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# The role of XPC: Implications in cancer and oxidative DNA damage

**Joost P.M. Melis**[1,2], **Mirjam Luijten**[1], **Leon H.F. Mullenders**[2], and **Harry van Steeg**[1,2,*]

Joost P.M. Melis: J.P.M.Melis@lumc.nl; Mirjam Luijten: Mirjam.Luijten@rivm.nl; Leon H.F. Mullenders: L.Mullenders@lumc.nl

[1]National Institute of Public Health and the Environment, Laboratory for Health Protection Research, Bilthoven, The Netherlands [2]Leiden University Medical Center, Department of Toxicogenetics, Leiden, The Netherlands

## Abstract

The accumulation of DNA damage is a slow but hazardous phenomenon that may lead to cell death, accelerated aging features and cancer. One of the most versatile and important defense mechanisms against the accumulation of DNA damage is Nucleotide Excision Repair (NER), in which the Xeroderma pigmentosum group C (XPC) protein plays a prominent role. NER can be divided into Global Genome repair (GG-NER) and Transcription Coupled repair (TC-NER). XPC is a key factor in GG-NER where it functions in DNA damage recognition and after which the repair machinery is recruited to eliminate the DNA damage. Defective XPC functioning has been shown to result in a cancer prone phenotype, in human as well as in mice. Mutation accumulation in XPC deficient mice is accelerated and increased, resulting in an increased tumor incidence. More recently XPC has also been linked to functions outside of NER since XPC deficient mice show a divergent tumor spectrum compared to other NER deficient mouse models. Multiple *in vivo* and *in vitro* experiments indicate that XPC appears to be involved in the initiation of several DNA damage-induced cellular responses. XPC seems to function in the removal of oxidative DNA damage, redox homeostasis and cell cycle control. We hypothesize that this combination of increased oxidative DNA damage sensitivity, disturbed redox homeostasis together with inefficient cell cycle control mechanisms are causes of the observed increased cancer susceptibility in oxygen exposed tissues. Such a phenotype is absent in other NER-deficient mice, including *Xpa*.

### Keywords

Xpc; Nucleotide Excision Repair; mutation; cancer; oxidative DNA damage



*Contact information: Harry van Steeg, Laboratory for Health Protection Research, National Institute of Public Health and the Environment, P.O. Box 1, 3720 BA Bilthoven, The Netherlands. Phone: 31-30-274-2102; Fax: 31-30-274-4446; Harry.van.Steeg@rivm.nl.

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## 1. Introduction

Biologically, DNA is considered to be the key to life, since it determines the whole genetic make up and many predispositions and appearances. DNA is well protected for this matter. For one, DNA is packaged in an ingenious manner so its vulnerability is diminished. Additionally, surveying scavengers try to eliminate harmful molecules in cells to prevent DNA damage. However, cells endure a massive attack daily, which makes it impossible to counteract all insults. This is the paradoxical nature of DNA; it is the key to life, but at the same time in the end, it is also the key to death since DNA damage will eventually lead to mutations and an imbalance in homeostasis, resulting in cancer or other age-related diseases. When inescapable DNA damage does occur, organisms rely on DNA repair pathways to prevent and postpone damage in a way it will give nature time to mend and to live a longer and healthier life.

## 2. DNA damage

Genomic assaults are abundant due to environmental factors and continuously ongoing metabolic processes inside the cell [1]. Endogenous DNA damage occurs at an estimated frequency of approximately 20,000 – 50,000 lesions per cell per day in humans [2;3], which roughly adds up to 10 - 40 trillion lesions per second in the human body. Endogenously generated lesions can result in hydrolysis (e.g. depurination, depyrimidination and deamination), oxidation (8-oxoG, thymine glycol, cytosine hydrates and lipid peroxidation products) and non-enzymatic methylation of the DNA components [4;5]. Besides these endogenous insults to the DNA, exogenous factors can play a significant role in damaging the DNA. Examples of exogenous insults are ionizing radiation (IR), ultraviolet (UV) radiation and exposure to chemical agents. One hour of sunbathing for example generates around 80,000 lesions per cell in the human skin [6]. The endogenous and exogenous primary lesions can result in persistent DNA damage if left unattended. Therefore, repair pathways and cellular responses are of vital importance in the prevention of cancer and age-related diseases. DNA repair pathways come in many varieties, Figure 1 shows a schematic overview of DNA repair responses to several types of DNA damage.

Excision repair pathways and reversal of DNA damage are responsible for the fundamental repair of damaged nucleotides, resulting into the correct nucleotide sequence and DNA structure. Besides damaged nucleotides, cells often sustain fracture of the sugar-phosphate backbone, resulting in single- or double-strand breaks [5]. Repairing the DNA damage can occur in an error-free (e.g. Nucleotide Excision Repair (NER), Base Excision Repair (BER), Homologous Recombination (HR)) or by an error-prone pathway like Non-Homologous End-Joining (NHEJ). Besides DNA repair pathways, DNA damage tolerance mechanisms are active to bypass lesions that normally block replication like Translesion Synthesis (TLS) or template switching. Template switching occurs in an error-free way, while TLS acts in an often error-prone manner (although a few polymerases of this pathway are able to handle the lesions in an error-free way). Even though error-prone mechanisms do not result in the original coding information they do enhance the chances of cell survival, which is preferred over correct genomic maintenance in these cases. In this light, cell cycle checkpoint activation and scheduled cell death (apoptosis) also enhance chances of genomic stability and in some cases cell survival [7]. These responses greatly facilitate the efficiency of repair and damage tolerance. Arrested cell cycle progression will result in an increased time window for DNA repair or damage tolerance to occur. In addition, apoptosis will attenuate the risk of genomic instability by programming the cells with extensive DNA damage for cell death. Hereby, annulling the possible negative effect of the DNA damage in those cells and hence maintaining homeostasis [7].

## 3. Nucleotide excision repair

The abundant targeting of bases and nucleotides in the genome makes the Nucleotide Excision Repair (NER) one of the most essential repair pathways. NER is able to repair a wide range of DNA lesions and can restore the correct genomic information. Additionally, replication and transcription can be continued. This pathway can deal with a broad spectrum of (mostly) structurally unrelated bulky DNA lesions, arisen from either endogenous or exogenous agents. Nucleotide excision repair comprises over 30 proteins that eliminate the helix-distorting lesions. As mentioned, lesions of this matter can originate upon exposures to several damaging agents. For instance, UV radiation (sunshine) is a physical DNA damaging agent that mainly produces cyclobutane pyrimidine dimers (CPDs) and pyrimidine-(6,4)-pyrimidone products (6-4PP) but is also believed to induce oxidative DNA damage [8]. Exposure to numerous chemicals or alkylating agents can result into helix-distorting bulky adducts, for example polycyclic aromatic hydrocarbons (present in cigarette smoke or charcoaled meat) [9] (Figure 1).

### 3.1 Global Genome-NER and Transcription Coupled-NER

NER is divided into two subpathways which mechanistically initiate in a divergent manner, but after damage recognition both pathways proceed along the same processes (see Figure 2). The subpathways are designated Global Genome NER (GG-NER) and Transcription Coupled NER (TC-NER). GG-NER recognizes and removes lesions throughout the entire genome, and is considered to be a relatively slow and less efficient process, since it scans the whole genome for DNA damage [10]. However, UV induced helix-distorting lesions like 6-4PPs, are rapidly cleared by GG-NER [11]. TC-NER is responsible for eliminating lesions in the transcribed strand of active genes. This repair process takes care of lesions blocking the transcription machinery and potential subsequent dysfunctions. Since TC-NER is directly coupled to the transcription machinery it is considered to be faster acting and more efficient than GG-NER, but is only initiated when transcription of a gene is blocked.

### 3.2 DNA damage recognition

The difference between the two subpathways is the initial damage recognition step (Figure 2). As mentioned previously, a helical distortion and alteration of DNA chemistry appears to be the first structural element that is recognized. For GG-NER, the XPC/hHR23B complex (including centrin2), together with the UV-Damaged DNA Binding (UV-DDB) protein (assembled by the DDB1 (p127) and DDB2/XPE (p48) subunits), are involved in lesion recognition [12]. The XPC/hHR23B complex is also essential for recruitment of the consecutive components of the NER machinery to the damaged site, also known as the preincision complex [13;14].

It has been shown that XPC itself has affinity for DNA and can initiate GG-NER *in vitro*, but its functionality is enhanced when hHR23b and centrin2 are added [15;16]. Centrin2 as well as hHR23B stabilize the heterotrimer complex, putatively by inhibiting polyubiquitination of XPC and hence preventing subsequent degradation by the 26S proteasome [15]. XPC recognizes various helix-distorting base lesions that do not share a common chemical structure. Biochemical studies have revealed that XPC recognizes a specific secondary DNA structure rather than the lesions themselves [17-19]. XPC (together with DDB1 and DDB2) appears to scan the DNA for distortions by migrating over the DNA, repeatedly binding and dissociating from the double helix [20]. When XPC encounters a lesion the protein changes its conformation and aromatic amino acid residues of XPC stack with unpaired nucleotides opposite the lesion, thereby increasing its affinity and creating a conformation which makes it possible to interact with other NER factors [20].

The binding affinity of XPC to the DNA seems to correlate with the extent of helical distortion. 6-4PP products substantially distort the DNA structure and are more easily recognized by XPC than CPDs, which only induce a minimal helical distortion [21]. More recent studies have indicated that the UV-DDB protein complex facilitates recognition of lesions that are less well-recognized by the XPC-hHR23B complex, like CPDs [22]. The UV-DDB is able to recognize UV-induced photoproducts in the DNA and is now believed to precede binding of XPC-hHR23B to the damaged site. CPD repair is UV-DDB dependent [22;23]. Since affinity of the XPC-hHR23B to CPD sites is low, DDB2 is needed for efficient binding [23]. Upon ubiquitylation DDB2 is degraded by the 26S proteasome [22;24], hereby increasing binding affinity of XPC to the DNA as well as stimulating the interaction of XPC with hHR23B [16;25;26]. Degradation of UV-DDB enhances the binding of XPC-hHR23B to the DNA *in vitro* [21]. Timing of the programmed degradation of DDB2 determines the recruitment of XPC-hHR23B to the UV-damaged site [27].

The XPC protein contains several binding domains: a DNA binding domain, a hHR23B binding domain, centrin2 binding domain and a TFIIH binding domain [28]. TFIIH is a multifunctional transcription initiation factor but is also a core NER component comprising amongst others the helicases XPB and XPD (Figure 2). The complex is essential for the continuation of the NER pathway and is responsible for unwinding the DNA helix after damage recognition by XPC/hHR23B. XPC has been shown to physically interact with TFIIH and *in vivo* and *in vitro* studies show that recruitment of the NER complex to unwind the DNA is executed in a XPC-dependent manner [5;28].

The XPC protein is redundant in TC-NER. Here a stalled RNA polymerase II (RNA polII) is the onset of the NER machinery. CSA and CSB play a crucial role in setting the transcription coupled repair in motion but are also implicated in RNA polII transcription functions. The CSB protein interacts with RNA polII [29], while CSA does not [30]. CSA mainly interacts with CSB, XAB2 (XPA binding protein 2) and the p44 subunit of the TFIIH complex [31;32]. The function of CSA remains to be elucidated but seems to be implicated in TC-NER during elongation of the transcription process [33;34]. Both CSA and CSB are part of RNA PolII associated complexes, but for CSB additional functions are assigned outside NER [35].

In TC-NER, CSB is thought to be responsible for displacement of the stalled RNA polymerase. Additionally, as with XPC in GG-NER, the preincision complex of NER is recruited in a CSB-dependent manner [36;37]. But first, as in GG-NER, the TFIIH complex is recruited after damage recognition.

### 3.3 DNA helix unwinding

Since the focus of this review is on XPC, the remainder of the NER machinery will be discussed only briefly. After DNA damage recognition and subsequent recruitment of TFIIH, GG-NER and TC-NER converge into the same pathway. The TFIIH complex consists of 10 proteins: XPB, XPD, p62, p52, p44, p34, p8 and the CDK-activating kinase (CAK) complex: MAT1, CDK7 and Cyclin H. TFIIH forms an open bubble structure in the DNA helix [38;39]. The DNA helicases XPB and XPD facilitate the partial unwinding of the DNA duplex in an ATP-dependent manner, allowing the preincision complex to enter the site of the lesion [40] (Figure 2). The preincision complex further consists of the XPA, RPA and XPG proteins and is assembled around the damage site [41] (Figure 2). The function of XPA is verification of the lesion and additionally acts, together with the single strand DNA binding complex RPA, as an organizational factor, so that the repair machinery is positioned around the lesion. Both XPA and RPA are believed to protect the undamaged strand [42;43] and leads to complete opening of the damaged DNA. Some studies suggested this step is

essential for the initiation of incision/excision of the damaged DNA [44;45]. Furthermore RPA interacts with several other factors of the nucleotide excision repair pathway, like the endonucleases XPG and the ERCC1-XPF dimer, which are required for the dual incision of the damaged strand (Figure 2). RPA hereby facilitates the correct positioning of the endonucleases and regulates the open complex formation [46;47].

### 3.4 Incision, DNA repair synthesis and ligation

When the preincision complex is accurately positioned in relation to the damaged site, DNA incisions are made by the endonucleases XPG and ERCC1-XPF (Figure 2). A general consensus is that the concerted actions of XPG and ERCC1-XPF result in the excision of a 24-32 nucleotide single strand fragment including the damaged site [48]. XPG is responsible for the 3′ incision and is putatively recruited by the TFIIH complex[41]. According to some studies presence of XPG appears to be necessary for ERCC1-XPF activity, which is responsible for carrying out the 5′ incision [5;49]. Others propose a ‘cut-patch-cut-patch’ mechanism for the incision and resynthesis process within NER, where the 5′ incision possibly precedes the 3′ incision[50].

The excision of the damaged fragment is restored in original (undamaged) state by DNA synthesis and ligation steps. The cross play of over 40 proteins identified to date, is involved in NER to counteract DNA damage in an error free manner described above.

## 4. NER in cancer and aging

DNA repair is vital to all organisms and a defect in one of the genes involved can result in severe syndromes or diseases by loss of genomic stability. Essential consequences of genomic instability can be cancer and other age-related diseases, such as neurological disorders like Huntington's disease and ataxias [5]. DNA damage for example can cause mutations that trigger (pre-)oncogenes, inactivate tumor suppressor genes or other indispensable genes which cause loss of homeostasis. Therefore, organisms that harbor defective DNA repair are often more prone to develop cancer or (segmental) age-related diseases.

In humans, several syndromes have been identified which are the result of an impaired nucleotide excision repair pathway, of which Xeroderma pigmentosum (XP), Cockayne syndrome (CS) and Trichothiodystrophy (TTD) are the most well-known. Since NER is the major defense against UV-induced DNA damage, all three syndromes are hallmarked by an extreme UV-sensitivity, of which XP ensues a highly elevated risk of developing skin cancer [5;51].

The involvement of NER genes in rare and severe syndromes underscores the vital importance of this repair pathway. It is known that accumulative DNA damage is one of the most important causes in cancer development and loss of homeostasis in organisms [2;5;6;9;51]. Defects in DNA repair pathways are therefore also considered to accelerate aging and tumorigenesis. In defective NER both types of endpoints occur, XP patients are predisposed to cancer development while CS and TTD patients are not. The latter exhibit premature aging features which XP patients lack [5;9;51]. Reason for this might be the involvement of several NER proteins in other cellular mechanisms. CSB is believed to be involved in (TC-)BER, while XPD is assigned to be involved in replication and transcription. Some of these affected mechanisms could overshadow the cancer prone phenotype of a NER deficiency. Severely affected developmental and neurological processes could be more life threatening on the shorter term than tumor development is. This could be the rationale behind the fact that CS and TTD patients are extremely short-lived and not cancer prone.

## 5. Xeroderma pigmentosum

Xeroderma pigmentosum (XP), meaning parchment pigmented skin, was the first human causal NER-deficient disease identified [51]. It is a rare, autosomal inherited neurodegenerative and skin disease in which exposure to sunlight (UV) leads to skin cancer. In Western Europe and the USA the incidence frequency is approximately 1:250.000, rates are higher in Japan (1:40.000). XP-C and XP-A are the most common complementation groups of XP [52].

Early malignancies (from 1-2 years of age) in the skin, eyes and the tip of the tongue develop due to sun-exposure (Table 1). Additionally, benign lesions like blistering, hyperpigmented spots and freckles are abundant. XP is associated with a more than 1000-fold increase in risk of developing skin cancer, comprising basal and squamous cell carcinomas (45% of the XP patients) and to a lesser extent melanomas [5] (Table 1). Besides skin cancers, XP patients have a 10-20 fold increased risk of developing internal cancers [53]. The mean latency time for cutaneous neoplasms is 8 years, which is much shorter as compared to the general population in which the mean latency time is 50 years longer [54]. Progressive neurological degeneration occurs in approximately 20% of the XP patients and can be correlated to deficiencies in specific XP genes (XPA, XPB, XPD and XPG) [51]. XP-C and XP-F patients rarely develop neurological disorders [5;54]. The heterogeneity in symptoms is correlated to the genetic heterogeneity in XP patients. XP-A, XP-B, XP-D and XP-G patients are in general severely affected, possibly because these patients are defective in both the GG-NER and TC-NER subpathways. Solely GG-NER is defective in XP-C and XP-E patients. This could be the reason that XP-C patients suffer less from sunburn. XP-C and XP-E cells have shown higher survival rates after UV exposure than XP-A and XP-D cells for example [5].

## 6. *Xpc* deficient mouse model

Two independent *Xpc*-deficient mouse models were created in the mid-nineties [55;56]. The $Xpc^{-/-}$ mouse model (from hereon, referred to as *Xpc*) is informative for human XP and cancer development in general. The model is especially interesting since it is only defective for GG-NER and not for TC-NER. As in humans, *Xpc* mice are highly predisposed to UV radiation-induced skin cancer [56-60]. Contrasting to $Xpa^{+/-}$ mice for example, heterozygous *Xpc* mice are more susceptible to UV-induced skin cancer when compared to their wild type littermates [61]. This haploinsufficient sensitivity could mean that XPC is a rate limiting factor in NER.

In a mixed genetic background (C57BL/6J/129) no decrease in survival was found for Xpc mice compared to wild type mice, even though *Xpc* mice showed an extremely high and significantly increased lung tumor incidence (100%). However, the wild type mice were not genetically related to the *Xpc* mice in this study [63]. The spontaneous survival characteristics of *Xpc* mice in a pure genetic C57BL/6J background together with their related wild type littermates were also investigated and again exhibited a significant increase in lung and liver tumors [64]. Here, *Xpc* mice show a divergent tumor spectrum from the *Xpa*-deficient mice in the same genetic C57BL/6J background. The additional increase in lung tumor development in two independent spontaneous survival studies indicate XPC is involved in other pathways besides NER. A corresponding strong increase in mutational load during aging was found in lungs of the C57BL/6J *Xpc* mice, which was not the case in *Xpa* mice [64]. Since lungs are constantly being exposed to oxygen, a putative cause for the observed increase in mutational load could be the lack of an adequate oxidative stress response. In *Xpc* mice, this hypothesis was supported by a 39-week exposure study with *Xpc*- and *Xpa*-deficient (C57BL/6J) mice to oxidative stressors (di(2-ethylhexyl) phthalate

(DEHP) and paraquat). *Xpc* mice exhibited a significant increase in mutational load in the liver when compared to wild type and *Xpa* mice (unpublished results). This indicates that XPC might be directly or indirectly involved in the removal or prevention of oxidative DNA damage. Gene expression profiling of liver tissue of *Xpc* mice exposed to the pro-oxidant DEHP for 39 weeks showed a decreased anti-oxidant response and an upregulation in cell cycle progression compared to wild type and *Xpa* mice (unpublished results). Therefore, the protein might be linked to other DNA repair pathways like base excision repair or might be involved in redox homeostasis and/or cell cycle regulation.

## 7. Possible novel functions of XPC

Based on the results obtained with the *Xpc* mouse model and *in vitro* data, it is plausible to assume that XPC has some additional functions besides being a DNA damage recognition factor in NER. Verification in XP-C patients of these possible novel functions is troublesome. So far, only a few *in vivo* studies in mice are available to support *in vitro* studies that implicate XPC in other mechanisms besides NER. Using the current available *in vivo* and *in vitro* data these possible novel traits are presented and discussed below and are summarized schematically in Figure 3. It is clear that an *Xpc* deficiency results in an increase of mutations due to dysfunctional NER, which can lead to genomic instability and cancer predisposition (Route 1, Figure 3). However when XPC is dysfunctional alternative routes towards genomic instability are also proposed.

### 7.1 XPC and oxidative DNA damage – NER and BER?

Several studies have assigned XPC to a more elaborate role in DNA repair besides the removal of chemically or UV induced bulky adducts that trigger NER. A secondary role in prevention or repair of oxidative DNA damage is proposed for XPC. As mentioned before, an increase in tumor incidence in lungs was observed in two independent *in vivo* studies. Additionally, we showed a correlated increase in mutational load was apparent in lungs of *Xpc* mice, while this increase was not visible in *Xpa* and wild type mice. Also *in vivo* exposure to pro-oxidant DEHP showed an increase in mutational load in *Xpc* mice only. Besides our *in vivo* data, another short term *in vivo* study pointed to the implication of XPC in the prevention of oxidative damage. A two week exposure of *Xpc* knockout mice to equine estrogen showed an increase in 8-hydroxyguanosine in liver as compared to wild type mice although not at significant levels [65].

*In vitro* studies supplied more evidence regarding the sensitivity of *Xpc* deficient cells to oxidative DNA damage. D'Errico *et al.* showed that primary keratinocytes and fibroblasts derived from XP-C patients are hypersensitive to DNA-oxidizing agents and the effect could be reverted by expression of wild type XPC [66]. XPC deficient cells accumulated 8,5′-cyclopurine 2′deoxynucleosides in their DNA after exposure to X-rays and KBrO3. We also showed that mouse embryonic fibroblasts (MEFs) derived from $Xpc^{-/-}$ mice were more sensitive, in terms of survival and mutation accumulation, to oxygen exposure than MEFs derived from $Xpa^{-/-}$ or wild type mice [64]. In summary these data show oxidative DNA damage accumulation is increased in absence of functional XPC (shown in Figure 3). But several mechanisms can underlie this observed increase in sensitivity to oxidative DNA damage.

One option is that NER is responsible for at least part of the removal of oxidative DNA damage (Route 2, Figure 3). NER mainly recognizes bulky DNA adducts and helix-distorting damage and it has been reported that several oxidative DNA lesions give rise to these helix-distorting structures [67;68]. As such, it is also possible that NER is responsible for repairing these lesions as well. It was reported that even non-bulky lesions, like 8-oxoG and thymine glycol, are able to at least partially stall RNA polymerase II during

transcription [69], although other studies show RNA pol II is capable of bypassing this lesion [70-74]. Competition between BER and TC-NER for 8-oxoG repair has been proposed [75-77]. 8,5′-cyclopurine 2′deoxynucleosides are a particular class of (endogenous) oxidative DNA lesions which are capable of blocking RNA pol II transcription and are repaired by NER [78-80]. It has been reported that these lesions accumulate in XPC-deficient cells after exposure to oxidative stress [66].

It is plausible to assume that lesions capable of inducing NER are also removed by this DNA repair pathway. However, the differences in oxidative DNA damage sensitivity observed between *Xpc* and *Xpa* deficient mice and cells indicate that XPC has additional functions outside of NER.

One of the possibilities for the increased sensitivity towards oxidative DNA damage in the absence of functional XPC is reduced functionality of BER, which is the primary pathway for repairing oxidative lesions (Route 3, Figure 3). It has been postulated that the XPC-hHR23B complex acts as a co-factor in the base excision repair of 8-hydroxyguanosine products by stimulating the activity of the BER DNA glycosylase [66]. This interaction was later confirmed by the investigation of specific XPC mutations[81]. XPC is also able to interact with the repair factors thymine DNA glycosylase (TDG) and SMUG1, supporting the hypothesis that XPC might be involved in BER or G/T mismatch repair [82]. Also, the hHR23B factor was found to interact with BER protein 3-methyladenine DNA glycosylase [83]. The XPC-hHR23B complex also recognizes 5R-thymine glycol (5R-Tg) lesions which modulate BER. Recently, fibroblasts from different XP-C patients also showed to be impaired in base excision repair of oxidative DNA damage induced by methylene blue plus visible light [84].

It is shown by numerous studies that CSB deficiency also increases the amount of oxidative DNA damage [85;86]. Evidence has been provided that CSB, as XPC, may participate in OGG1-mediated repair. CSB affects the repair of 8-oxoG lesions, but no physical interaction has been found yet [87;88]. CSB has been shown to interact with BER proteins PARP1 and APE1 [89;90]. The CSB/PARP1-complex appears to be able to relocate to sites of DNA damage after oxidative stress [89]. Additionally, the repair of 8-oxoA and 8-oxo-G is impaired when CSB is not functional [35;75;88;91]. On the other hand, CSB does not affect the incision activities of two other glycosylases, thymine glycol DNA glycosylase and uracil DNA glycosylase [92].

Taking into account the multitude and diversity of presented interactions, either physical or regulatory, it is plausible to assume XPC is also involved in BER. XPC appears non-essential for BER, but might contribute to the effectiveness of this repair pathway by possibly recognizing or enabling recognition of oxidative lesions through signaling and regulatory functions.

### 7.2 XPC and oxidative DNA damage – a link with redox homeostasis?

Recently, several studies provided evidence for another possible cause responsible for the increase in DNA damage upon oxidative stress in the absence of XPC, namely a disturbed redox homeostasis (Route 4, Figure 3) [93-95]. For example, when siRNA silenced XPC human glioma cells were exposed to arsenic trioxide, repair of the induced DNA damage was not affected, but XPC appeared to be involved in intracellular redox homeostasis, leading to a diminished anti-oxidant status [93]. Previously, it has been reported that NER factors (amongst which XPC) were upregulated at increased levels of oxidative stress and also the glutathione anti-oxidant response was implied in NER regulation[96]. Recently, Rezvani et al. reported that silenced XPC triggers metabolic alterations that drive mutation accumulation and tumorigenesis amongst others due to a disturbed redox homeostasis.

Accumulation of unrepaired DNA due to XPC deficiency increases DNA-dependent protein kinase (DNA-PK) activity, which subsequently activates AKT1 and NADPH oxidase 1 (NOX1) resulting in ROS production and accumulation of specific deletions in mitochondrial DNA[94;95]. Another link between Xpc deficiency and redox homeostasis was proposed when defective XPC combined with haploinsufficiency of the *Apex* gene was shown to increase skin cancer predisposition after UV-B exposure. *Apex* is required for activation of many transcription factors (including *Trp53*) by both redox-dependent and redox-independent mechanisms and therefore an imbalance in redox homeostasis could possibly alter cancer susceptibility [97]. Recently, we found in Xpc mice that upon exposure to the pro-oxidant DEHP, the anti-oxidant (glutathione) response was missing in *Xpc* deficient mice, which appeared to be fully active under the same conditions in wild type and *Xpa* mice (unpublished results).

XPC is known to be involved in DNA damage recognition and subsequent signaling and might also perform or facilitate this activity for oxidative DNA damage. Therefore, the absence of XPC might have consequences for the anti-oxidant responses that counteract the oxidative DNA damaging agents.

### 7.3 XPC and cell cycle control

Besides the removal of DNA lesions, evidence exists that NER factors are connected to cell cycle checkpoints. These checkpoint controls play an important role in DNA repair, apoptosis and cell cycle arrest and thereby contribute to prevention of cancer. Impairment of cell cycle control checkpoints might lead to fixation of (oxidative) induced DNA damage into mutations and increased genomic instability (Route 5, Figure 3).

Key regulators in the DNA damage response in mammals are ATM and ATR protein kinases. ATM and ATR are able to phosphorylate many cellular substrates, for example the tumor suppressor protein p53 [98]. Generally, ATM and ATR respond to different types of DNA damage. ATM is the primary mediator of the response to double strand breaks (DSBs). ATR, on the other hand, acts as a back-up mechanism in the DSB response, but directs the principle response to UV damage and DNA replication stalling [99]. Both proteins are able to regulate DNA damage responses throughout the cell cycle, leading to G1 or G2 arrest or S phase delay. Several studies have implicated NER factors, including XPC, in ATM and ATR signaling and regulation [100-106]. *Xpc* deficiency reduced p53 responses to cisplatin treatment. XPC was suggested to play a critical role in initiation of the signal transduction process after cisplatin induced DNA damage resulting in p53 activation and cell cycle arrest [100]. It was later shown that XPC was required for the association of ATM to the genomic DNA [101]. More recently, SNF5/INI1, a chromatin remodeling component, was demonstrated to promote NER by influencing ATM recruitment. SNF5 was shown to colocalize and interact with XPC after UV-radiation. This interaction facilitates the access of ATM to the damage site [102]. Furthermore, ATR appeared to be required for GG-NER, exclusively in S phase of human cells [103;104].

It has been well documented that tumor suppressor and cell cycle mediator p53 is also a key player in DNA damage-induced checkpoints and apoptosis. In humans, p53 positively regulates the expression of XPC and DDB2 [107-109]. If p53 function is compromised, GG-NER activity might be reduced, which could facilitate accumulation of mutations and, consequently, a carcinogenic process. Vice versa, it has been shown that XPC defects enhance metastasis in lung adenocarcinomas ([110]). Transcriptional p53 activity is modulated by XPC. XPC has been demonstrated to stabilize hHR23B to form an hHR23B-p53 complex, thereby preventing p53 degradation [110]. Additionally, XPC deficiency is strongly correlated with p53 mutations and malignancy observed in bladder tumors [111]. Extensive mutational analyses of the Trp53 of UVB-induced skin tumors in $Xpc^{-/-}$ mice

also revealed a mutational hotspot at a nondipyrimidinic CpG site in codon 122, which was not detected in *Xpa*$^{-/-}$ and *Csa*$^{-/-}$ mice [82;112;113].

## 8. XPC human SNPs

In human, Xeroderma pigmentosum is accompanied by a severe and early onset of skin cancer, generally overshadowing potential tumors from different origin like the liver and lung tumors observed in mice. The small number of XP-C patients investigated display, besides skin tumors, also higher incidences of lung, liver, and colon cancer [114]. Human Single Nucleotide Polymorphisms (SNPs) can be informative of cancer susceptibility and might link the aforementioned findings about XPC to a human clinical outcome. Some SNPs in the *XPC* gene are associated with increased lung cancer susceptibility [115-118], indicating that phenotypical responses of XPC-deficiency in human and mouse could be comparable. However, some case-control studies are conflicting and other tumor types are also linked to polymorphisms in *XPC*. Francisco *et al.* [117] performed meta-analysis on 33 published case-control studies, investigating the effect of Lys939Gln and Ala499Val XPC polymorphisms. Statistically significant associations between lung cancer and the recessive genetic model (Lys/Lys+Lys/Gln *vs* Gln/Gln) were found, odds ratio (OR) 1.30; 95% CI: 1.113-1.53, whereas for breast cancer a reduced but non-significant risk was identified for the same model (OR 0.87; 95% CI: 0.74-1.01). Results for Ala499Val showed an overall increase in cancer risk (OR 1.15; 95% CI: 1.02-1.31), but no significant risk for lung cancer. A significant association for bladder cancer was found for this polymorphism, as well as for the Lys939Gln and the XPC poly(AT) insertion/deletion polymorphism (PAT$^{+/-}$) [119]. Another recent elaborate meta-analysis study investigated 38 DNA repair genes and their possible association to cancer susceptibility, and XPC SNPs were linked to increased susceptibility for bladder, breast, colorectal, lung and skin cancer [120]. XPC-PAT$^{+/+}$ is associated with head and neck [121], lung [122] and bladder cancer [119] and shows a borderline association with gastric cancer [123]. Furthermore, the C/A polymorphism in intron 11 of the XPC gene plays a crucial role in the modulation of an individual's susceptibility to sporadic colorectal cancer [124].

Regarding the XPC polymorphisms found to be associated with internal cancers, it is possible that oxidative DNA damage is a contributing or even driving factor to cancer development. Internal tissues are not exposed to UV and exposure to chemicals that induce bulky adducts is probably low. Lungs are known to be exposed to higher levels of oxidative stress. Also, increased oxidative stress levels have been implied in colorectal, bladder and lung carcinogenesis [125-130]. Urinary bladder cells also come into contact with harmful (environmental) agents for extended periods of time through urine, which can cause DNA damage. Recent studies demonstrate reduced levels of XPC protein in tumors for a majority of bladder cancer patients [111;114;131].

Furthermore, internal and skin tumors of XP-C patients have been compared in the past and results indicated a different mutation spectrum for internal tumors compared to skin tumors. These mutations were believed to result from unrepaired lesions caused by oxidative damage [132]. The mutational data derived from patients plus the polymorphisms associated with internal cancers can provide a useful tool to study potential novel functions of XPC. Vice versa, the additional functions of XPC can also be of clinical relevance for XP-C patients and people who have associated SNP variants of XPC.

## 9. Conclusions

Up to now, it has remained difficult to exactly pinpoint the interactions and mechanisms which are responsible for the increased sensitivity towards oxidative DNA damage and

possible subsequent cancer risk for XPC deficiency. Considering the accumulating evidence it is likely that XPC performs additional roles besides NER. XPC appears to be involved in the initiation of several DNA damage-induced cellular responses, which are represented in Figure 3. Based on all the available *in vivo* and *in vitro* data it can be postulated that NER is responsible for repairing and/or preventing at least several of the oxidative lesions, and it is plausible that XPC and CSB interact with glycosylases and other proteins to establish this. The increase in oxidative lesions and increase in mutations seen in some studies could additionally be the result of the disturbed anti-oxidant response and redox homeostasis, eventually leading to more ROS and subsequent mutation induction. Moreover, this outcome can be accentuated if cell cycle control is disturbed by XPC deficiency.

ATM and ATR were, besides DSBs and UV-damage, also linked to oxidative DNA damage. Multiple recent studies show ATM is an important sensor of reactive oxygen species [133-136]. Since XPC has been associated with both increased sensitivity towards oxidative DNA damage and several key factors in cell cycle control, it is plausible that the NER recognition factor is a link between these cellular responses. Recent gene expression data obtained with Xpc mice upon exposure to DEHP showed that *Xpc* deficient mice up regulated their cell cycle progression response in the liver after exposure to this pro-oxidant. Such a response was absent in wild type and *Xpa* mice (unpublished results). In *Xpc* deficient cells or animals, the combination of increased oxidative DNA damage sensitivity (either by function in concert with BER, disturbed redox homeostasis and/or decreased anti-oxidant responses) together with a disturbed cell cycle control can explain the increased mutational load and cancer susceptibility in oxygen exposed tissues compared to for example *Xpa* deficient and wild type cells or animals.

Since these interactions and novel functionalities have been difficult to pinpoint solely by transcriptional analyses, epigenetic regulation like phosphorylation, deacetylation or hypermethylation are (also) believed to play an important role in the regulation of XPC, as was indicated by some studies [114;131;137;138]. In addition, microRNA regulation in DNA damage response presents another option that should be explored further [139]. With the ever growing technical possibilities it is possible to eventually elucidate all these important functions of XPC in detail.

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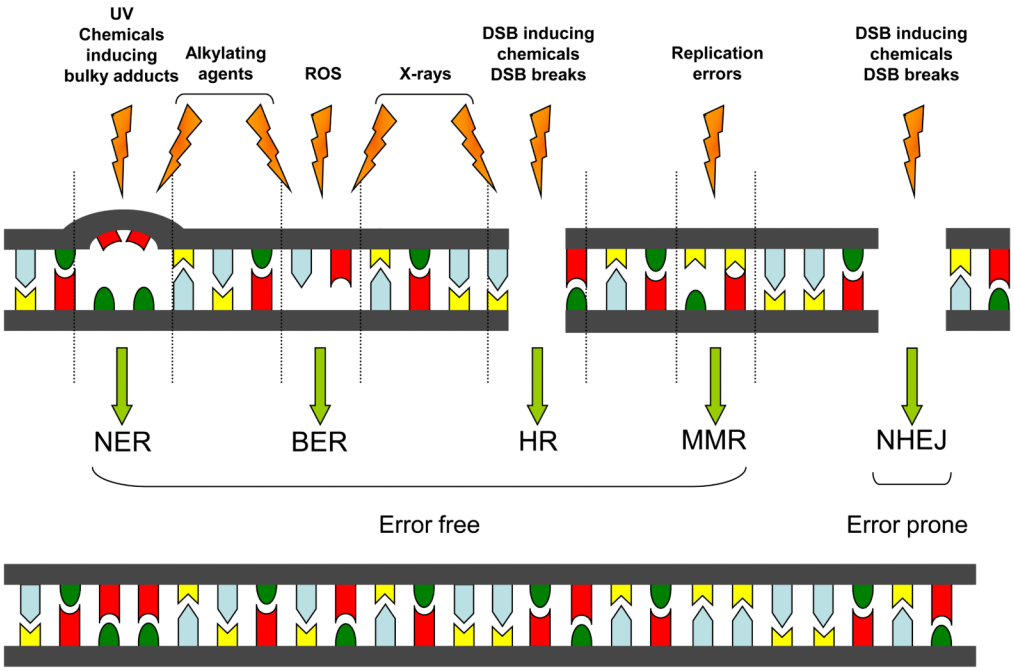


**Figure 1. DNA Repair pathways**

Schematic overview of DNA repair pathways. Several types of induced DNA damage can trigger different repair pathways, which can repair the DNA in an error-free or an error-prone manner.

NER (Nucleotide Excision Repair), BER (Base Excision Repair), HR (Homologous Recombination), MMR (Mismatch Repair), NHEJ (Non-Homologous End-Joining).

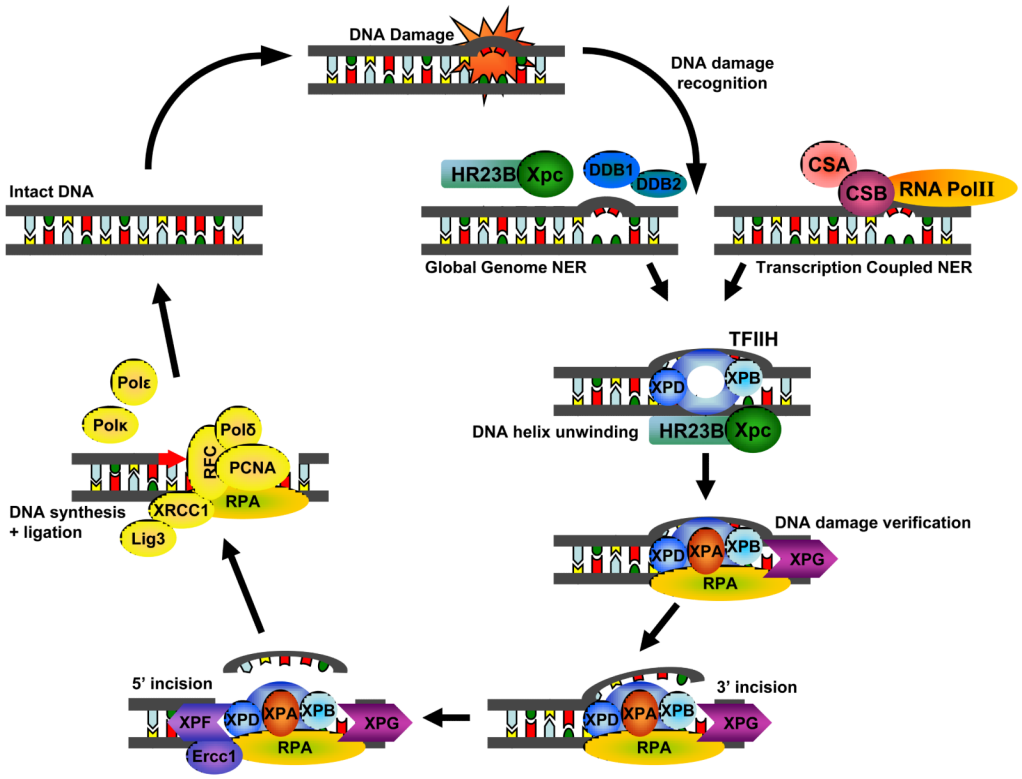


**Figure 2. Nucleotide Excision Repair**

Schematic overview of the Nucleotide Excision Repair (NER) pathway. Damaged DNA is recognized by either initial factors of the Global Genome Repair (a.o. Xpc) or Transcription Coupled Repair (CSA and CSB), which constitute the two different repair pathways in NER. After DNA damage recognition the repair route progresses along the same way. After helix unwinding and verification of the damage incisions are made to remove the faulty stretch of DNA. Finally, DNA synthesis and subsequent ligation reproduce the correct DNA sequence.

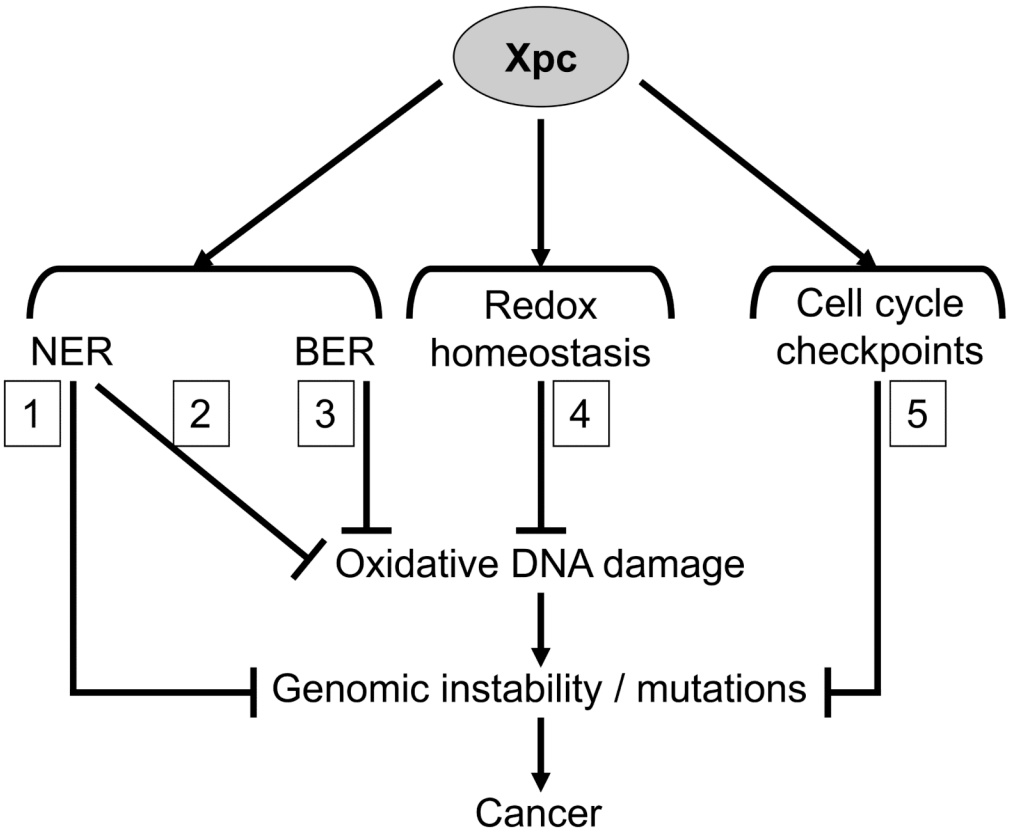


**Figure 3. Potential XPC functions**

Schematic overview of potential XPC functions and their subsequent consequence for cancer risk. XPC deficiency results into increased oxidative DNA damage, mutational load and genomic instability. Besides its functionality in NER (Route 1&2), XPC appears to be involved in BER (Route 3), anti-oxidant response (Route 4) and cell cycle progression (Route 5).

## Table 1

Overview of most abundant XP features and their average age of onset or frequency. Adapted from [5]

| Feature | % / age | Feature | % / age |
|---|---|---|---|
| *Cutaneous abnormalities* | | *Neurological abnormalities* | |
| Median age of onset of symptoms | 1.5 yr | Median age of onset | 6 mo |
| Median age of onset of freckling | 1.5 yr | Association with skin problems | 33% |
| Photosensitivity | 19% | Association with ocular abnormalities | 36% |
| Cutaneous atrophy | 23% | Low intelligence | 80% |
| Cutaneous telangiectasia | 17% | Abnormal motor activity | 30% |
| Actinic keratoses | 19% | Areflexia | 20% |
| Malignant skin neoplasms | 45% | Impaired hearing | 18% |
| Median age of first cutaneous neoplasm | 8 yr | Abnormal speech | 13% |
| *Ocular abnormalities* | | Abnormal EEG | 11% |
| Frequency | 40% | Microcephaly | 24% |
| Median age of onset | 4 yr | *Abnormalities associated with neurological defects* | |
| Conjunctival injection | 18% | Slow growth | 23% |
| Corneal abnormalities | 17% | Delayed secondary sexual development | 12% |
| Impaired vision | 12% | | |
| Photophobia | 2% | | |
| Ocular neoplasms | 11% | | |
| Median age of first ocular neoplasm | 11 yr | | |