HHS Public Access

Author manuscript

Photochem Photobiol. Author manuscript; available in PMC 2016 March 01.

Published in final edited form as:

Photochem Photobiol. 2015 March ; 91(2): 254–264. doi:10.1111/php.12406.

Molecular Regulation of UV-Induced DNA Repair

Palak Shah and **Yu-Ying He***

Department of Medicine, Section of Dermatology, University of Chicago, Chicago, IL, USA

Abstract

Ultraviolet (UV) radiation from sunlight is a major etiologic factor for skin cancer, the most prevalent cancer in the U.S., as well as premature skin aging. In particular, UVB radiation causes formation of specific DNA damage photoproducts between pyrimidine bases. These DNA damage photoproducts are repaired by a process called nucleotide excision repair, also known as UV-induced DNA repair. When left unrepaired, UVB-induced DNA damage leads to accumulation of mutations, predisposing people to carcinogenesis as well as to premature aging. Genetic loss of nucleotide excision repair leads to severe disorders, namely, xeroderma pigmentosum (XP), trichothiodystrophy (TTD) and Cockayne syndrome (CS), which are associated with predisposition to skin carcinogenesis at a young age as well as developmental and neurological conditions. Regulation of nucleotide excision repair is an attractive avenue to preventing or reversing these detrimental consequences of impaired nucleotide excision repair. Here we review recent studies on molecular mechanisms regulating nucleotide excision repair by extracellular cues and intracellular signaling pathways, with a special focus on the molecular regulation of individual repair factors.

INTRODUCTION

Ultraviolet (UV) radiation from sunlight is a major etiologic factor for skin cancer, the most prevalent cancer in the U.S. (1–6), as well as premature skin aging. UV radiation is classified into 3 types based on the wavelength- UVA (315–400 nm), UVB (280–315 nm) and UVC (100–280 nm) (7, 1). All UVC is blocked by the ozone layer, preventing it from reaching the surface of the earth (1). UVB forms only about 5% of all UV radiation reaching the earth's surface, which effectively causes DNA damage (8, 9, 2). UVA forms about 95% of all UV radiation entering the earth, but is weaker than UVB in terms of causing DNA damage (8, 10, 2, 11).

UVB and UVC are absorbed directly by DNA, causing the formation of thymine dimers, mainly cyclobutane pyrimidine dimers (CPD) and pyrimidine (6-4) pyrimidone photoproducts (6-4PP) (2, 5). UVA exposure also causes thymine dimers; in addition, it leads to generation of reactive oxygen species (ROS) via photosensitizing reactions, and thus indirectly causes oxidative DNA damage lesions (2, 12, 11).

In humans and mice UV-induced CPD and 6-4PP lesions are repaired by nucleotide excision repair (NER), the most versatile DNA repair system. NER eliminates a wide variety of

*Corresponding author: yyhe@medicine.bsd.uchicago.edu.

helix-distorting base lesions induced by environmental carcinogenic sources, including UV and air pollutants (13–20). Even though a primitive, more efficient DNA repair mechanism involving photolyases has been identified, it is absent in humans (20, 21). When NER is defective and the damage is left unrepaired, it leads to various disorders including xeroderma pigmentosum (XP), Cockayne syndrome (CS), and trichothiodystrophy (TTD) (Table 1) (17, 16, 22). These disorders are characterized by increased carcinogenesis in various organs, developmental and immunological defects, neuronal and retinal degeneration, and aging (Table 1) (17, 16, 22). Defective NER predisposes affected individuals to carcinogenesis in the skin, brain, and lungs, and sensitizes mice to carcinogenesis in the skin, lungs, and liver (23, 24, 17, 25–27). Even though the versatile NER pathway can correct bulky nucleotide adducts distorting the DNA structure from a variety of environmental carcinogens, it is crucial for correction of UV-induced DNA photoproducts in the skin, since NER defective patients have high propensity to develop sunlight exposure induced skin cancer (27). Patients with defective NER manifest a 2,000–10,000 fold increase in risk of skin cancer, have a significantly lower age of onset of skin cancer compared to the general population, and have skin cancer as the most common cause of death as compared to other internal cancers (27). This establishes the most significant association of NER defects with UV-associated skin cancer amongst all cancers. Essential NER factors have been identified, including xeroderma pigmentosum complementation group A–G (XPA-XPG) and cockayne syndrome group A (CSA) and B (CSB) (17, 16, 22).

There are two main types of NER: global genome nucleotide excision repair (GG-NER) and transcription coupled nucleotide excision repair (TC-NER) (16, 17). GG-NER is mainly responsible for removing most of the CPD and 6-4PP damage in non-transcribed regions, whereas TC-NER does the same in regions under active transcription in the genome (16, 17). These two pathways differ in their damage recognition, but the following steps are the same in both pathways (Figure 1). In GG-NER, XPE (also known as DNA damage binding protein 2, or DDB2) and XPC first bind to the damage site and are responsible for UV-induced DNA damage recognition, in the heterodimeric complex with DDB1 (DNA damage binding protein 1) and HR23B, respectively (16, 17). For TC-NER, CSA and CSB proteins mediate recognition of UV-induced DNA damage in actively transcribed regions by relieving the stalled RNA polymerase II (RNA pol II) at these sites (16, 17).

Following recognition, the rest of the NER pathway is the same for both the GG-NER and the TC-NER pathways (16, 17) (Figure 1). Upon recognition of the DNA damage, XPB and XPD, which form part of the transcription factor II H (TFIIH) complex, unwind the DNA through their helicase activity (16, 17) (Figure 1). XPA and RPA (replication protein) define the cleavage sites and strand specificity, to which XPG (also known as excision repair cross-complementation group 5, ERCC5) and the nuclease complex XPF-ERCC1 (excision repair cross-complementation group 1) bind to cleave the damaged site, followed by its excision (16, 17). The excised portion is replaced with a newly synthesized patch with the help of proliferating-cell nuclear antigen (PCNA) and replicative polymerase (Pol) δ (16, 17) (Figure 1).

Unrepaired DNA damage leads to replication fork breakdown and subsequent genomic instability during cell division, since regular high fidelity DNA polymerases cannot

synthesize past DNA lesions (28–31). Translesion synthesis (TLS) polymerases can bypass the DNA damage and allow DNA replication to continue (28, 32–38). Even though TLS polymerases were originally considered low fidelity polymerases contributing to mutagenesis, recent advances suggest that TLS could be error-prone or error-free in a damage-specific and polymerase-specific manner (31, 28, 39–43).

Translesion synthesis across unrepaired CPD lesions is mediated by Pol η (initiation and extension) in an error-free manner (28, 43, 41, 44–46). When Pol η is absent, for example in XP-V patients, a two-step process involving initiation (TLS Pol ι,κ and/or an unknown polymerase) and extension (TLS Pol ζ or κ) mediates translesion synthesis across the CPD lesion in an error-prone manner (28, 47, 48). TLS across 6-4PP lesions is carried out by Pol ζ in an error-free manner, and alternatively by Pol η or Pol ι in an error-prone manner (49, 42). Since TLS is potentially mutagenic, regulating the comparatively error-free NER would be more desirable (50, 31).

Hence it is important to understand how NER is regulated, which could be exploited to prevent or ameliorate pathologies associated with defective NER. In this review, we summarize recent advances regarding the regulators of individual factors involved in NER, emphasizing the molecular regulation of NER through controlling the expression or activity of NER proteins.

XPC REGULATION

XPC is an indispensable factor for initial recognition of bulky DNA damage in non-transcribed regions (17, 16, 22). Loss of XPC function inhibits UV-induced CPD and 6-4PP DNA lesion repair, leading to accumulation of mutations upon replication, and increased cancer risk with UV exposure (17, 16, 22). Being such an important protein, XPC is regulated at multiple levels: genetic (mutations and polymorphisms), transcriptional, and post-translational, in addition to regulation under specific conditions like immunosuppression.

XPC polymorphisms

In spite of having normal NER, the Lys939Gln polymorphism in XPC has been associated with various cancers, indicating that NER-independent function of XPC is also important for cancer (51, 52). The XPC intron 11-5C/A SNP causes a reduction in DNA repair capacity due to a change in the frequency of alternatively spliced XPC mRNA.(53)

Promoter methylation of XPC

Recent studies have shown that XPC promoter methylation is increased by $BRAF^{V600E}$ (V600E mutant V-Raf Murine Sarcoma Viral Oncogene Homolog B), leading to decreased XPC mRNA levels and reduced DNA repair capacity (54) (Figure 2). This may play an important role in promoting spontaneous as well as UVB-induced melanomagenesis (54). XPC promoter hypermethylation is also associated with reduced XPC expression in lung tumors from patients (55). In lung cancer cell lines, the XPC promoter region, which consists of 17 CpG islands, was shown to be associated with XPC hypermethylation, leading to XPC repression (55).

Transcriptional regulation of XPC

Various distinct transcription factors, namely p53, nuclear factor erythroid 2-related factor 1 (Nrf1, also called NFE2L1), Hypoxia-inducible factor-1 alpha (HIF-1α), AMP-activated protein kinase (AMPK), E2F transcription factor 4 (E2F4), and 130 kDa retinoblastoma-associated protein (p130), have been found to regulate XPC expression, and non-transcription factors also have been found to act via some of these transcription factors to modulate XPC expression (Figure 2).

The p53 tumor suppressor signaling is well known to regulate XPC to enhance NER (56). In HaCaT keratinocytes, Nrf1 promotes CPD repair by increasing XPC expression (57). Nrf1 increases XPC expression via increasing glutathione availability (57). HIF-1α also contributes to increased XPC transcription after UVB (58). In mouse skin and normal human epidermal keratinocytes, the AMPK pathway promotes UVB-induced DNA repair by increasing XPC expression (59). Under growth arrest conditions, E2F4 and p130 repressors were found to bind the XPC promoter region in a genome-wide binding screen (60). In MEF cells, ARF was shown to reduce the binding of the E2F4-p130 repressor complex to XPC promoter, thus leading to increased expression of XPC (61, 62). ARF was shown to be required for efficient NER of UVC-induced CPD and 6-4PP lesions, due to its function of regulating XPC expression (62).

Loss of phosphatase and tensin homolog (PTEN), an important tumor suppressor, was shown to inhibit CPD repair and to a lesser extent 6-4PP repair *in vitro* (in HaCaT cells) and *in vivo* (in mouse epidermis) via decreasing XPC protein levels, by regulating XPC transcription (63). In *in vitro* cell culture models (MEFs and human keratinocytes), sirtuin 1 (SIRT1) inhibition impairs CPD and 6-4PP repair by increasing XPC transcription (64). SIRT1 increases XPC transcription by activating PTEN through its deacetylase activity, which inhibits phosphorylation of AKT and impairs the nuclear localization of p130 transcriptional repressor (64).

XPC regulation by post-translational modifications and protein-protein interactions

XPC can be regulated by two types of post-translational modifications: ubiquitylation and sumoylation (65). XPC can be polyubiqutinated by the UV-DDB E3 ligase complex consisting of DDB2, DDB1 (DNA damage binding protein 1), Cul4A, and several other proteins (66–69) (Figure 3). Ubiquitination of XPC increases XPC binding to DNA (68). Other studies also report that the UV-DDB complex mediates targeting of the XPC-HR23B complex to the site of CPD DNA damage (70, 71). Additionally, it was shown that DDB2 is necessary for degradation of XPC after UV-induced DNA photoproduct formation, but DDB1 and Cul4A, which are members of the same UV-DDB complex, inhibit XPC degradation upon UVC-induced DNA damage (72). After UV-induced DNA photoproduct formation, degradation of XPC was shown to be necessary for recruiting XPG at DNA damage sites and thus for efficient NER (72). XPC deubiquitination by ubiquitin-specific protease 7 (USP7) prevents XPC degradation and promotes NER (73). Sumoylation of XPC after UVC-induced DNA damage has also been shown to prevent its degradation (65). The K655 site on XPC is critical for sumoylation, as well as for degradation of XPC (72). RING

finger protein 111 (RNF111) can polyubiquitinate sumoylated XPC to promote XPC's binding to damaged DNA (65, 74).

In addition, XPC interacts with other proteins to regulate its protein stability. For example, XPC-binding protein Rad23 (yeast homolog of HR23B) was shown to stabilize XPC (75, 76) (Figure 3). Inhibition of the proteasome pathway or overexpression of Rad23 increases the stability of Rad4 (yeast homolog of XPC) (77). The authors further show that Rad23 significantly impacts NER capacity via two independent but simultaneous mechanisms (77, 78). With p53-null cell lines, retinoblastoma protein RB was shown to increase the half-life/stability of XPC protein to enhance NER, through a direct interaction with XPC (79).

XPC regulation by immunosuppressants in organ transplant recipients

Organ transplant patients are at high risk of developing skin cancer (80). These skin cancers have long been attributed to the immunosuppressive therapy post-transplant, and the level of immunosuppression affects the development of skin cancer (80, 81). However, cyclosporin A (CsA), an immunosuppressant used for organ transplant recipients, promotes UVB-induced skin carcinogenesis in an immunosuppression-independent manner by (i) impairing DNA repair by suppressing XPC transcription, and (ii) impairing checkpoint and DNA damage response by upregulating CypA (82). Other reports have also shown that CsA inhibits NER in fibroblasts and lymphoblasts (83, 84). In contrast to keratinocytes, in fibroblasts CsA inhibits NER by reducing XPA and XPG but not XPC (85). In keratinocytes, the immunosuppressants tacrolimus and mycophenolate mofetil reduce UVB-caused DNA damage repair and apoptosis, and tacrolimus also impairs UVB-mediated checkpoint signaling, and thus may promote skin cancer in both an immunosuppression-dependent and -independent manner (86).

REGULATION OF XPE/DDB2

As an essential factor in DNA damage recognition, DDB2 is regulated at both transcriptional and post-translational levels. In response to UVC, DDB2 transcription is regulated by p53 in human cells, but not in mice (87, 88). In addition, DDB2 activity is modulated by multiple pathways. UV irradiation was shown to cause constitutive photomorphogenesis 9 (COP9) signalosome (CSN) dissociation from the DDB2 complex (89, 69). This in turn increased the ubiquitin-ligase activity of DDB2 (90, 69). Upon being polyubiquitinated by the DDB complex itself, DDB2 signals for its degradation by proteasomes and loses its DNA binding activity (68). Poly (ADP)-ribosylation (PARylation) of DDB2 was shown to inhibit DDB2 ubiquitination and degradation, to allow DDB2 more time to mediate chromatin modification (91, 92). In addition to DDB2 complex-mediated chromatin regulation, DDB2 itself can regulate NER through chromatin remodeling by (i) Poly (ADP-ribose) polymerase 1 (PARP-1) mediated PARylation of chromatin, and (ii) recruiting chromatin remodeler Amplified in Liver Cancer 1 (ALC1) (91, 93–95).

REGULATION of CSA and CSB

As an ubiquitin-ligase in TC-NER, CSA activity is decreased by UV irradiation via rapid association of COP9 signalosome (CSN) with CSA (69). CSA was shown to ubiquitinate

CSB to target it for degradation via the ubiquitin proteasome pathway, ultimately aiding the reinitiating of transcription after DNA repair (96). UVSSA (UV-sensitive syndrome protein) was shown to recruit USP7 to deubiquitinate and stabilize CSB, thus opposing CSA-mediated ubiquitination and degradation of CSB (97, 98).

REGULATION OF RNA pol II

Following UV-induced DNA photoproduct formation at actively transcribed genes, stalled RNA pol II recruits CSA and CSB (99–102). RNA pol II is then polyubiquitylated by CSA- and CSB-complex, which leads to the degradation of RNA pol II in the proteasomes to allow the recruitment of downstream NER factors (99–102). Alternatively, RNA pol II degradation factor 1 (Def1) can mediate degradation of RNA pol II via ubiquitination independent of TC-NER (103). In addition, the VHS (Vps-27, Hrs and STAM) domain of UVSSA was found to be essential for ubiquitination and dephosphorylation of RNA pol II and for efficient TC-NER, and this ubiquitination of RNA pol II does not target RNA pol II for degradation (104). The authors also suggest that since UVSSA interacts with TFIIH, UVSSA probably ubiquitinates RNA pol II by recruiting TFIIH, helping to remove stalled RNA pol II from the damage sites to allow the TC-NER factors access to the DNA damage (104).

XPD REGULATION

XPD functions at the merging point of the GG-NER and TC-NER pathways. XPD is a part of the TFIIH complex, and along with XPB serves to unwind the recognized DNA damage via its helicase activity. In keratinocytes, immediately after UVB irradiation, XPD normally undergoes a small decrease, followed by its upregulation (58).

XPA REGULATION

XPA level and activity are regulated through various mechanisms under physiological and stress conditions. XPA level is increased by deficiency in toll-like receptor 4 (TLR4) (105). In keratinocytes, αMSH/MC1R complex (α-Melanocyte-Stimulating Hormone/ Melanocortin 1 Receptor complex) enhances the GTPase activity of XPA-binding protein 1 (XAB1), which in turn induces nuclear translocation of XPA, thus regulating NER for UVB-induced DNA damage via a pigmentation-independent mechanism (106) (Figure 4). PKA-mediated ATR phosphorylation enhances ATR-XPA interaction and rapid recruitment of XPA to DNA damage sites, ultimately promoting NER and reducing UVB or UVC-caused mutations (107). In addition, PARP-1 directly interacts with XPA to enhance NER (108). Arsenic is known to inhibit NER, and zinc was shown to protect against the detrimental effects of arsenic on DNA damage (109–112). In cell-based systems, XPA and PARP-1 (both zinc finger proteins) were shown to be molecular targets for arsenite (113–116). Cadmium, copper, nickel and cobalt also inhibited XPA by decreasing binding of XPA to UVC-damaged DNA (117). The mechanism of NER impairment by metals needs to be further investigated.

REGULATION OF RPA and PCNA

RPA binds to the unwound DNA damage site and to XPA. XPA and RPA together define the cleavage sites and strand specificity for the downstream nucleases. After excision of the damaged DNA by the nucleases, PCNA promotes filling of the gap by DNA synthesis. Transcription of RPA and PCNA may be regulated by E2F1 (E2F Transcription Factor 1) and E2F4, which were found to bind to the promoter region of RPA3 and PCNA genes (118). E2F4 and p130 repressors, under growth arrest conditions, were also found to bind to the PCNA promoter region in a genome wide binding screen (60).

REGULATION OF XPG/ERCC5

XPG/ERCC5 participates in cleavage and excision of the damaged DNA lesion via its endonuclease activity. XPG level and activity are regulated by transcription and protein-protein interaction, respectively. In H23 or H460 human lung adenocarcinoma cell lines, CCAAT/enhancer-binding protein gamma (CEBPG) was shown to increase ERCC5 transcription (119) (Figure 5). Human interferon β (IFN-β) treatment was shown to increase XPG mRNA levels in fibroblasts isolated from CSA and CSB patients with defects in TC-NER (120). IFN-β-mediated upregulation of XPG could be a possible mechanism for IFN-β-mediated resistance to UVC-induced cell death, in a TC-NER-independent manner (121). Other mechanisms may also have a role in the effect of IFN-β and remain to be determined.

Gadd45 (Growth Arrest And DNA-Damage-Inducible) has been shown to improve NER (122, 123). Gadd45a directly interacts with XPG to cause active DNA demethylation (124). Gadd45a-mediated DNA demethylation probably stimulates DNA repair via XPG and XPB, due to the association between DNA repair and DNA demethylation (124, 125). The precise mechanism remains to be elucidated.

ERCC1 REGULATION

XPF-ERCC1 dimer participates in cleavage and excision of the damaged DNA lesion via its endonuclease activity. ERCC1 mutations contributing to NER disorders have rarely been found. A patient with a homozygous Exon 7 mutation in ERCC1 is reported to have CS symptoms, and a patient with ERCC1 deficiency had developmental failure and a mild defect in NER (126, 127). Ercc1 knockout mice have similar critical developmental disorders and neonatal lethal characteristics (128). Deletion of Smad4 (SMAD family member 4) decreases ERCC1 transcription to cause defective CPD repair via reduced Snail expression, leading to increased UVA and UVB-induced SCC in murine models with keratinocyte-specific Smad4 loss (129).

OTHER NER REGULATORY PATHWAYS

Melanin, MSH, and Melanocortin

In melanocytes with functional MC1R, total melanin and eumelanin contents (MC and EC) were found to be inversely proportional to CPD damage (130). Additionally, melanocytes with loss of MC1R function have higher UVB-induced CPD damage and lesser repair of these lesions, independent of their total melanin and eumelanin content (130).

MSH and adrenocorticotropic hormone (ACTH) have been shown to activate MC1R, leading to increased repair capacity of UVB-induced DNA photoproducts and decreased ROS generation (131–134). Forskolin was also shown to have effects similar to those of αMSH on UV-induced repair of DNA photoproducts, due to forskolin-mediated activation of the cAMP pathway, a downstream pathway common to melanocortins (131, 135, 136). Tetrapeptide and tripeptide analogs of melanocortin, containing a modified αMSH core with N capped groups and C terminal modifications respectively, also enhance CPD repair, by activating MC1R as MSH does (131, 137, 138).

Chromatin modification

Chromatin modification could be an important regulator of NER, since chromatin in an open conformation facilitates the binding of DNA repair factors to the damaged DNA (67, 139, 140, 99). In cell extracts and reconstituted human excision nuclease systems, with reconstituted nucleosomes, the NER rate was inhibited to only 10% of that in naked DNA (141). The repair kinetics for acetylaminofluorene-guanine (AAF-G) adduct is increased by the SWI/SNF complexes (SWItch/sucrose nonfermentable) through multiple mechanisms (142–152). In addition, by increasing the access of NER factors to nucleosomal DNA, NER can be increased by ACF (Asymmetric Crying Facies), an ATP-utilizing chromatin assembly and remodeling factor (153–155).

The DDB2 complex also facilitates NER by carrying out ubiquitination of H2A, H3, and H4 histone proteins, indicating DDB2's role as a chromatin remodeler to allow the NER factors access to damaged DNA lesions (93–95). Histone acetylation mediates chromatin unfolding even after lesion detection, which is important for efficient NER. Indeed, histone acetyltransferases, such as GCN5 (general control of amino-acid synthesis 5), have been shown to be involved in this process (156–159). p53 was also shown to mediate whole genome relaxation to facilitate lesion detection and NER (159). The UV-DDB complex is also able to associate with GCN5 and p300, suggesting another probable mechanism of DDB-mediated chromatin regulation to facilitate NER (160–162).

E2F1 has been shown to facilitate NER by recruiting GCN5 at sites of UVC- or UVB-induced DNA photoproducts (158). GCN5 mediates histone H3 Lysine 9 (H3K9) acetylation to allow increased access of NER factors to the damaged DNA (158). The S29A mutation (S29 in mice, equivalent to human S31) in E2F1 hinders E2F1 recruitment and E2F1-mediated recruitment of GCN5 and H3K9 acetylators at damage sites, reducing access of the NER factors XPC and XPA to the DNA damage lesions (163). After removal of DNA damage, restarting of transcription is enhanced by rapid removal and exchange of H2A and H2B at UVC-induced DNA photoproducts, and by placement of H3.3 histone (164–166). In yeast, the loss of H2A histone variant HTZ1 (H2A.Z) inhibits UVC-induced CPD damage removal (167). HTZ1 promotes CPD repair by recruiting GCN5, leading to histone H3K9/K14 acetylation and increasing Rad14 (ortholog of XPA) binding to damaged DNA (167). Through their histone acetylase activity, p300 and CREB Binding Protein (CBP) redundantly lead to DDB2 recruitment to CPD lesions in compacted chromatin regions, facilitating repair of UVC-induced CPD lesions (168). p300 phosphorylation at S1834 is

seminal for efficient CPD repair through facilitating DDB2 recruitment to the CPD lesion (168).

CONCLUSION AND PERSPECTIVES

UV-induced DNA repair, or NER, essentially removes DNA damage by inevitable environmental factors like solar UVB radiation and air pollutants. NER is vital to maintaining genomic integrity to protect animals and humans from skin, lung and brain cancer as well as neurological and developmental disorders, and thus justifiably has multiple factors and signaling mechanisms for its regulation. Recent studies have demonstrated that UV-induced DNA repair is regulated at multiple levels including transcriptional modulation and posttranslational modifications. Both extracellular cues and intracellular signaling regulate UV-induced DNA repair capacity. These regulations are achieved through regulating the availability or activity of individual repair factors, or modifying chromatin structure. Better understanding of the NER regulation can elucidate new opportunities to enhance the NER capacity and therefore improve our ability to prevent cancer initiation and progression, as both processes involve genetic mutations and/or genomic instability.

Acknowledgments

We apologize to those investigators whose work could not be directly referenced owing to space limitations. Work in the authors' laboratory was supported by NIH/NIEHS grants ES016936 (YYH), the American Cancer Society (ACS) grant RSG-13-078-01 (YYH), the University of Chicago Cancer Research Center (P30 CA014599), the CTSA (NIH UL1 TR000430), and the University of Chicago Friends of Dermatology Endowment Fund.

ABBREVIATIONS

6-4PP	pyrimidine (6-4) pyrimidone photoproducts
αMSH/MC1R complex	α-Melanocyte-Stimulating Hormone/Melanocortin 1 Receptor complex
AAF-G	acetylaminofluorene-guanine
ACF	Asymmetric Crying Facies
ACTH	Adrenocorticotropic Hormone
AICAR	5-aminoimidazole-4-carboxamide ribotide
Akt	V-Akt Murine Thymoma Viral Oncogene Homolog
ALC1	Amplified in Liver Cancer 1
AMPK	AMP-activated protein kinase
ARF	Alternative reading frame
ATM	Ataxia Telangiectasia Mutated
ATR	Ataxia Telangiectasia and Rad3 Related
BCC	basal cell carcinoma

BRAF^{V600E}	V600E mutant V-Raf Murine Sarcoma Viral Oncogene Homolog B
Camp	cyclic AMP
CBP	CREB Binding Protein
CEBPG	CCAAT/enhancer-binding protein gamma
CPD	cyclobutane pyrimidine dimmers
CS	Cockayne syndrome
CsA	Cyclosporin A
CSA	Cockayne syndrome group A
CSB	Cockayne Syndrome group B
CSN	constitutive photomorphogenesis 9 (COP9) signalosome
Cul4A	Cullin 4A
DDB1	Damage-Specific DNA Binding Protein 1
DDB2	Damage-Specific DNA Binding Protein 2
Def1	RNA polymerase II degradation factor 1
DOT1L	DOT1-like protein
DP1	DRTF polypeptide 1
E2F1	E2F Transcription Factor 1
E2F4	E2F transcription factor 4
Epac	Exchange protein activated by cyclic AMP
ERCC1	excision repair cross-complementation group 1
ERCC5	excision repair cross-complementation group 5
Gadd45	Growth Arrest And DNA-Damage-Inducible
GCN5	general control of amino-acid synthesis 5
GG-NER	global genome nucleotide excision repair
H2A.Z	H2A histone variant HTZ1
H3K9	Histone H3 Lysine 9
HIF-1α	Hypoxia-inducible factor-1 alpha
HIRA	HIR (Histone Cell Cycle Regulation Defective) Homolog A
HMGN1	High Mobility Group Nucleosome Binding Domain 1
HR23B	RAD23 Homolog B
HRE	hypoxia response element

IFN-β	interferon β
MC and EC	total melanin and eumelanin contents
MFA2	Mating Factor A
MSH	Melanocyte Stimulating Hormone
NAP1L1	Nucleosome Assembly Protein 1-Like 1
NAP1L4	Nucleosome Assembly Protein 1-Like 4
NEDD8	neural precursor cell expressed, developmentally down-regulated 8
NER	nucleotide excision repair
NOX1	NADPH Oxidase 1
Nrf1	also called NFE2L1, nuclear factor erythroid 2-related factor 1
p130	130 kDa retinoblastoma-associated protein
p38 MAPK	p38 mitogen-activated protein kinases
PARP-1	Poly (ADP-ribose) polymerase 1
PARylation	Poly (ADP)-ribosylation
PCNA	proliferating-cell nuclear antigen
PI3K	Phosphatidylinositol-3-kinase
PKA	Protein Kinase A
Pol	polymerase
PTEN	phosphatase and tensin homolog
R4B	Rad4 binding domain
RB	retinoblastoma protein
RNA pol II	RNA polymerase II
RNF111	RING finger protein 111
ROC1	Regulator of Cullins 1
ROS	reactive oxygen species
RPA	replication protein A
RPA3	Replication protein A3
SCC	squamous cell carcinoma
SHM	somatic hypermutation
SIRT1	sirtuin 1
Smad4	SMAD family member 4

SWI/SNF	SWItch/sucrose nonfermentable
TC-NER	transcription coupled nucleotide excision repair
TFIIH	transcription factor II H
TLS	Translesion synthesis
TTD	trichothiodystrophy
UBL	Ubiquitin-like domain
USP7	Ubiquitin-specific-processing protease 7
UV	Ultraviolet
UVSSA	UV-sensitive syndrome protein
VHS	Vps-27, Hrs and STAM domain
XAB1	XPA-binding protein 1
XP	xeroderma pigmentosum
XPA	xeroderma pigmentosum, complementation group A
XPB	xeroderma pigmentosum, complementation group B
XPC	xeroderma pigmentosum, complementation group C
XPD	xeroderma pigmentosum, complementation group D
XPE	xeroderma pigmentosum, complementation group E
XPF	xeroderma pigmentosum, complementation group F
XPG	xeroderma pigmentosum, complementation group G
YY1	Yin Yang 1
ZEB1	Zinc Finger E-Box Binding Homeobox 1

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Biographies

Palak Shah is currently pursuing a PhD in Molecular Pathogenesis and Molecular Medicine under the guidance of Dr. Yu-Ying He at the University of Chicago. She is also simultaneously pursuing an MS in Translational Sciences as part of the Howard Hughes Medical Institute PhD/MS Translational Training Program (TTP) offered at the University of Chicago. She received her B.Tech in Pharmaceutical Chemistry and Technology in 2010 from the Institute of Chemical Technology, Mumbai, India. Next she obtained Masters in Biotechnology in 2012 from the University of Pennsylvania. She is the recipient of the Dean's International Student Fellowship from the University of Chicago in 2013. Her research interests are in genomic instability dependent and independent pathways in skin cancer.

Yu-Ying He is an Assistant Professor of Medicine at the University of Chicago. She received her PhD in Chemistry in 2000 from the Chinese Academy of Sciences in China. Then she received the Humboldt Research Fellowship working with Dr. Donat-P. Häder at the University of Erlangen-Nuerenburg in Germany. In 2001, she came to the NIEHS/NIH for her postdoctoral training with Dr. Colin Chignell. In 2007, she joined the faculty in the Department of Medicine at the University of Chicago. During her research career, Yu-Ying He has received several awards, including the first NIEHS Science Day Early Career Award, the NIH **F**ellows **A**ward for **R**esearch **E**xcellence (FARE), the American Skin Association Research Scholar Award, the American Cancer Society Research Scholar award, and the Outstanding New Environmental Scientist Award. Her research interests are in the genetic and environmental determinants of genomic stability using skin and skin cells as models.

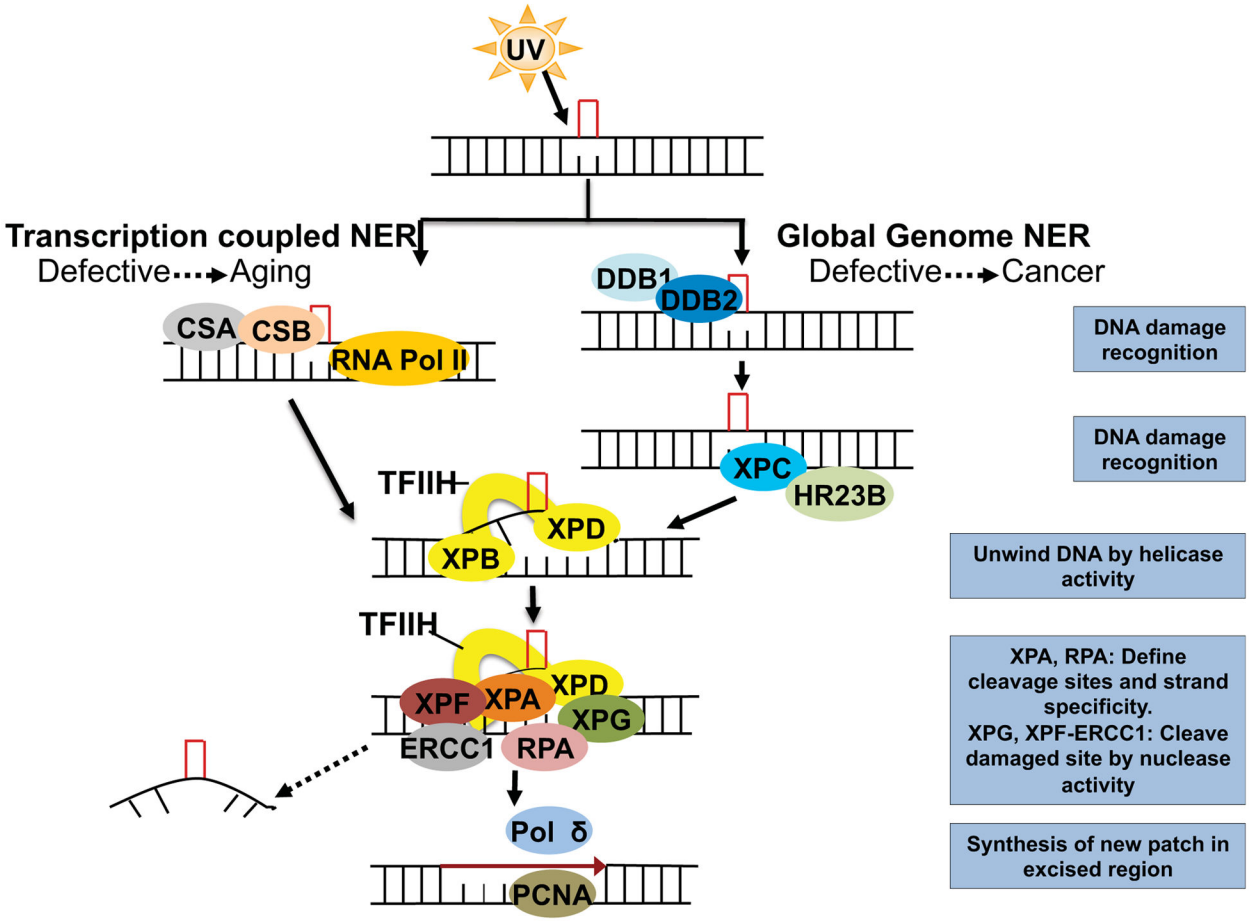

Figure 1.

Sequential assembly of molecular players to remove UV-induced CPD and 6-4PP DNA damage lesions in global genome nucleotide excision repair (GG-NER) and transcription coupled nucleotide excision repair (TC-NER).

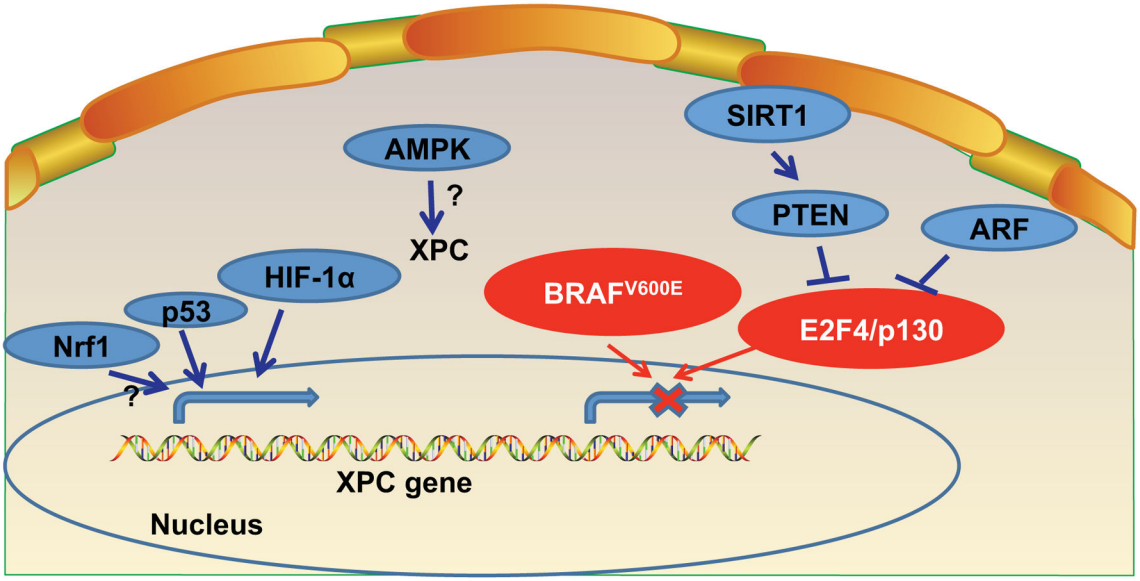

Figure 2.
Transcriptional Regulation of XPC.

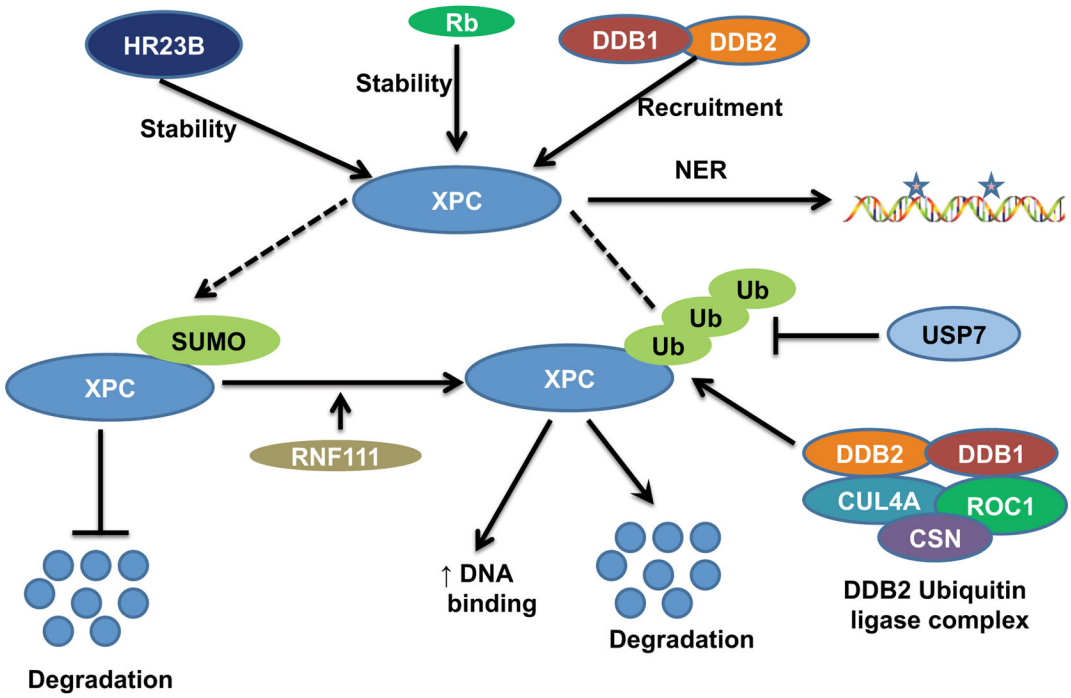

Figure 3.
Post-translational regulation of XPC.

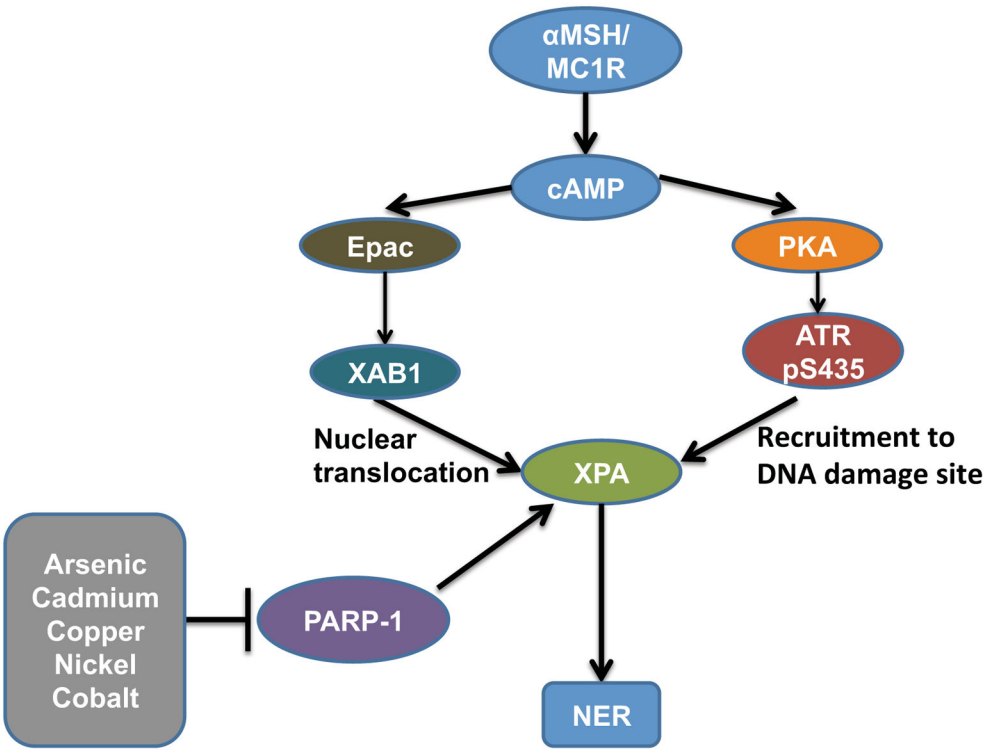

Figure 4.
Molecular Regulation of XPA.

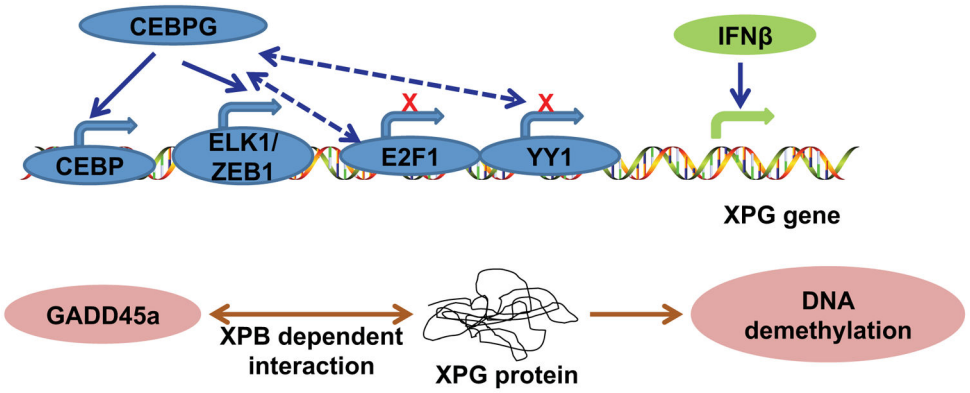

Figure 5.
Molecular regulation and interactions of XPG.

Table 1

Disorders associated with defective NER (See Ref (17)).

Disease due to defective NER	Genes causing disorder	Characteristics
Xeroderma pigmentosum(XP)	*XPA, XPB, XPC, XPD, XPE, XPF, XPG, XPV (Xeroderma Pigmentosum Variant)*	Sunlight exposure predisposes to various cancers, especially squamous cell carcinoma, basal cell carcinoma and melanoma skin cancer.
Trichothiodystrophy (TTD)	*XPB, XPD, TTDN1 (TTD non- photosensitive 1 protein or M- phase-specific PLK1- interacting protein) and TTDA (general transcription factor IIH, polypeptide 5 (GTF2H5))*	Brittle, sulfur-deficient hair and ichthyosis, mental retardation
Cockayne syndrome (CS)	*CSA, CSB, XPD* and *XPG*	Developmental and neurological disorders, decreased lifespan