulting single-strand gap is filled by DNA polymerase. Biochemical studies using cell-free NER reactions revealed that this DNA repair synthesis depends on proliferating cell nuclear antigen (PCNA) (124,125). PCNA forms a homotrimeric clamp (126), which is loaded onto the 3' end of primers on template strands and supports processive chain elongation by DNA polymerases. Loading of the PCNA clamp requires a heteropentameric, DNA-dependent ATPase complex, called replication factor C (127–129). Purified PCNA, replication factor C and either DNA polymerase δ or ε have been used successfully for reconstitution of the *in vitro* repair synthesis, followed by strand rejoining by DNA ligase I (43,130).

It has been well documented that RPA bound to single-stranded templates stimulates many DNA polymerase activities. Indeed RPA is necessary not only for dual incision but also for subsequent repair synthesis *in vitro* (130). RPA probably binds and protects the undamaged strand and, upon dual incision, may recruit PCNA and replication factor C (75,131,132). Interaction between XPG and PCNA has been reported (133,134), which may also be involved in coordinating the dual incision and repair synthesis steps.

XP variant gene and TLS

Among the eight complementation groups, XP-V was found to be exceptional in that fibroblasts from those patients are proficient in NER, but have some defects in DNA replication after UV irradiation (135). In a cell-free simian virus 40 DNA replication system with substrates containing a site-specific CPD, blockage of strand elongation at the lesion site was evident in XP-V cell extracts but not in normal cell extracts (136). This finding led to identification of the *XPV* gene product as a DNA polymerase that can bypass CPDs on the template strand (137,138). This enzyme, designated as pol η, shares significant amino acid sequence homology with *S. cerevisiae* Rad30p and *Escherichia coli* DinB and UmuC (138,139), but not with 'classical' DNA polymerases. However, overall molecular structures of those DNA polymerases have turned out to be quite similar (140). The identification of pol η was followed by discovery of many new DNA polymerases in mammals, a number of which possesses TLS activity (141–146).

In general, replicative DNA polymerases exhibit such high fidelity that, like RNA polymerases in transcription, they often stall at damaged sites on the template strands (147). Since GGR of CPDs is particularly slow even in NER-proficient cells as discussed above, there is consequently a high probability for DNA replication forks to encounter CPDs, once the cells are exposed to UV. Stalling DNA polymerases need to be switched with TLS polymerases, but bypass efficiency as well as fidelity of the individual enzymes differ from each other depending on the type of lesions. For instance, pol η can elongate a DNA strand across the template CPD quite efficiently and accurately, while it can hardly bypass 6-4PPs (148–150). Other TLS polymerases are either unable to bypass CPDs or highly prone to misincorporation opposite the lesions (151–155). In XP-V patients lacking pol η, CPDs are bypassed by other TLS polymerases that are less accurate, thereby leading to a high incidence of misincorporation (Figure 2). DNA polymerase ζ may be involved in such a process, as it has been implicated in UV-induced mutagenesis (156–159), whereas a 'two-polymerase' model has also been proposed in which 6-4PP could be bypassed through sequential actions of pol η and pol ζ (160). Once replication errors occur at UV-damaged sites, mutations are fixed either by the following NER or by the next round of replication. Because low fidelity is a common characteristic of TLS polymerases (153,161–163), the length of strand elongation by pol η must be minimized to avoid superfluous mutations by switching back to replicative polymerases. This seems to be regulated at several levels, including low processivity of the enzyme itself (150,164), altered binding affinities for different template–primer structures (165) and interaction with a monoubiquitylated PCNA clamp (166,167).

Additional functions of the XP genes

As discussed above, each XP gene product plays an essential role in either removal of or replication bypass across UV-induced photolesions, explaining why XP patients are susceptible to UV-induced mutagenesis and carcinogenesis. However, evidence has accumulated that shows almost all of the XP factors have additional functions that appear to have further implications in carcinogenesis and/or other pathological consequences.

Transcriptional function of TFIIH. The most obvious examples of such multiple functions are found in XPB and XPD, both of which are essential components of the basal transcription factor TFIIH (80,81). Like unwinding of DNA duplex at damaged sites, TFIIH is involved in opening promoter regions prior to the initiation of RNA synthesis (168). Although both XPB and XPD helicases are essential for NER, the XPD helicase activity seems to be dispensable for transcription (84,169).

Since TFIIH is involved not only in both GGR and TCR but also in transcription, clinical outcomes caused by mutations in the *XPB* and *XPD* genes are quite variable (170,171). Within the TFIIH complex, XPD structurally connects the cdk-activating protein kinase complex with the core of TFIIH (172). Some mutations in the *XPD* gene compromise phosphorylation of nuclear receptors and other transcriptional activators by cdk7 in TFIIH, thereby affecting transactivation of the corresponding hormone-responsive genes (173–177). This may explain, at least partly, some clinical phenotypes of XP-D patients, such as the developmental defects and hypoplasia of the adipose tissues.

In addition to typical XP, there are a few cases of XP-B, XP-D and XP-G patients with combined features of XP and CS (63). As mentioned above, XPG strongly interacts with and stabilizes the TFIIH complex (72,100), and may be involved in initiation of TCR (178). Taken together with the cases of CS-A and CS-B, the CS features of these XP/CS patients (e.g. severe neurological dysfunctions) are probably due to defects in TCR (and possibly in transcription), in which involvement of some oxidative base lesions has been implicated. Furthermore, some of the *XPB* and *XPD* mutations have been shown to

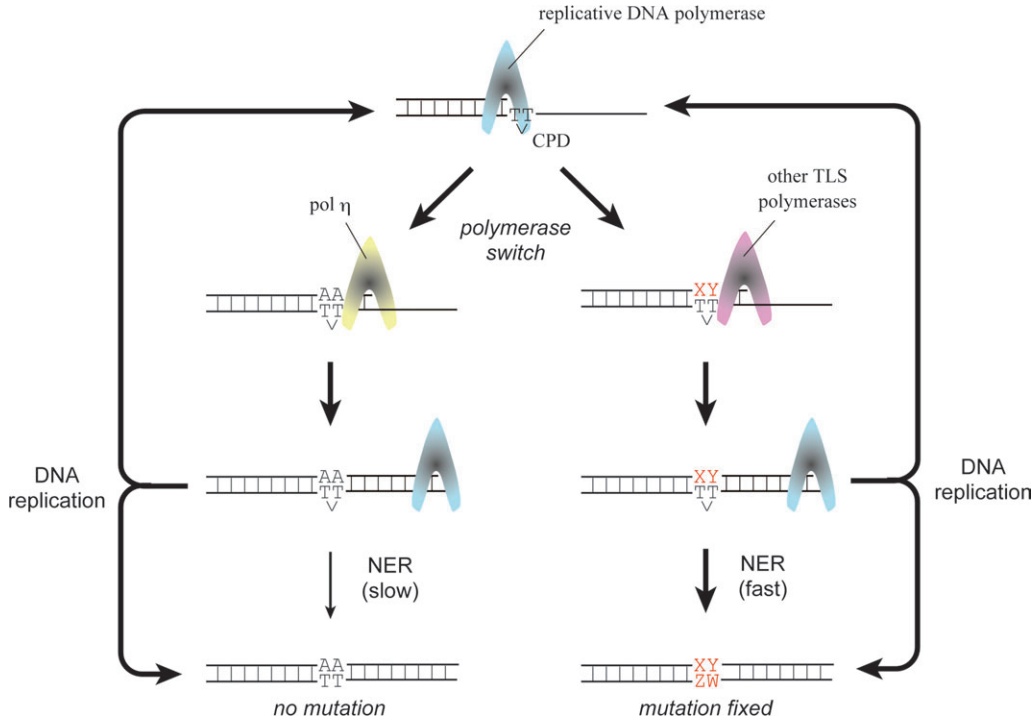

Fig. 2. Role of pol η in suppression of UV-induced mutagenesis. When replicative DNA polymerase stalls at CPD, pol η assumes strand elongation, incorporating the correct bases opposite of the lesion (left). In XP-V patients lacking pol η, CPD is bypassed by other TLS polymerases that are more prone to misincorporation (right). Once such mismatched CPDs occur, they are more easily recognized by NER than normal CPDs (14), thereby promoting fixation of mutations.

cause trichothiodystrophy (TTD) (170,179). Although TTD patients often exhibit sun sensitivity, the most characteristic symptom of this disease is brittle hair and nails caused by marked reduction in content of cysteine-rich matrix proteins. Physical and mental retardation as well as ichthyotic skin are also commonly associated with TTD, whereas development of skin cancers, as in CS, is usually unassociated. It has been recently shown that another repair deficient form of TTD (called TTD group A) is caused by mutations in the *GTF2H5* gene encoding one of the TFIIH subunits, TFB5 (p8) (69). Regardless of the affected genes (*XPB*, *XPD* or *TTDA*), fibroblasts from those TTD patients exhibit not only a severe defect in GGR but also greatly reduced levels of TFIIH (69,180). Thus, some defects in transcription in addition to NER deficiency have been implicated in TTD.

XP proteins involved in epigenetic control. In higher organisms, methylation of cytosine in DNA comprises an important epigenetic control mechanism, suppressing gene expression (181). The DNA methylation is induced and maintained through action of a family of enzymes called DNA methyltransferases. On the other hand, DNA can be 'passively' demethylated during replication, whereas molecular mechanisms underlying 'active' demethylation still remain to be understood (182). Recently it has been reported that the growth arrest and DNA damage-inducible protein 45α (Gadd45a) is involved in this active demethylation process (183). Expression of Gadd45a is induced in a p53-dependent manner in response to DNA damage as well as other various cellular stresses, and its functions have been implicated in DNA repair, damage checkpoints, centrosome duplication, and so on (184,185). Intriguingly, XPG and XPB (probably as part of the TFIIH complex) seem to be involved in the DNA demethylation induced by overexpression of Gadd45a. It is proposed that NER may serve as an active demethylation system excising the oligonucleotide containing a 5-methylcytosine, although evidence for participation of the whole repair machinery is lacking. If this were the case, XP patients (except for XP-V) might have defects not only in NER but also in inducing expression of a certain set of genes in response to DNA damage.

Stimulation of BER: implications in spontaneous mutagenesis. Many base excision repair (BER) substrates including oxidative base lesions poorly distort DNA duplex, so that they are usually not recognized by NER. However, some XP gene products have been shown to interact with and stimulate specific DNA glycosylases, initiators of BER, beyond their functions in NER.

The first example was reported for XPG, which interacts with human NTH1 protein (186). Human NTH1 is a DNA glycosylase that initiates BER by removing thymine glycol as well as other oxidized pyrimidine bases (187,188). This does not depend on the endonuclease activity of XPG, whereas XPG seems to promote binding of human NTH1 to the DNA substrates. Another XP protein related to BER is XPC, which was shown to interact with thymine DNA glycosylase (TDG) (189). TDG initiates BER by removing T (or U) from a G/T (or G/U) mismatch that can arise from spontaneous deamination of 5-methylcytosine (or C) (190). Thus, TDG is supposed to contribute to suppression of spontaneous mutations, although direct *in vivo* evidence for this is lacking. Unlike the stimulation of human NTH1 by XPG, XPC seems to enhance enzymatic turnover of TDG by promoting dissociation from its own product abasic sites (189,191). More recently, it has been reported that XPC also stimulates *in vitro* activity of hOGG1, which is mainly responsible for removal of a major mutagenic oxidative lesion, 8-oxoguanine (192). In this case, XPC appears to promote both DNA binding and turnover of hOGG1. This is in line with the recent report that XP-C fibroblasts are deficient in transcriptional reactivation of oxidized plasmid DNA (193). Furthermore, defective expression of *XPC* can somehow cause hypersensitivity to ionizing radiation, although this seems to be due to the impaired non-homologous end-joining pathway of double-strand break repair (194).

Given that the BER activities are compromised in some XP patients, elevation of spontaneous mutation frequency (derived from deamination and/or oxidation) may make certain contributions to the promotion of carcinogenesis in skin in addition to UV-induced mutations. Although some endogenously produced oxidative DNA lesions, like 8, 5′-cyclopurine 2′-deoxynucleosides, are recognized

by NER and have been implicated in occurrence of cancer and neurological degeneration in XP (195,196), the impaired BER activities may be responsible, at least partly, for development of internal tumors in XP patients (197). Elevated spontaneous mutagenesis as well as development of lung tumors was also observed in *Xpc*-deficient mice (198,199).

Checkpoint and apoptosis functions of XP genes. Besides removal of lesions *per se*, checkpoint controls play crucial roles in coordinating DNA repair, cell cycle arrest and apoptosis, thereby contributing to prevention of carcinogenesis through maintenance of genome integrity and exclusion of abnormal cells. The ataxia telangiectasia-mutated gene and its related gene *ATR* encode protein kinases, both of which belong to a family of phosphatidylinositol kinase and are involved in signaling pathways of DNA damage checkpoints (200). Particularly, the ataxia telangiectasia mutated and Rad3-related (ATR) kinase has been shown to be activated by various treatments causing DNA replication arrest, for instance, with DNA-damaging agents including UV as well as with inhibitors of DNA synthesis. An RPA-coated, single-stranded DNA region, which can be generated by stalling DNA polymerases, has been supposed to recruit ATR through interaction with the ATR-interacting protein (201–203). The activated ATR then phosphorylates target proteins including the main downstream effector Chk1 kinase.

A recent report has revealed that the ATR signaling pathway is compromised in XPA-deficient cells during S phase, as shown by translocation of ATR-interacting protein to subnuclear UV-damaged areas as well as by UV-induced phosphorylation of Chk1 and RPA (204). Similar defects were not observed in other NER-defective XP and CS cells, suggesting that XPA may be somehow involved in S phase checkpoint signaling apart from its NER functions. Another study has indicated that, in G_0/G_1 and G_2/M phases, the UV-induced phosphorylation of Chk1 and p53 depends on damage recognition by GGR, but not by TCR (205). Intriguingly, in yeast *S. cerevisiae*, the XPA homolog Rad14p interacts with Ddc1p (206), a component of the heterotrimeric checkpoint complex (a counterpart of the Rad9–Rad1–Hus1 complex in *Schizosaccharomyces pombe*) that shows a structural similarity to the PCNA clamp. On the other hand, UV-induced ATR activation is apparently enhanced in XP-V cells (204), possibly because their defect in TLS causes a delay of replication, thereby giving rise to more single-stranded regions after UV irradiation.

It has been well documented that p53 tumor suppressor plays key roles in DNA damage-induced checkpoints and apoptosis. Expression of the two human XP genes involved in the GGR damage recognition, *XPC* and *DDB2*, is positively regulated by p53 (40,207,208). Once p53 function is compromised, therefore, GGR activity might be reduced, which could further facilitate accumulation of mutations and, consequently, a carcinogenic process. In mice, however, the *DDB2* gene does not respond to p53 transactivation because of some mutations in its promoter sequence (209), whereas Chinese hamster cells are even deficient in the *DDB2* expression *per se* (41,210). These facts may explain the reduced GGR capacity of rodent cells, particularly removing UV-induced CPDs. In addition, it has been reported that a loss of functional DDB2 results in a severe decrease in p53 levels and in prevention of UV-induced apoptosis (211,212). This could result in anomalous survival of damaged cells and also contribute to the promotion of carcinogenesis. UV-DDB has been reported to interact also with the transcription factor E2F-1 (213,214), the c-Abl tyrosine kinase (215) and the histone acetyltransferases CBP/p300 (216), further suggesting its roles in DNA damage-responsive transcriptional regulation and/or chromatin remodeling processes.

Roles for ERCC1–XPF in other repair pathways. Among the NER-deficient XP groups, XP-F cells are quite unique, because they show an extremely high sensitivity to chemical compounds, such as cisplatin and mitomycin C, which can induce interstrand crosslink lesions (ICLs) (217,218). In bacteria, a molecular mechanism for repair of such ICLs has been proposed, where the whole NER machinery (the UvrABC system) is involved in making the first dual incision in either strand at the cross-linked site (219). Although the precise mechanism of ICL repair in eukaryotes still remains to be established, ERCC1–XPF endonuclease appears to have functions beyond NER. Notably, at least *in vitro*, ERCC1–XPF can make an incision within a DNA substrate that mimics the structure of a replication fork encountering an ICL (220), so that it may be capable of initiating ICL repair in a replication-coupled manner, independently from other XP factors. Alternatively, ERCC1–XPF may be required for a process repairing double-strand breaks, which can be generated when replication forks stall at ICLs (221). In line with such roles in ICL repair, ERCC1-deficient mice are known to exhibit very severe phenotypes including hematopoietic defects (222), which are not commonly associated with XP. Instead, such defects are characteristic of Fanconi anemia (223,224), another human cancer-prone syndrome, and cells from the patients with this disease show hypersensitivity to ICL-inducing agents (225).

Some types of DNA recombination and double-strand break repair also require functions of ERCC1–XPF. Its counterpart in *S. cerevisiae*, Rad1p–Rad10p, was shown to be involved in a certain pathway of double strand break repair called 'single-strand annealing' (226). ERCC1–XPF seems to be required for a similar process in mammalian cells (227) and plays an essential role in homologous gene targeting in mouse embryonic stem cells (228). Furthermore, in mammalian cells, ERCC1–XPF has recently been identified as a component of the telomeric TRF2 complex, thereby involved also in regulation of telomere integrity through its endonuclease activity (229,230). It has been proposed that an overexpression of TRF2 may result in telomere shortening through recruitment of ERCC1–XPF, thereby leading to premature aging and a cancer predisposition (231). Reduced DNA repair capacity caused by sequestration of ERCC1–XPF by telomeres may also contribute to manifestation of senescence features observed in the TRF2 transgenic mice, since a new progeroid syndrome and its relationship to DNA damage have recently been described with a patient carrying a particular missense mutation in the *XPF* gene and also with ERCC1–XPF-deficient mice. (232)

TLS polymerases in somatic hypermutation and homologous recombination. Unlike replicative DNA polymerases, pol η and other TLS polymerases commonly show quite low fidelity on undamaged DNA templates. In some cases, such 'error-prone' synthesis by TLS polymerases is vitally utilized to create sequence variability of specific genes. A most remarkable example is found in somatic hypermutation in the immunoglobulin genes (233,234). This process is supposed to be triggered by deamination of cytosine to uracil, which is catalyzed by an enzyme called activation-induced cytidine deaminase (235,236). The resulting U/G mismatch then can be processed by BER involving uracil DNA *N*-glycosylase (237), and misincorporation by TLS polymerases may occur during the DNA repair synthesis and/or a replication bypass across an intermediate abasic site (238,239). Accumulating evidence indicates that pol η is indeed involved in somatic hypermutations in the immunoglobulin genes, particularly at sites containing an A–T base pair (240–245). Although initiation of somatic hypermutation must be a strictly regulated event, it remains to be elucidated to what extent such low fidelity polymerases can be involved undesirably in NER, BER and other DNA transactions, thereby giving rise to mutations. In this regard, it is also notable that pol η has been recently shown to be involved in homologous DNA recombination (246,247).

Conclusions

As discussed above, the molecular mechanisms underlying human NER and the functions of seven XP proteins (XPA through XPG) therein have been elucidated to a considerable extent. However, *in vivo* regulation of this repair system has not yet been addressed extensively. For instance, both XPC and UV-DDB play key roles in a damage recognition process for GGR, but it remains to be elucidated how

these factors actually survey for occurrence of DNA damage throughout the huge genome. Do they perpetually move around within the nucleus and find lesions by chance? A mechanism that systematically scans along DNA seems more attractive, although evidence is lacking for the presence of such a mechanism. In this regard, involvement of chromatin structure and cell cycle regulation would need to be considered. Accumulating evidence indicates that *in vivo* NER processes may involve specific histone modifications like phosphorylation (248) and ubiquitylation (56,57,249) as well as chromatin remodeling factors such as CAF-1 (250,251).

Since CPD is removed by GGR quite slowly even in normal cells, the accurate replication bypass across this lesion is particularly important to prevent UV-induced mutagenesis. This is accomplished by XPV (pol η) with a highly efficient and accurate bypassing activity across CPD. Depending on the types of lesions that block replication, however, correct TLS polymerases must be chosen, and such a selection mechanism has been the interest of many researchers. Since the hypermutability of TLS polymerases seem to be vitally utilized in some cases, it is important to understand how participation of these enzymes is regulated *in vivo*.

Extra functions, beyond NER or TLS, of XP gene products differ from each other, explaining some of the heterogeneity of clinical phenotypes among different genetic complementation groups. Some of those functions, especially those related to DNA repair and cellular damage responses, are making it much more complicated than before to understand how the defect of each XP gene affects development of cancers and other clinical features. It would be also important to elucidate possible association of the polymorphisms of the XP genes with altered functions and a cancer risk (252). Further studies on the XP proteins, such as identification of new interacting partners, may unveil additional functions that would provide novel insights to the molecular pathology of this disease.

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