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# DNA Damage Recognition for Mammalian Global Genome Nucleotide Excision Repair

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## 1. Introduction

As a blueprint for genetic information, the structural and functional integrity of DNA must be maintained during cell division and gamete formation. However, this fundamental principle is threatened continuously by the vulnerability of DNA itself and/or by assaults from endogenously produced agents, such as reactive oxygen species and other metabolites, as well as various environmental agents including ultraviolet light (UV), ionizing radiation and chemical compounds (Friedberg et al., 2006). Among the DNA components, bases in particular are frequently the targets for such insults. Because DNA replication and transcription rely on the formation of specific base pairs, even a subtle change in the base structures can compromise faithful propagation and the expression of genetic information. For instance, replicative DNA polymerases, which exhibit very high intrinsic fidelity, are often blocked at sites where template bases are modified, which can lead to replication fork collapse and consequent chromosomal aberrations and/or cell death. This problem is overcome, at least partly, by translesion DNA synthesis, which is an error-prone process (Friedberg et al., 2005). To minimize the risk of mutagenesis, it is crucial for growing cells to detect and to remove damaged bases as much as possible before replication forks collide with them.

Nucleotide excision repair (NER) is a major DNA repair pathway that can eliminate an extremely broad spectrum of base damage. The NER substrates include dipyrimidinic UV photolesions, such as cyclobutane pyrimidine dimers (CPDs) and pyrimidine-pyrimidone (6-4) photoproducts (6-4PPs), intrastrand crosslinks caused by bifunctional alkylating agents (e.g., cisplatin), and bulky base adducts induced by numerous chemical carcinogens (Gillet & Schärer, 2006). The common feature shared by all of these insults does not reside in their chemical structure, but rather in the accompanying distortions of the otherwise regular DNA helical structure. Two subpathways are associated with mammalian NER: global genome NER (GG-NER) and transcription-coupled NER (TC-NER). GG-NER is a general pathway that operates throughout the genome. It minimizes the collision of replication forks with damaged bases and, thereby, contributes to the maintenance of genome integrity (Gillet & Schärer, 2006). TC-NER is specialized to remove transcription-blocking lesions from the template DNA strands, which ensures rapid recovery of transcriptional activity and thus averts apoptosis (Hanawalt & Spivak, 2008). In humans, hereditary defects in NER are associated with several autosomal recessive disorders, including xeroderma

pigmentosum (XP), Cockayne syndrome (CS) and trichothiodystrophy (TTD) (Bootsma et al., 2001). The clinical hallmarks exhibited by patients with XP, which include marked photosensitivity and a predisposition to skin cancer, explicitly indicate that the impaired repair of UV-induced DNA photolesions promotes mutagenesis and carcinogenesis in the skin. Numerous genetic complementation groups have been identified for the above diseases, including 8 for XP (XP-A through -G, and variant), 2 for CS (CS-A and -B) and 1 for TTD (TTD-A). Cloning of the responsible genes has revealed that all of them encode proteins involved in the NER pathway. The notable exception is the XP variant (*XPV*) gene encoding DNA polymerase  $\eta$  that is involved in translesion DNA synthesis, but not in NER. Another important milestone in elucidating the NER mechanism has been the establishment of the cell-free system, which faithfully recapitulates the NER reaction with human whole cell extracts. Together, genetic and biochemical studies have successfully identified more than 30 polypeptides that are involved in mammalian GG-NER (Fig. 1). A fundamental challenge for GG-NER is that the cells must detect a small number of injured bases among the vast excess of normal bases comprising the huge genome. Although the complete network of mechanisms has not yet been entirely uncovered, recent studies have revealed some of the sophisticated molecular mechanisms that accomplish this difficult task, which involves concerted actions of multiple protein factors. This chapter overviews the latest progress in our understanding of the damage-recognition mechanism for mammalian GG-NER.

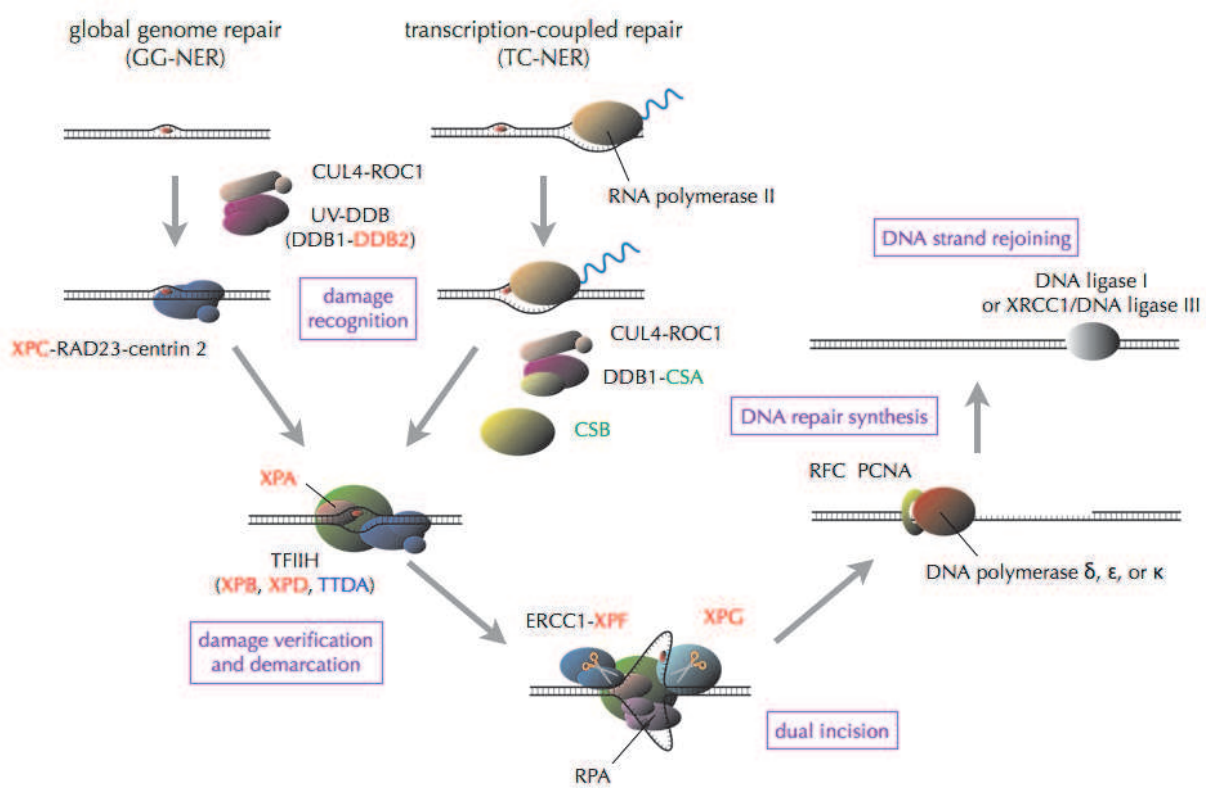


Fig. 1. Model of the mammalian NER mechanism. The 2 subpathways, GG-NER and TC-NER, differ in their strategies for initial damage recognition, but converge into a common process. The disease-related gene products are indicated by letters in different colors: XP, red; CS, green; TTD, blue.

## 2. Primary damage sensors for the initiation of GG-NER

One of the remarkable characteristics of GG-NER resides in its extremely broad substrate specificity, which encompasses UV-induced photolesions and other bulky base adducts that can be induced by numerous chemical compounds (Gillet & Schärer, 2006). These GG-NER substrates are associated with considerable levels of DNA helical distortion. This situation is in marked contrast to substrates for base excision repair (BER), such as uracils and oxidative base lesions, which are supposed to induce only marginal structural distortions. Initial damage detection for BER is accomplished by a set of DNA glycosylases, each of which exhibits a certain (partially overlapping) range of substrate specificity. In contrast, a virtually infinite spectrum of helix-distorting insults can be handled by the unified molecular machinery in GG-NER. In addition, GG-NER must survey the huge genome continuously and discriminate a small number of injured bases from normal bases with very high efficiency and accuracy. Recent biochemical studies have uncovered some of the sophisticated molecular mechanisms that achieve this difficult task.

### 2.1 Indirect sensing of DNA damage by XPC

The XPC gene was isolated from a cDNA expression library (Legerski & Peterson, 1992) that corrected the UV sensitivity of fibroblasts from patients with XP-C. Cells lacking XPC are incompetent for GG-NER, but TC-NER functions normally (Venema et al., 1990). By using the cell-free NER system, a protein factor that is missing in XP-C cells was purified from HeLa cell extracts (Masutani et al., 1994; Shivji et al., 1994). This biochemical approach revealed that the XPC protein forms a stable complex in vivo with 1 of the 2 human homologues of *Saccharomyces cerevisiae* Rad23p (designated RAD23A and RAD23B). Depletion of RAD23 markedly destabilized the XPC protein, thereby compromising GG-NER function (Ng et al., 2003; Okuda et al., 2004). Another component of the XPC complex, centrin-2 (Araki et al., 2001; Nishi et al., 2005), belongs to the calmodulin superfamily of small calcium-binding proteins containing 4 conserved EF-hand motifs. A subpopulation of centrin-2 localizes to the centrosomes and plays a vital role in cell cycle regulation (Lutz et al., 2001; Salisbury et al., 2002). Centrin-2 also binds to an  $\alpha$ -helix near the C-terminus of XPC: this interaction potentiates the DNA-binding activity of the complex (Bunick et al., 2006; Nishi et al., 2005; Popescu et al., 2003; Thompson et al., 2006).

The XPC protein complex has been known to be associated with DNA-binding activity since it was first purified (Masutani et al., 1994; Shivji et al., 1994), although its preference for damaged DNA was discovered sometime later (Batty et al., 2000; Sugasawa et al., 1998). With conventional electrophoretic mobility shift assays (EMSAs) and DNase I footprint analyses with defined DNA substrates, we demonstrated that XPC prefers to associate with sites containing a helix-distorting lesion, such as 6-4PP or *N*-(guanin-8-yl) *N*-acetyl-2-amino-fluorene (dG-AAF) adduct (Sugasawa et al., 1998; Sugasawa et al., 2001). However, the addition of an appropriate competitor DNA was necessary to reveal the damage specificity, by preventing XPC from binding to the undamaged part of the DNA. Several physicochemical approaches subsequently were undertaken to assess the affinities of XPC for various DNA structures in more dynamic states (Hey et al., 2002; Roche et al., 2008; Trego & Turchi, 2006).

Involvement of the XPC complex in the very early stages of NER was first proposed on the basis of the results obtained with the cell-free NER system (Sugasawa et al., 1998). In this system, 2 plasmid DNAs containing AAF adducts were preincubated separately with

different sets of NER factors, for which either XP cell extracts or purified recombinant proteins were used. After the 2 mixtures were combined and missing NER factors, if any, were supplemented, the initial repair rates of the 2 damaged DNA substrates were compared directly in one reaction. Damaged DNA preincubated in the presence of XPC was always repaired preferentially compared to DNA preincubated in its absence. Because a similar repair bias was not observed with other NER factors, these findings strongly suggest that XPC initiates *in vitro* NER, and its binding to damaged DNA is sufficient to recruit the whole repair machinery.

Several subsequent studies have supported this model. Local UV irradiation through micropore membrane filters has been used to visualize the recruitment of NER factors in cultured cells to the sites of DNA damage. Use of this method revealed that XPC accumulates at subnuclear UV-damaged areas, even when any other XP genes were mutated (Volker et al., 2001). Conversely, none of the other NER-related XP proteins (except for DDB2; see below) was recruited to the sites of DNA damage in XPC-deficient cells, consistent with the role of XPC as the initiator of GG-NER. Through the use of paramagnetic beads immobilized with a damaged DNA substrate, more refined biochemical studies were undertaken to determine the order of arrival and departure of individual NER proteins at the lesion: these studies also concluded that XPC arrives first (Riedl et al., 2003). It should be noted that only GG-NER is impaired in XP-C (and also XP-E) cells, unlike other NER-deficient XP cells, in which both GG-NER and TC-NER are affected. Considering that TC-NER is supposed to be triggered by RNA polymerase II stumbling at damaged bases on the template DNA strand, it could be assumed that the 2 NER subpathways vary only in their strategies for initial damage recognition and eventually merge into a common process.

Because XPC appeared to bind specifically to various lesions that did not share any common chemical structure, it was of great interest to understand which feature of DNA determined its binding specificity. To examine this, using EMSA, we tested XPC binding with various DNA substrates containing a defined lesion and/or artificial structure (Sugasawa et al., 2001; Sugasawa et al., 2002). XPC was able to recognize and to bind DNA duplexes containing a partially single-stranded region, such as bubble and loop structures, even though these substrates contained only base mismatches, but no chemical modifications. Further analyses using various oligonucleotides as competitors revealed that XPC was targeted preferentially to a branched DNA structure containing a double-stranded region attached to a single-stranded 3'-overhang. On the basis of these results, it might be better to refer to XPC as a *structure-specific DNA-binding factor*, rather than as a damage recognition factor.

The binding of XPC to sites of DNA damage seems to depend solely on the extent of local unwinding of the DNA duplex caused by a given lesion: typically, XPC showed very little affinity for sites of CPD, because of the subtle DNA helical distortion associated with this lesion. In contrast, the presence of 1 or 2 mismatched bases opposite the photodimer significantly enhanced binding by XPC (Sugasawa et al., 2001). Accordingly, this biochemical feature of XPC may provide an important molecular basis for the substrate specificity of GG-NER, including an infinite range of helix-distorting lesions, but not a number of nonbulky lesions, such as oxidized and deaminated bases.

More recently, a structural study corroborated this DNA-binding mode of XPC (Min & Pavletich, 2007). The *S. cerevisiae* NER protein Rad4p is presumed to be the counterpart of mammalian XPC: both proteins share several conserved structural domains in their C-terminal regions, including the transglutaminase-homology domain (TGD) and 3



consecutive  $\beta$ -hairpin domains (designated BHD1, BHD2, and BHD3). The X-ray crystal structure was solved with the C-terminal region of Rad4p bound to a short DNA duplex containing a CPD (which was placed within 3-base mismatches to enhance recognition by Rad4p). Consistent with the results of our footprint analyses with XPC, the results showed that Rad4p binds asymmetrically to the damaged DNA: it interacts with an 11-base pair segment of DNA duplex on the 3' side of CPD, mainly through TGD and BHD1, leaving the other double-stranded part on the 5' side of the lesion completely free. In the closer vicinity of the lesion, BHD3 is inserted into the major groove, such that BHD2 and BHD3 appear to pinch the phosphate-sugar backbone of the undamaged strand. As a result, 2 "normal" bases on the undamaged DNA strand are flipped out and held by BHD2-BHD3, while the CPD is also flipped out structurally disordered, and devoid of any contact with the protein (Fig. 2). The Rad4p binding results in a  $\sim 42^\circ$  bend of DNA, as observed by our scanning force microscopy with the XPC-DNA complex (Janićijević et al., 2003). In conclusion, XPC/Rad4p appears to function as a versatile damage-recognition factor that senses the presence of oscillating normal bases within the DNA duplex.

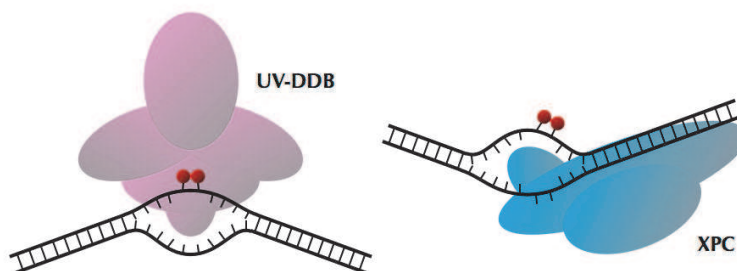


Fig. 2. Different binding modes of UV-DDB and XPC to damaged DNA sites. The  $\beta$ -hairpin of UV-DDB on the DDB2  $\beta$ -propeller is inserted between the two strands of the DNA, so that DDB2 interacts directly with the damaged nucleotides flipped out of the DNA duplex. In contrast, XPC interacts with normal bases on the undamaged DNA strand without any contact with the damaged bases.

## 2.2 UV-DDB facilitates detection of UV-induced photolesions

In accordance with the proposed function of XPC as the initiator of GG-NER, most of the DNA lesions that are subject to GG-NER *in vivo* are recognized by XPC *in vitro*. However, CPD serves as a noticeable exception. Like other GG-NER substrates, CPDs are not removed from the global genome in XPC-deficient cells, although XPC by itself cannot find this type of insult (as described above). From this apparent discrepancy, it can be assumed that a certain factor (other than XPC) is responsible for the initial detection of CPDs, whereas XPC must be involved in later steps.

UV-damaged DNA-binding protein complex (UV-DDB) was first discovered as a factor that bound UV-damaged DNA with high affinity and specificity. The factor responsible for this binding activity was purified and revealed as a complex consisting of 2 subunits, designated DDB1 and DDB2, respectively (for a review, see Tang & Chu, 2002). It was later demonstrated that mutations in the *DDB2* gene constitute the XP genetic complementation group E (Rapić-Otrin et al., 2003). Recent studies have redefined DDB1 as an adaptor protein that mediates interactions between the CUL4-ROC1 ubiquitin ligase complex and a member of the substrate-recruiting subunit family, called DDB1-CUL4 associating factor (DCAF)

(Angers et al., 2006; Lee & Zhou, 2007). The DNA-binding specificity of purified UV-DDB has been characterized extensively (Fujiwara et al., 1999; Payne & Chu, 1994; Reardon et al., 1993; Treiber et al., 1992; Wittschieben et al., 2005). Concerning UV-induced photolesions, UV-DDB exhibits extraordinarily high affinity and specificity for 6-4PPs, although it also binds CPDs moderately. Although binding to chemical-induced base adducts seems not to be pronounced, abasic sites are relatively good substrates for UV-DDB.

Despite the above biochemical characteristics that explicitly point to roles in UV-damage recognition, the impact of defects in UV-DDB on NER has remained enigmatic. Cells from patients with XP-E have defects in GG-NER, but not in TC-NER. However, in contrast to XP-C, cells from patients with XP-E are proficient in removal of 6-4PPs from the global genome, while repair of CPDs seems to be affected profoundly (Hwang et al., 1999; Tang et al., 2000). As a result, among the NER-deficient XP groups, XP-E cells show the highest levels of residual UV-induced unscheduled DNA synthesis (>50% of normal cells) and resistance to killing by UV (Tang & Chu, 2002).

Unlike other XP-related gene products, DDB2 reportedly accumulates to local UV-damaged areas within the nucleus, even in the absence of XPC (Wakasugi et al., 2002), although XPC can relocate to sites containing UV-induced DNA damage in a DDB2-independent manner (Moser et al., 2005). Although UV-DDB and XPC appear to be recruited independently, UV irradiation always induces a mixture of various sorts of DNA injuries, including 6-4PPs, CPDs, and other less frequent insults. To solve this problem, elegant experiments have been undertaken, in which 6-4PPs were erased soon after local UV irradiation with the aid of an ectopically expressed 6-4PP photolyase (Fitch et al., 2003). Under these conditions where the remaining photolesions were mostly CPDs, DDB2-dependent recruitment of XPC became evident. These results clearly indicate that differential pathways are used for the deployment of XPC to sites of UV damage, depending on the type of lesions.

Considering the role for UV-DDB in CPD repair and its much stronger binding to 6-4PPs, one could assume that UV-DDB plays a role in the detection and repair of 6-4PPs. However, 6-4PPs are rapidly removed from the global genome even in the absence of DDB2 (most likely through direct recognition by XPC), so that stimulation by UV-DDB, if any, cannot be clearly discerned. Additionally, DDB2 undergoes degradation by the proteasome in response to UV irradiation (see below) (Fitch et al., 2003; Rapić-Otrin et al., 2002). Since this degradation is quite fast – particularly at relatively high UV doses – this situation further overshadows possible effects of UV-DDB on the repair of 6-4PPs.

Recently, the local UV irradiation technique has been applied to the quantification of 6-4PPs, which appear as fluorescent spots developed by an antibody specific for the photolesion (Moser et al., 2005). With this method, the total number of generated photolesions per cell was reduced substantially, and retardation of 6-4PP repair in the absence of UV-DDB became discernable. Similar conclusions were drawn from our experiments using fluorescence recovery after photobleaching (FRAP) (Nishi et al., 2009), which is a widely used method to assess the *in vivo* mobility of fluorescence-labeled proteins. With cells expressing NER factors fused to green fluorescent protein (GFP), global UV irradiation before photobleaching resulted in the significant retardation of fluorescence recovery within the bleached subnuclear region. This result indicated that the proteins concerned are sequestered at the sites of UV photolesions and engaged in NER (Houtsmuller et al., 1999).

The reduction in the mobility of GFP-XPC showed a unique biphasic relationship with the pre-UV dose. The immobilization of GFP-XPC was saturated at relatively low UV doses (5~10 J/m<sup>2</sup>): higher UV doses resulted in further dose-dependent retardation of fluorescence

recovery, which eventually became saturated again at extremely high doses (around 80~100 J/m<sup>2</sup>). Notably, the reduction in XPC mobility seemed to depend on the remaining 6-4PPs rather than on CPDs. Overexpression and siRNA knockdown of DDB2 revealed that the first immobilization of GFP-XPC (observed with low UV doses) was due to entrapment by UV-DDB bound to 6-4PPs (Nishi et al., 2009). These results indicate that UV-DDB likely contributes to the efficient detection of both of the major photolesions, particularly when the density of the induced lesions is low enough (in terms of physiologically relevant levels), and thereby recruits XPC and other NER factors.

Although the precise molecular mechanism underlying XPC recruitment by UV-DDB remains unclear, we have shown the presence of a direct physical interaction between these 2 damage-recognition factors by coimmunoprecipitation experiments (Sugasawa et al., 2005). Among the components of each complex, XPC and DDB2 appeared to be responsible for the interaction. More recently, researchers have solved the crystal structure for UV-DDB bound to a DNA duplex containing a 6-4PP (Scrima et al., 2008). DDB1 shows a unique structure containing 3  $\beta$ -propeller domains (designated BPA, BPB, and BPC), whereas DDB2 has a  $\beta$ -propeller that is exclusively involved in its interaction with DNA. The N-terminal extension of DDB2 contains a helix-loop-helix motif, which mediates its interaction with DDB1. In this structure, UV-DDB approaches the lesion and inserts its evolutionarily conserved  $\beta$ -hairpin on the surface of the DDB2  $\beta$ -propeller into the minor groove of the DNA, thereby causing a  $\sim 40^\circ$  kink in the DNA. This  $\beta$ -hairpin seems to push the 2 affected bases out of the DNA duplex: these bases interact extensively with the amino acids that form a binding pocket on the surface of DDB2 (Fig. 2). The size of the binding pocket seems fit to accommodate 2 nucleotides, which suggests that DDB2 has evolved to recognize dinucleotide lesions, such as UV-induced photodimers. Considering that XPC interacts with the undamaged strand, XPC may gain access to the lesion from the side opposite to UV-DDB, sandwiching the DNA in between. However, the formation of such a ternary complex has not been demonstrated by EMSA or other methods.

### 2.3 Roles of ubiquitylation in GG-NER damage recognition

As mentioned above, UV-DDB is thought to be part of the ubiquitin ligase complex. Expression of the epitope-tagged DDB2 in cells and isolation of the protein complexes under relatively mild conditions have revealed that DDB2 associates *in vivo* with not only DDB1, but also with CUL4A-ROC1 and the COP9 signalosome (CSN) (Groisman et al., 2003). CSN, which is an 8-subunit complex possessing deneddylation and deubiquitylation activities, is believed to function as a negative regulator of the cullin-based ubiquitin ligase family (Lyapina et al., 2001; Yang et al., 2002). Upon UV irradiation of cells, UV-DDB relocates onto chromatin, where the associating ubiquitin ligase seems to be activated, judging from dissociation of CSN and neddylation of CUL4A (Groisman et al., 2003).

We have demonstrated that XPC is one of the substrates for this ubiquitin ligase (Sugasawa et al., 2005). After UV irradiation, slowly migrating, ubiquitylated forms of XPC became apparent. The appearance of these forms peaked around 1 h postirradiation, at which time the repair of 6-4PPs was rapidly ongoing. This transient ubiquitylation of XPC was detected even in NER-deficient XP and CS cells, with the only exception being XP-E cells. Notably, treatment of cells with a protein synthesis inhibitor, cycloheximide, revealed that ubiquitylated XPC had mostly reverted to its unmodified form, instead of being degraded. Subsequently, the recombinant DDB1-DDB2-CUL4A-ROC1 ubiquitin ligase complex was



purified and successfully used for *in vitro* reconstitution of the XPC ubiquitylation. In this reaction, not only XPC but also DDB2 and CUL4A were found to be polyubiquitylated. It was previously reported that DDB2 undergoes degradation by the proteasome in response to UV irradiation (Fitch et al., 2003; Rapić-Otrin et al., 2002). These results suggest that the fates of the modified XPC and DDB2 are different, even though they seem to be ubiquitylated by the same ligase.

To elucidate the roles of ubiquitylation in the mechanism of GG-NER, we performed DNA-binding assays using paramagnetic beads immobilized with DNA containing the UV photolesions, CPD or 6-4PP (Sugasawa et al., 2005). *In vitro* ubiquitylation reactions in the presence of these DNA beads revealed that polyubiquitylation of DDB2 completely abolished the strong damaged DNA-binding activity of UV-DDB. In contrast, polyubiquitylated XPC in the same reaction continued to bind to DNA, with a slightly higher affinity than the unmodified form. Considering the remarkable difference in their affinities for UV-damaged DNA, it is conceivable that XPC cannot simply displace UV-DDB that is already bound to the site containing a photolesion.

When UV-DDB was added to cell-free NER reactions involving 6-4PP as a defined DNA substrate, only inhibition (and not stimulation) of dual incision was observed (Sugasawa et al., 2005). This finding suggested that UV-DDB tightly bound to the lesion may adversely block access to XPC and other NER factors, at least *in vitro*. Since this inhibition was partially alleviated by the addition of all of the components required for ubiquitylation, we proposed that damage handover from UV-DDB (strong binder) to XPC (weak binder) may be promoted by polyubiquitylation (Sugasawa et al., 2005; Sugasawa, 2006). Apart from these insights into the damage-recognition mechanism, the precise biological meanings of the UV-induced proteasomal degradation of DDB2 and the reversible polyubiquitylation of XPC remain to be understood.

*Ddb2*-deficient mice are characterized by a defect in UV-induced cellular apoptosis, in addition to a predisposition to skin cancer that was predicted from the phenotypes of human patients with XP-E (Itoh et al., 2004; Yoon et al., 2005). Although there have been some contradictory reports (Stubbert et al., 2007; Stubbert et al., 2009), the disappearance of DDB2 and/or the modification of XPC may be involved in a signal transduction pathway that regulates cellular responses to UV (Stoyanova et al., 2009). Among the known NER proteins, the expression of DDB2 and XPC is under the control of the p53 tumor suppressor (Adimoolam & Ford, 2002; Amundson et al., 2002; Hwang et al., 1999), whereas DDB2 conversely regulates p53 expression, thereby forming a regulatory circuit (Itoh et al., 2003).

Structural studies have suggested that the N-terminus of the rod-shaped CUL4 molecule anchors to the BPB domain of DDB1 (Angers et al., 2006; Scrima et al., 2008). In contrast to DDB2 and the other 2  $\beta$ -propellers of DDB1 that seem to be fixed on the lesion, the BPB domain is supposed to exhibit considerable conformational flexibility. As a result, the ubiquitin ligase catalytic center assembled on the other tip of CUL4 is expected to move around within a certain spatial range (like a crane arm), and potentially ubiquitylate various targets around the lesion. Other substrates for the UV-DDB ubiquitin ligase include histones H2A (Kapetanaki et al., 2006), H3, and H4 (Wang et al., 2006). H3 and H4 ubiquitylation by the ligase reportedly leads to the dissociation of histone octamers from DNA. In this regard, it should be noted that the nucleosome assembly of DNA containing 6-4PPs interferes *in vitro* with lesion access to XPC, as well as the subsequent dual incision (Hara et al., 2000; Yasuda et al., 2005). On the other hand, owing to the substantial nonspecific DNA-binding activity of XPC, its specific binding to 6-4PP (observed with EMSAs) was easily competed

out by the addition of undamaged DNA: this inhibition was dramatically attenuated by the organization of the competitor DNA into nucleosomes. Taken together, these studies indicate that nucleosome assembly may contribute to the masking of the undamaged part of the genomic DNA from useless surveillance by XPC, so that specific remodeling of the chromatin structures at relevant lesion sites can enhance damage discrimination tremendously.

In addition to ubiquitin ligase, the histone acetyltransferases CBP/p300 reportedly interact with UV-DDB (Datta et al., 2001; Rapić-Otrin et al., 2002), which suggests that multiple histone modifications may be involved in the reorganization of chromatin environments to allow the initiation of GG-NER. In the reconstituted cell-free system, UV-DDB is dispensable for and could even inhibit the repair of 6-4PPs, as described above. Moreover, its influence on CPD repair has been somewhat elusive, despite the obvious stimulatory effect observed *in vivo*. In some studies, significant stimulation of dual incision was obtained with the CPD substrate (Aboussekhra et al., 1995; Wakasugi et al., 2001; Wakasugi et al., 2002). However, other systems (including ours) showed no or only a minimal effect of UV-DDB on CPD repair, even in the presence of the components required for ubiquitylation (Reardon & Sancar, 2003; Sugasawa et al., 2005). As suggested by others, the involvement of chromatin structures may be important to reproduce the role for UV-DDB in the efficient recognition and repair of CPDs (Rapić Otrin et al., 1998).

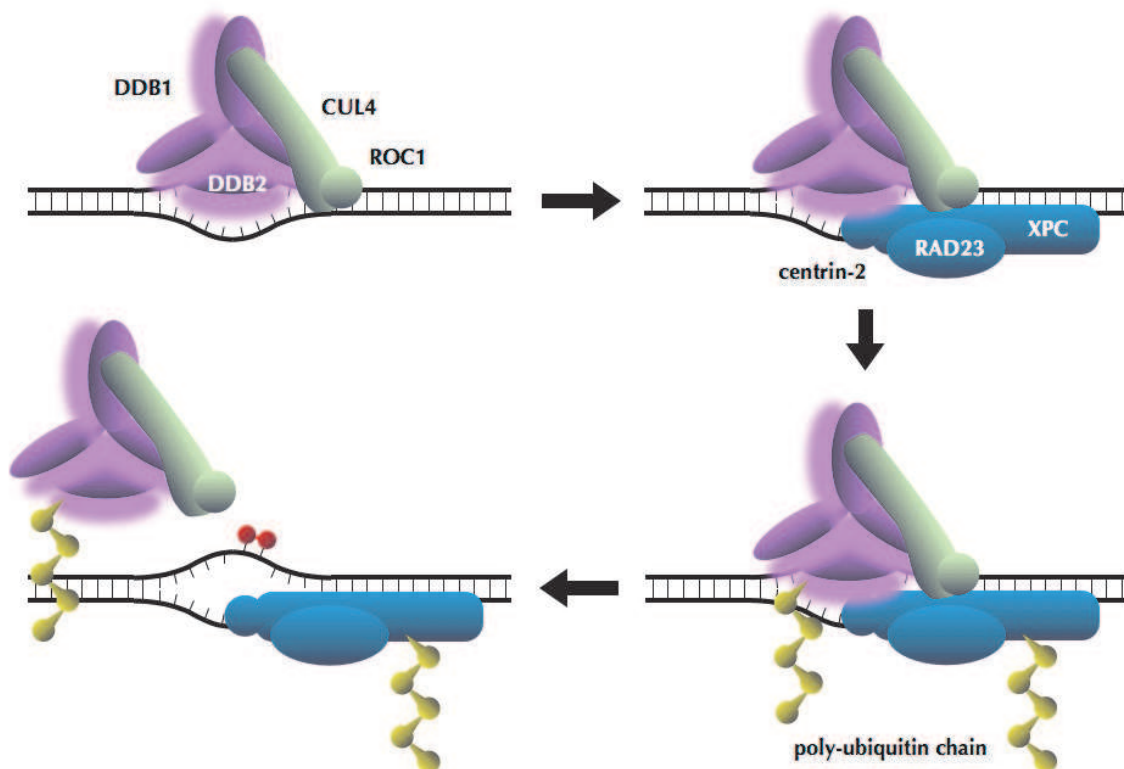


Fig. 3. Ubiquitylation-mediated damage handover model. Once UV-DDB binds to a UV photolesion, it recruits the XPC complex. The associating CUL4-ROC1 ubiquitin ligase is subsequently activated, thereby polyubiquitylating both XPC and DDB2. With the polyubiquitylation of DDB2, UV-DDB loses its affinity for damaged DNA, which results in the successful transfer of the lesion from UV-DDB to XPC.

### 3. The contribution of damage verification to the accuracy of GG-NER

As discussed in the previous section, there are at least 2 branches of damage-recognition pathways in GG-NER: sensing by XPC of unpaired bases associated with a wide variety of highly distorting lesions, and UV-DDB-dependent deployment of XPC that works specifically for UV-induced photolesions. However, particularly in the former pathway, XPC may bind to sites devoid of damage (e.g., bubble-like structures). The reason for this binding is that XPC can detect certain secondary structure of DNA, but not any feature of DNA chemistry. To avoid incision by NER at damage-free sites that could adversely challenge genomic stability, the verification of damage after XPC binding is fundamental.

#### 3.1 Bipartite substrate discrimination model

Important clues to understand the structural determinants of NER substrate specificity were obtained from a series of biochemical studies. Among the key substrates were artificial DNA backbone lesions at the C4' position of the deoxyribose moiety (Buschta-Hedayat et al., 1999; Hess et al., 1997). Although these lesions were associated with little helix distortion and, thus, were hardly excised in human cell-free extracts, they were excised efficiently when combined with a small bubble structure. On the other hand, bubble structures devoid of lesions were never incised by NER. Based on these findings, the *bipartite substrate discrimination theory* was proposed, which states that efficient NER substrates must simultaneously contain 2 structural elements: disruption of canonical Watson-Crick base pairing (i.e., the presence of unpaired bases), and some aberrant modification of DNA chemistry. It should be noted that XPC senses the former, but not the latter, as described above. We later tested other DNA substrates containing a bubble structure and a dG-AAF adduct in various combinations (Sugasawa et al., 2001). XPC could bind to the bubble regardless of the presence or absence of the lesion, whereas *in vitro* NER incision occurred only when the AAF adduct existed at the bubble site. These results clearly indicate that DNA binding by XPC does not lead to dual incision in a straightforward manner. Instead, the presence of an alteration of DNA chemistry must be verified thereafter: in the case of no lesion, the repair process is aborted at a certain step.

One of difficulties with biochemical studies of the NER mechanism has been that its early process includes only assembly/disassembly of protein factors and unwinding of the DNA duplex: no chemical change in DNA occurs before dual incision, which is quite a late step in the repair reaction. However, mechanistic dissection of the early NER process was advanced recently by the finding that the 2 structural elements comprising NER substrates (i.e., unpaired base and chemical modification) are spatially separable (Sugasawa et al., 2009). With the C4' backbone lesions, it was already shown that those abnormal structures could be recognized and incised by NER *in vitro*, even if they resided a few bases apart from the end of a bubbled region (Buschta-Hedayat et al., 1999). Very recently, we showed that the distance between the 2 elements can be much longer (Sugasawa et al., 2009). Although CPDs are very poor substrates in our *in vitro* NER system because of the small helical distortion, enormous stimulation of dual incision was observed when a 3-base bubble was inserted about 60 bases on the 5' side of the lesion. Footprint analyses revealed that XPC was targeted to the bubble site, rather than to the CPD. This result indicated that the NER machinery was capable of searching around the XPC-bound site and finding the lesion at a distal position. More intriguingly, this stimulatory effect upon CPD recognition was abolished when the bubble was moved to the 3' side of the lesion.

The observed position specificity provided crucial insights into the molecular mechanism underlying the damage search. This mechanism was difficult to explain, if we assumed that the NER factors assembled at the XPC-bound site interacted in trans with the distal CPD. Instead, it seemed more likely that the damage search was accomplished by scanning the DNA strand in the 5' to 3' direction. This scanning mechanism was further supported by the observation that the stimulation of CPD removal was attenuated reciprocally by increasing the distance between the bubble and CPD. The damage search seemed to reach at least 160 bases from the bubble, but the efficiency declined if the distance was 400 bases or more.

### 3.2 Roles for TFIIH helicases in damage verification

Given the existence of a 5' to 3' scanning mechanism in damage verification, the transcription factor IIIH (TFIIH) is thought to be the most likely candidate for performing the scan. TFIIH was originally identified as a basal transcription factor that is essential for the initiation of transcription by RNA polymerase II. TFIIH consists of 10 subunits, including 3 disease-related gene products, XPB, XPD, and TTDA (Giglia-Mari et al., 2004). Electron microscopic analyses of the purified TFIIH complex have revealed a ring-shaped structure, in which the spatial arrangement of individual subunits has been proposed (Chang & Kornberg, 2000; Schultz et al., 2000). Notably, the XPB and XPD subunits possess DNA-dependent ATPase and helicase activities: the XPD helicase translocates on a DNA strand in the 5' to 3' direction (Schaeffer et al., 1994; Sung et al., 1993), whereas the contribution of XPB helicase activity with the opposite (3' to 5') polarity seems only marginal (Coin et al., 1998; Schaeffer et al., 1994). These activities have been implicated in the local unwinding of the DNA duplex at promoter sites (for transcriptional initiation) (Holstege et al., 1996) and at sites containing DNA damage (for NER) (Evans et al., 1997; Mu et al., 1997).

The XPB ATPase activity is necessary for both transcription and NER (Hwang et al., 1996; Tirode et al., 1999). In contrast, ATP-hydrolysis by XPD seems dispensable for transcription, but not for NER (Winkler et al., 2000). TTDA (also known as p8) is a very small protein that recently was identified as a subunit of TFIIH (Giglia-Mari et al., 2004). TTDA stimulates the ATPase activity of XPB in the NER reaction, but it is not directly involved in transcription, which suggests that it performs NER-dedicated roles (Coin et al., 2006). However, TTDA appears to affect the stability of the gross TFIIH complex, because cells from patients with TTD-A show substantially reduced levels of TFIIH and transcriptional activity (Giglia-Mari et al., 2004).

The observed polarity of the XPD helicase coincides with the 5' to 3' scanning model of damage verification. In this regards, there have been notable reports that the helicase activity of Rad3p, the *S. cerevisiae* XPD homolog, is inhibited in the presence of DNA damage (Naegeli et al., 1992). This finding evokes the notion that damage verification may depend on obstruction of the TFIIH helicase translocation at sites where the DNA structure is chemically altered (Dip et al., 2004; Gillet & Schärer, 2006; Wood, 1999). Similar results were obtained recently with an archaeal XPD homologue (Mathieu et al., 2010), although some contradictory data have been also documented (Rudolf et al., 2010), which might be explained by differences in the DNA substrates used. Using paramagnetic beads immobilized with DNA containing a CPD and a 5'-loop, we showed that a certain NER protein complex assembled at the loop site indeed moves to the CPD in an ATP-dependent manner (Sugasawa et al., 2009). In addition to XPC, both XPB and XPD ATPase activities as well as XPA seemed to be involved in this process. Considering that XPB, another TFIIH-



related helicase, exhibits the opposite (3' to 5') polarity, it has been proposed that XPB and XPD may be loaded onto different DNA strands and may move toward the same direction (Dip et al., 2004). This process would enable the simultaneous inspection of both strands, so that discrimination between damaged and undamaged strands can be made depending on which helicase is blocked. However, our results strongly suggest that only 1 strand is subjected to scanning, such that lesions on the other strand, if any, are ignored. Recent mutational analyses have revealed that the ATPase, but not the helicase, activity of XPB is required for NER (Coin et al., 2007): this finding implies that XPB may not mediate the opening of the DNA duplex or movement along a DNA strand.

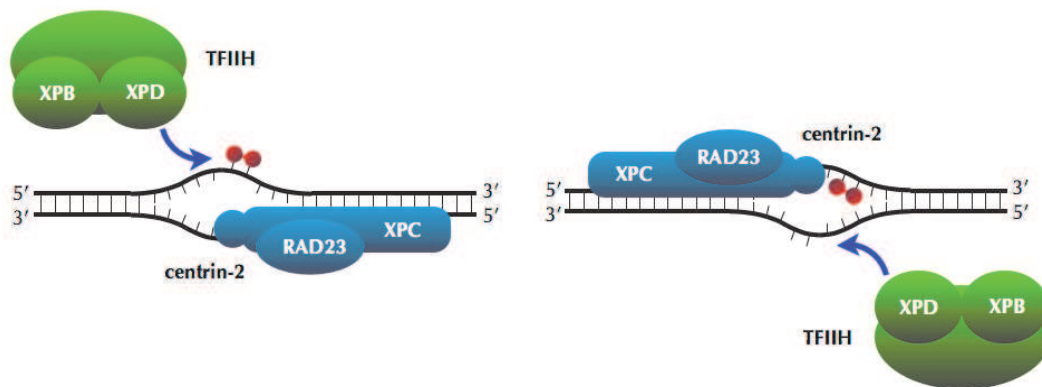


Fig. 4. Polarity of the XPC binding regulates which DNA strand is scanned by the XPD helicase. For successful loading of XPD onto the damaged strand, XPC must interact with the undamaged strand.

Another point made by this study was the importance of the XPC binding polarity. As demonstrated by the aforementioned biochemical and structural studies (Min & Pavletich, 2007; Sugasawa et al., 2002), XPC binds to a site containing unpaired bases in an asymmetric fashion. This binding polarity can be controlled intentionally by using a loop structure, in which only 1 DNA strand has unpaired bases. When a loop with either polarity was substituted for a bubble positioned on the 5' side of the CPD, incision at the lesion site was stimulated only by a looped-out sequence in the "undamaged" (CPD-free) DNA strand. In the case where both the loop and CPD were present in the same strand, incision was completely blocked (Sugasawa et al., 2009). These findings strongly suggest that, after XPC interacts with unpaired bases in 1 DNA strand, the XPD helicase in subsequently recruited TFIIH may be loaded onto the other strand and may start scanning in the 5' to 3' direction. According to this model, XPD would be forced to bind the undamaged strand erroneously, if the damage-containing strand is looped out.

Although this model was deduced from the results of *in vitro* experiments using rather artificial DNA substrates, it might also apply to normal NER reactions, in which unpaired bases and chemical modifications coexist in close proximity. To induce productive NER, XPC must interact with unpaired bases opposite the lesion, so that the XPD helicase can be loaded successfully onto the damaged strand immediately on the 5' side of the lesion. Intriguingly, with DNA containing a bulky lesion (such as the dG-AAF adduct), XPC exhibits a propensity to bind in a correct orientation in the absence of other factors, most likely because of steric effects preventing interactions between XPC and the modified base (Sugasawa et al., 2009). On the other hand, footprints of XPC on a 6-4PP appear rather

symmetric (Sugasawa et al., 1998), which suggests that a substantial fraction of 6-4PP repair events that are initiated directly by XPC may be abortive. In the UV-DDB-mediated damage recognition pathway, however, XPC may be properly guided to interact with the undamaged strand, because the UV photolesions are already occupied by UV-DDB.

### 3.3 Possible roles for XPA and RPA

XPA, which was the first cloned XP gene (Tanaka et al., 1990), complemented UV sensitivity of fibroblasts from patients with XP-A. Cultured cells lacking expression of functional XPA are defective in both GG-NER and TC-NER, and show extreme sensitivity to killing by UV. The XPA gene product is a relatively small protein that is essential for *in vitro* NER. It shows a DNA-binding activity with a significant preference for various types of damaged DNA (Asahina et al., 1994; Jones & Wood, 1993).

Replication protein A (RPA) is a heterotrimeric protein complex exhibiting remarkable single-stranded DNA-binding activity. RPA is supposed to promote the unwinding of the DNA duplex, stabilize the single-stranded conformation, and stimulate various enzymatic activities, such as DNA polymerases. As the eukaryotic counterpart of bacterial SSB, RPA has been implicated in various DNA metabolisms, including replication, repair, and recombination (Wold, 1997). Its involvement in NER was demonstrated by fractionation and reconstitution of human cell-free extracts used for *in vitro* NER (Coverley et al., 1991). RPA also binds damaged DNA with significant specificity (Burns et al., 1996; Clugston et al., 1992; He et al., 1995), and the reported interaction between XPA and RPA seems to enhance their damage-specific DNA-binding activities (Buschta-Hedayat et al., 1999; He et al., 1995; Li et al., 1995; Wakasugi & Sancar, 1999).

Although the above findings suggest that the XPA-RPA complex could be responsible for initial damage recognition, the observed specificity and affinity of this complex for damaged DNA seem less pronounced than those of XPC or UV-DDB. In addition, accumulating evidence from biochemical and cell biological studies has supported the conclusion that these factors are more likely to be involved in later stages of the NER process. Both XPA and RPA are essential for the assembly of the NER preincision intermediate complex that contains the fully opened DNA duplex. RPA likely stabilizes the single-stranded conformation of DNA and protects the undamaged strand specifically, while XPA binds around the end of the unwound region on the 5' side of the lesion (Krasikova et al., 2010). Considering the reported physical interactions with a number of NER factors, one of the roles for these factors may be orchestrating the assembly of the preincision complex and correctly arranging other factors, including the 2 incision endonucleases, ERCC1-XPF and XPG.

The XPA protein possesses a zinc-finger domain, which NMR studies revealed is involved in the interaction with RPA. In contrast, its DNA-binding functionality was assigned to a different domain in the protein (Buchko et al., 1998; Buchko et al., 1999; Ikegami et al., 1998). Intriguingly, the DNA-binding domain in XPA shows structural resemblance to DNA binding  $\beta$ -hairpins (particularly BHD2) in XPC/Rad4p (Min & Pavletich, 2007), which suggests their evolutionary and functional relationship.

So far, the precise roles for the (rather weak) damage-specific DNA-binding activity of XPA remain unclear. XPA reportedly exhibits remarkable binding affinities for DNA containing highly kinked conformations, such as 3-way junctions and the Holliday junction-like structure (Camenisch et al., 2006; Missura et al., 2001). From mutational analyses, it has been

proposed that XPA may be suitable for sensing abnormal electrostatic potentials of DNA, which could be caused by certain distorted DNA conformations in the damage-containing DNA duplex that are unwound by the helicase activities of TFIIH (Camenisch et al., 2007). In addition to such "proofreading" functions, our recent DNA-binding assays have raised the possibility that XPA may be required for launching the DNA scanning complex from the XPC-bound sites (Sugasawa et al., 2009). We also have shown that XPA may stimulate the TFIIH helicase activity under certain conditions, presumably through their reported physical interaction (Li et al., 1998; Park et al., 1995). Based on these findings, it is conceivable that a ternary complex involving XPC, XPA, and TFIIH scans DNA strands to search for damage: this model is reminiscent of the damage-recognition mechanism in the bacterial NER system. As for *E. coli*, 2 damage recognition pathways have been proposed (Van Houten et al., 2005): the UvrA homodimer directly recognizes and binds to distorted sites and then recruits UvrB, or preassembled complexes involving 2 UvrA and 1 or 2 UvrB molecules bind DNA in a nonspecific manner and then search for damage by scanning the DNA strands. In this analogy, UvrB seems to correspond to TFIIH as the driving subunit with ATPase/helicase activities, whereas UvrA may have evolved into XPC and/or XPA. Although little amino acid sequence homology exists between these bacterial and mammalian counterparts, the fundamental principles underlying NER damage recognition may have been conserved throughout evolution.

### 3.4 Implications in the damage surveillance mechanism

Although the specific DNA binding of UV-DDB and XPC has been observed in vitro, it still remains to be understood how these factors survey DNA and eventually reach relevant sites. For many DNA-binding proteins with sequence- and/or structure-specificity, it has been supposed that the proteins first bind DNA in a nonspecific manner and then "slide" or "hop" to search for their target sites (Gorman & Greene, 2008). A recent report has suggested that BHD1 and BHD2 in XPC may serve as dynamic damage sensors by binding to DNA and rapidly scanning for the integrity of base pairing (Camenisch et al., 2009). Once it encounters a distorted site, BHD3 may be inserted into the duplex to form a stabilized damage-recognition complex.

Apart from these models, our findings that the NER protein complex driven by the XPD helicase can scan DNA strands provides interesting insights into the molecular mechanism underlying in vivo damage surveillance: for instance, the association of XPC even with inappropriate (damage-free) sites could help the NER machinery to survey the local genomic region and find damage at rather distal positions. Possible candidates for such XPC anchoring sites include base mismatches (caused by errors of replication/repair and deamination of bases), thermodynamic "breathing" of the DNA duplex, and other sequences that are intrinsically prone to melting (e.g., transcriptional promoters and replication origins), especially in the presence of topological stresses imposed by chromatin structure. In addition, some endogenous DNA damage, such as abasic sites and single-strand breaks, also may target XPC and thereby launch the "patrolling" system. It would be of great interest to examine how the timing and efficiency of GG-NER are regulated at different genomic loci.

## 4. Conclusion

Multiple protein factors are involved in the detection and verification of DNA damage, which, in conjunction with the GG-NER system, determine whether to incise DNA or not.

These factors sample all different structural aspects of DNA damage. XPC senses the presence of oscillating unpaired bases, which allows GG-NER to target an extremely broad spectrum of DNA insults. UV-DDB seems more customized for the detection and repair of UV-induced photolesions through direct interaction with the affected bases. As for CPDs (which are refractory to detection by XPC), UV-DDB further extends the substrate specificity of GG-NER. The XPD helicase in TFIIH scans DNA strands as a fine sensor of chemical changes in DNA structure. By integrating these different strategies, GG-NER as a whole can work as a highly versatile, efficient, and accurate system. Numerous biochemical and cell biological studies have confirmed that checks for different structural abnormalities in DNA are conducted in a sequential manner. Additionally, possible stochastic mathematical models have been also discussed (Kessler et al., 2007; Luijsterburg et al., 2010; Politi et al., 2005). Considering the *in vivo* situations, decondensation and some remodeling of the chromatin structure would also be expected to precede damage recognition by UV-DDB and XPC, although the underlying mechanism involved in this process remains unclear. These key issues need to be addressed at the molecular level in the near future.

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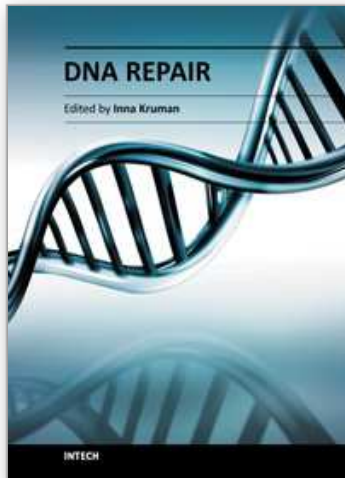
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