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Nucleotide Excision Repair and Cancer

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1. Introduction

Cancer ranks as one of the most frequent causes of death worldwide and in Western society it is competing with cardiovascular disease as the number one killer. This high frequency in Western countries can be attributed to lifestyle and environmental factors, only 5-10% of all cancers are directly due to heredity. Common environmental factors leading to cancer include: tobacco (25-30%), diet and obesity (30-35%), infections (15-20%), radiation, lack of physical activity and environmental pollutants or chemicals (Anand et al.,2008). Exposure to these environmental factors cause or enhance abnormalities in the genetic material of cells (Kinzler KW et al.,2002). These changes in the DNA or hereditary predisposition can result in respectively uncontrolled cell growth, invasion and metastasis. Cancer cells can damage tissue and disturb homeostasis leading to dysfunctions in the body that can eventually lead to death.
Under normal conditions cell growth is under strict conditions and control. Hereditary dysfunctions or introduced DNA damage in tumor suppressor genes, oncogenes or DNA repair genes can create an imbalance that may lead to cancer development. DNA repair and cell cycle arrest pathways are essential cellular mechanisms to prevent or repair substantial DNA damage which, if left unattended, can cause diseases.
Here, one of the most important and versatile DNA repair pathways, the Nucleotide Excision Repair (NER) pathway, will be discussed in relation to DNA damage accumulation and carcinogenesis together with its mechanistic mode of action.

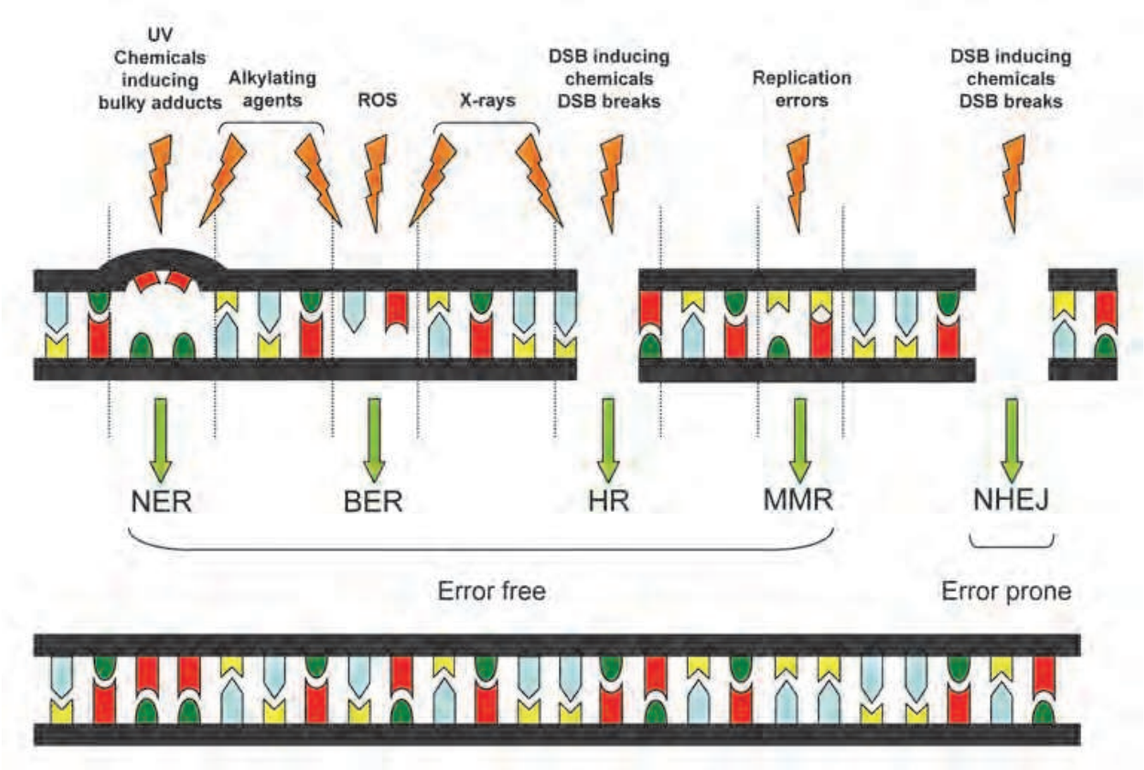
2. DNA damage

One of the initial steps in cancer development is the accumulation of DNA damage. These genomic assaults are abundant due to environmental factors and continuously ongoing metabolic processes inside the cell (Lodish et al.,2004). Endogenous DNA damage occurs at an estimated frequency of approximately 20,000 – 50,000 lesions per cell per day in humans (Lindahl,1993; Friedberg,1995), which roughly adds up to 10 - 40 trillion lesions per second in the human body. Endogenously generated lesions can occur through metabolic cellular processes and 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 (Cadet et al.,2003; Friedberg et al.,2006b). 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, ultraviolet (UV) radiation and exposure to chemical agents. One hour of sunbathing in Europe for example generates around 80,000 lesions per cell in the human skin (Mullaart et al.,1990). 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 biological responses to several types of DNA damage.
Reversal of DNA damage and excision repair pathways 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 (SSB or DSB) (Friedberg et al.,2006b). 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 lesion 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 light of this, cell cycle checkpoint activation and scheduled cell death (apoptosis) also enhance chances of genomic stability and in some cases cell survival. The responses, in which tumor suppressor factor p53 plays a major role, 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, thereby, annulling the possible negative effect of the DNA damage in those cells and hence maintaining homeostasis.

3. Nucleotide excision repair

The abundant targeting of bases and nucleotides in the genome makes the Nucleotide Excision Repair one of the most essential repair pathways. NER can restore the correct genomic information, but also replication and transcription after these types of damage. The pathway can deal with a broad spectrum of (mostly) structurally unrelated bulky DNA lesions, arisen from either endogenous or exogenous agents. NER for example removes DNA lesions from the genome such as photolesions, crosslinks, bulky aromatic hydrocarbon and alkylation adducts (Figure 1).
Nucleotide excision repair is a multistep pathway using 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 (Lo et al.,2005). Exposure to numerous chemicals can result in helix-distorting bulky adducts, for example polycyclic aromatic hydrocarbons (present in cigarette smoke or charcoaled meat) (de Boer et al.,2000). Interstrand crosslinks, alkylation adducts and oxygen free-radical induced minor base damage can trigger NER (Friedberg et al.,2006b).



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).

Fig. 1. DNA Repair pathways.

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 molecular route (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 somewhat more inefficient process, since it scans the whole genome for DNA damage (Guarente et al.,2008). However, UV induced helix-distorting lesions like 6-4PPs, are rapidly cleared by GG-NER (Garinis et al.,2006). 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 otherwise possible resulting 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 sub pathways 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 (Dip et al.,2004). The XPC/hHR23B complex is additionally essential for recruitment of the consecutive components of the NER machinery to the damaged site, also known as the preincision complex (Yokoi et al.,2000; Araujo et al.,2001).

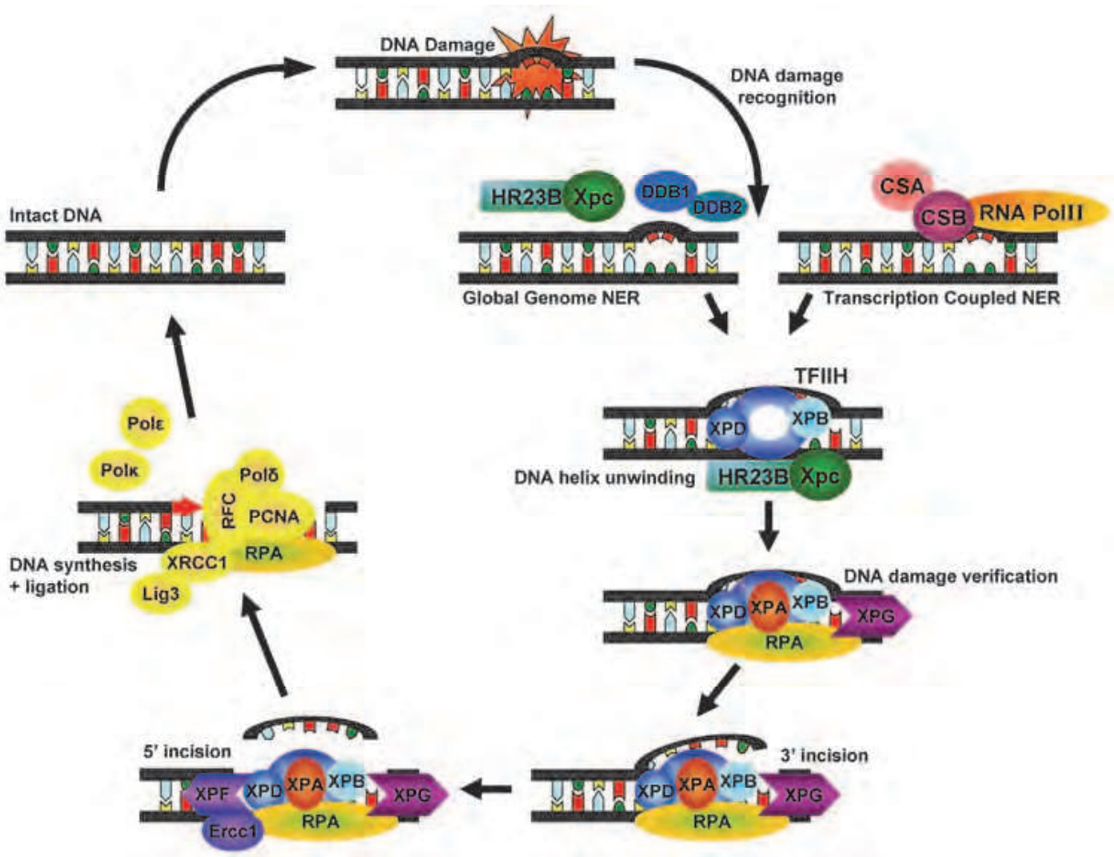


Fig. 2. Nucleotide Excision Repair.

Schematic overview of the Nucleotide Excision Repair (NER) pathway. Damaged DNA is recognized by either initial factors of the Global Genome Repair (e.g. 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.

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 (Nishi et al.,2005; Araki et al.,2001). The latter two are not able to bind to DNA themselves. Centrin2 as well as hHR23B stabilize the heterotrimer complex, putatively by inhibiting polyubiquitination of XPC and hence preventing subsequent degradation by the 26S proteasome (Nishi et al.,2005). 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 and the presence of single-

stranded DNA seems a crucial factor (Sugasawa et al.,2001; Sugasawa et al.,2002; Min et al.,2007). XPC appears to scan the DNA for distortions by migrating over the DNA, repeatedly binding and dissociating from the helix. When XPC encounters a lesion the protein changes its conformation and aromatic amino acid residues 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 (Hoogstraten et al.,2008).

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 therefore more easily recognized than CPDs, which only induce a minimal helical distortion (Sugasawa et al.,2005). More recent studies have indicated that UV-DDB facilitates recognition of lesions that are less well-recognized by the XPC-hHR23B complex, like CPDs, via ubiquitylation of XPC (Fitch et al.,2003).

The UV-DDB is able to recognize UV-induced photoproducts in the DNA and is now believed to precede the binding of XPC-hHR23B to the UV-damaged site. CPD repair is UV-DDB dependent (Fitch et al.,2003; Tang et al.,2000). Since affinity of the XPC-hHR23B to CPD sites is low, DDB2 is needed for efficient binding (Tang et al.,2000). Affinity of DDB2 for 6-4PP is also extremely high and the protein is furthermore able to bind to DNA lesions such as apurinic/apyrimidinic (AP) sites and mismatches (Nichols et al.,2000; Wittschieben et al.,2005). DDB2 is also part of the E3 ubiquitin ligase complex which is further comprised of CUL4A, ROC1/RBX1, COP9 signalosome (CSN) and DDB1 (Groisman et al.,2003). Live cell imaging studies show prompt recruitment of DDB1, DDB2 and Cul4a to UV induced lesions (Alekseev et al.,2008). CUL4A displays ubiquitin ligase activity and was shown to ubiquitylate DDB2 (Chen et al.,2001; Nag et al.,2001; Matsuda et al.,2005). The CSN subunit contains deubiquitylation capacities. This interactive mechanism is thought to be responsible for (poly)ubiquitylation of XPC and DDB2, but not in a similar fashion and result. Upon ubiquitylation DDB2 is degraded by the 26S proteasome (Fitch et al.,2003; Rapic-Otrin et al.,2002). XPC is not degraded after UV DNA damage, hereby increasing its binding affinity to the DNA as well as stimulating the interaction with hHR23B (Araki et al.,2001; Ortolan et al.,2004; Ng et al.,2003). Degradation of UV-DDB enhances the binding of XPC-hHR23B to the DNA *in vitro* (Sugasawa et al.,2005). Timing of the programmed degradation of DDB2 determines the recruitment of XPC-hHR23B to the UV-damaged site (El Mahdy et al.,2006).

The XPC protein contains several binding domains, a DNA binding domain, a hHR23B binding domain, centrin2 binding domain and a TFIIH binding domain (Sugasawa,2008). TFIIH is a multifunctional transcription factor and NER complex and amongst others contains the helicases XPB and XPD (Figure 2). This 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 have shown the recruitment of the NER complex to unwind the DNA is executed in a XPC-dependent manner (Sugasawa,2008; Friedberg et al.,2006b).

The XPC protein is redundant in TC-NER. Here a stalled RNA polymerase II (RNA polII) is the onset of the NER machinery. The proteins 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 (Tantin et al.,1997), while CSA does not (Tantin,1998). CSA mainly interacts with CSB, XAB2 (XPA binding protein 2) and the p44 subunit of the TFIIH complex (Henning et al.,1995; Nakatsu et al.,2000). The function of CSA

remains to be elucidated but is implicated to be required for TC-NER during elongation of the transcription process (Groisman et al.,2003; Kamiuchi et al.,2002). CSA is also part of an E3 ubiquitin ligase complex in which CUL4A, CSN and DDB1 are involved. Both CSA and CSB are part of RNA PolII associated complexes, but for CSB additional functions are assigned outside NER (Sunesen et al.,2002).
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 (Fousteri et al.,2008; Fousteri et al.,2006). But first, as in GG-NER, the TFIIH complex is recruited after damage recognition.

3.3 DNA helix unwinding

From DNA damage recognition and subsequent recruitment of TFIIH on, GG-NER and TC-NER converge into the same pathway. The TFIIH complex consists of 10 proteins: XPB, XPD, p62, pP52, 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 (Giglia-Mari et al.,2004; Goosen,2010). 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 (Figure 2) (Oksenych et al.,2010). The preincision complex consists of the XPA, RPA and XPG proteins and is assembled at the damage site (Zotter et al.,2006) (Figure 2). The function of XPA is verification of the lesion; in addition, XPA acts, together with the single strand DNA binding complex RPA, as an organizational orchestrator, so that the repair machinery is positioned around the lesion. The arrival of XPA and RPA leads to complete opening of the damaged DNA and catalyzes the release of the CAK complex from the TFIIH complex. Data suggest this step is essential for the initiation of incision/excision of the damaged DNA (Andressoo et al.,2006; Coin et al.,2008).
XPA and RPA in the preincision complex bind to the damaged DNA. Specific binding properties for certain structural DNA distortions have been reported for XPA, which suggests the protein recognizes conformations of the DNA and is able to verify the damage (Lao et al.,2000; Krasikova et al.,2010). XPA has no enzymatic activity to attribute to the incision step, but nevertheless is indispensable for DNA incision (Miyamoto et al.,1992). Through zinc finger motifs of XPA interaction with RPA is established (Ikegami et al.,1998). RPA consists of 3 subunits and with high affinity binds to the undamaged strand (de Laat et al.,1998b) (Figure 2). The protein roughly covers 30 nucleotides (corresponding in size to the excised product later in NER) and acts as a wedge between the DNA strands. It is also believed to protect the undamaged intact strand from inappropriate nuclease activity (de Laat et al.,1998a; Hermanson-Miller et al.,2002). RPA is concerned as the major component in the preincision complex, thereby also protecting the native template strand. 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 orchestrates the open complex formation (Krasikova et al.,2010; Park et al.,2006). Besides that, RPA later plays a role in the DNA repair synthesis and ligation steps (Shivji et al.,1995). XPA exhibits a moderate preference for binding to damaged DNA, as do other NER factors. Individually, the proteins XPA and RPA do not show sufficient selectivity to explain the high efficiency of NER lesion removal, which is most likely due to a discrimination cascade of recognition

and verification steps (Lin et al.,1992). XPA is thought to play a major role in verification, possibly by acting as a molecular sensor of aberrant electrostatic potential along the DNA substrate (Camenisch et al.,2008). Structural changes, like kinked backbones, in damaged DNA can induce deviant electrostatic potentials. Bulky adducts often result in sharply bent backbones due to the decrease of rigidity. Normally, base stacking supplies the DNA helix with strength and structure, but bulky lesions and hence loss of base stacking can weaken the sturdiness of the backbone. It is known that XPA has a higher affinity for kinked backbones. However how the exact recognition of the lesion is executed remains to be elucidated. But it is clear that the XPA-RPA complex is indispensable for the high efficiency of NER (Camenisch et al.,2008).

3.4 Incision, DNA repair synthesis and ligation

When the preincision complex is accurately positioned in relation to the damaged site by the XPA-RPA complex, single strand breaks are introduced by XPG and ERCC1-XPF (Figure 2). Several mechanistic theories were postulated over the years. A general consensus is that the combined actions of XPG and ERCC1-XPF result in excision of a 24-32 nucleotide long single strand fragment including the damaged site (Hess et al.,1997). XPG is responsible for the 3′ incision and is putatively recruited by the TFIIH complex (Zotter et al.,2006). According to some studies its presence appears to be necessary for ERCC1-XPF activity, which is responsible for carrying out the 5′ incision (Friedberg et al.,2006b; Wakasugi et al.,1997). 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 (Staresincic et al.,2009).

XPG is expected to have additional stabilization features, because of its ability to interact with XPB, XPD and several other subunits of the TFIIH complex(Friedberg et al.,2006b). Since loss of XPG results in very early death(Wijnhoven et al.,2007) the protein might be involved in systemic and important additional mechanisms, like transcription (Bessho,1999; Lee et al.,2002). Furthermore, XPG is suggested to have a role in oxidative damage removal (Dianov et al.,2000). The ERCC1-XPF seems to be a multifunctional complex as well, since it is also involved in interstand crosslink repair and homologous recombination (Niedernhofer et al.,2001; Al Minawi et al.,2009).

The excision of the damaged fragment is restored in original (undamaged) state by DNA synthesis and ligation steps (either by cut-patch-cut-patch mechanism or full excision followed by resynthesis and ligation). Both XPG and RPA are thought to be required for the transition between (pre)incision and post-incision events (Mocquet et al.,2008). XPG is thought to be involved in the recruitment of PCNA (Staresincic et al.,2009; Mocquet et al.,2008). Resynthesis of DNA requires PCNA because of its ability to interact with DNA polymerases (Mocquet et al.,2008). The mechanism of involvement of these polymerases in DNA resynthesis is not yet fully elucidated. Recent studies show at least three DNA polymerases are involved. Pol δ, Pol κ and Pol ε are recruited to damage sites (Figure 2). Recent *in vivo* studies show Pol β most likely plays no major role in NER (Ogi et al.,2010; Moser et al.,2007). To complete the repair of the damaged DNA site the resynthesized strand needs to be ligated. The primary participant in the subsequent ligation process of NER appears to be the XRCC1-Ligase 3 complex, which is shown to accumulate in both quiescent as well as proliferating cells after local UV irradiation (Moser et al.,2007). Ligase 1 appears to be involved in the ligation step in proliferating cells only (Moser et al.,2007). To date, the cross play of over 30 proteins in total is involved in NER to counteract DNA damage in the error free manner described above.

4. NER in cancer

DNA repair is vital to humans and other organisms and a defect in one of the genes can result in some 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 as Huntington's disease and ataxias (Friedberg et al.,2006b). DNA damage for example can cause mutations that trigger (pre-)oncogenes, inactivate tumor suppressor genes or other indispensable genes which cause loss of homeostasis. Defects in the DNA repair machinery will inflate the mutational load, since DNA damage will be left unattended and subsequently gene mutations will accumulate. 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 (Friedberg et al.,2006b; Cleaver et al.,2009).

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 (Mullaart et al.,1990; Lindahl,1993; Friedberg et al.,2006b; de Boer et al.,2000; Cleaver et al.,2009). 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 (Friedberg et al.,2006b; de Boer et al.,2000; Cleaver et al.,2009). Reason for this might be the involvement of several NER proteins in other significant cellular mechanisms. CSB is believed to be involved in (TC-)BER, while XPD is also associated with replication and transcription. Some of these affected mechanisms could overshadow the NER deficiency and ever increasing mutational load eventually predisposing an individual to cancer. Severely affected developmental and neurological systems 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 (Cleaver et al.,2009). It is a rare, autosomal inherited neurodegenerative and skin disease in which exposure to sunlight (UV) can lead 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 forms of XP (Bhutto et al.,2008).

Early malignancies (from 1-2 years of age) in parts of 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 (Figure 3). XP is associated with a more than 1,000-fold increase in risk of developing skin cancer. These cancers are mainly basal

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		

Adapted from Friedberg, E.C *et al.* 2006b

Table 1. Overview of some XP features and their average age of onset or frequency

and squamous cell carcinomas (45% of the XP patients) and to a lesser extent melanomas (Friedberg et al.,2006b) (Table 1). Besides skin cancers, XP patients have a 10-20 fold increased risk to develop internal cancers (Kraemer et al.,1984). The disease is mostly symptomatic during childhood. The mean latency time for cutaneous neoplasms is 8 years, this is in comparison to the general population in which the mean latency time is 50 years later (Kraemer,1997). Progressive neurological degeneration occurs in approximately 20% of the XP cases and can be correlated to deficiencies in specific XP genes (XPA, XPB, XPD and XPG) (Cleaver et al.,2009). XP-C and XP-F patients rarely develop neurological degeneration and if so with a later onset when compared for example to XP-A and XP-D patients (Kraemer,1997; Friedberg et al.,2006b). The heterogeneity in exhibited symptoms is correlated to the genetic heterogeneity in XP patients. XP-A, XP-B, XP-D and XP-G patients are in general the most severely affected and all these patients are defective in both GG-NER and TC-NER. Solely GG-NER is defective in XP-C and XP-E patients. XP-C and XP-E cells show higher survival rate after UV exposure than XP-A and XP-D cells for example (Friedberg et al.,2006b). This could be the reason that XP-C patients suffer less from sunburn. Most abundant XP variants in human are XP-A and XP-C (~50% of all XP cases) (Zeng et al.,1997).

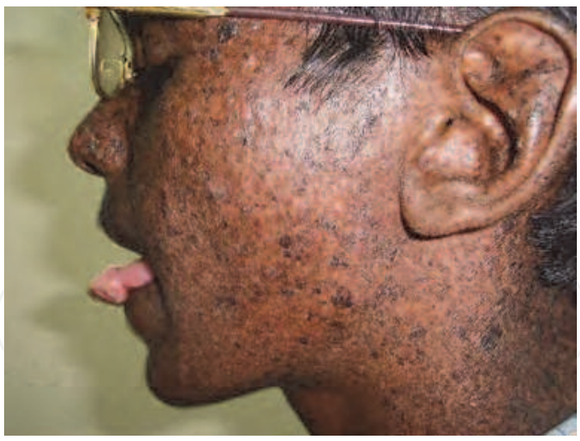


Fig. 3. Xeroderma pigmentosum.

Photo of a 19 year old Xeroderma pigmentosum patient suffering from hyperpigment skin lesions and a tongue carcinoma (IARC).

6. NER mouse models in cancer research

To investigate the role of the proteins involved in NER on survival and cancer development several transgenic mouse models were created, mimicking the existing NER mutations or deletions in humans. Table 2 shows an overview of NER mouse models and their accompanying spontaneous phenotypes. Selected knockout mouse models (*Xpa, Xpc* and *Xpe*) are described in more detail further below. These three models show a decreased lifespan in comparison to their concurrent wild type controls, but not as extreme as several other NER-deficient mouse models in Table 2. Therefore the mouse models survive long enough to study the effect of impaired NER on cancer development. Others, like *Xpb, Xpf, Xpg* and *Ercc1* deficient models are too short- lived to study carcinogenesis.

6.1 *Xpa* deficient mouse model

The first DNA repair defective models were the *Xpa*-deficient mouse models, generated by de Vries et al. (de Vries et al.,1995) and independently by Nakane et al (Nakane et al.,1995). *Xpa*-deficient mice appeared more cancer prone compared to their heterozygous and wild type littermates when exposed to carcinogenic and genotoxic compounds (de Vries et al.,1997b; Takahashi et al.,2002; Ide et al.,2001; Hoogervorst et al.,2005; Hoogervorst et al.,2004). As in humans, the mouse model exhibited a marked predisposition to skin cancer upon UV treatment of shaved dorsal skin (de Vries et al.,1995).

Survival studies without directed exposure were performed initially but always in a mixed genetic background, C57BL/6J/Ola129 (de Vries et al.,1997b) and C3H/heN strains(Takahashi et al.,2002) and fairly small numbers. However, both studies indicated that $Xpa^{-/-}$ mice (from here mentioned as *Xpa* mice) developed a significant number of spontaneous liver tumors. The C3H/heN strain wild type mice already showed 47% liver tumor incidence in the male mice within 16 months. The C57BL/6J/Ola129 mice were more resilient, no enhanced mortality was observed until the age of 1.5 years. The *Xpa* mice showed a 15% hepatocellular adenoma tumor incidence after 20 months, while there were no tumors in the wild type and heterozygous littermates. The lack of a pure genetic

Mouse model	Affected repair pathway	Enhanced spontaneous tumor response	Reference	Accelerated aging/developmental problems	Reference
Xpa$^{-/-}$	GG-NER/TC-NER	Yes, liver	(de Vries et al.,1997b; Melis et al.,2008; Tanaka et al.,2001)	Shorter life span, no pathology	(Melis et al.,2008)
Xpb$^{-/-}$	NER/transcription	n.a.		Impaired embryonic development	(Friedberg et al.,2006a)
Xpc$^{-/-}$	GG-NER	Yes, lung	(Hollander et al.,2005; Melis et al.,2008)	Shorter life span	(Melis et al.,2008)
Xpd^{TTD}	NER/transcription	No	(de Boer et al.,2002; Wijnhoven et al.,2005)	Shorter life span, aging and CR pathology	(de Boer et al.,2002; Wijnhoven et al.,2005)
Xpd^{XPCS}	NER/transcription	n.d.			
Xpe (DDB2)$^{-/-}$	GG-NER	Yes, various	(Ng et al.,2003; Yoon et al.,2005)		
Xpf$^{m/m}$	NER/ICL	n.a.		Very short life span, maximum 3 weeks	(Tian et al.,2004)
Xpg$^{-/-}$	TC-NER/transcription	n.a.		Very short life span, maximum 3 weeks	(Harada et al.,1999)
mHR23B$^{-/-}$	GG-NER	n.a.		Very short life span/embroynic lethality	(Ng et al.,2002)
Csa$^{-/-}$	TC-NER	No	(van der Horst et al.,2002)		
Csb$^{-/-}$	TC-NER/transcription	No	(van der Horst et al.,1997)	Normal life span, mild pathology	(van der Horst et al.,1997), unpublished results
Ercc1$^{-/-}$	NER/ICL	n.a.		Very short life span, maximum 4 weeks	(McWhir et al.,1993; Weeda et al.,1997)
Ercc1$^{\Delta 7/-}$	NER/ICL	No	Personal communication van Steeg/Dollé	Short life span of 4–6 months	(Weeda et al.,1997)

ICL = interstrand cross link, CR = caloric restriction
n.a.: not applicable, mouse models are too short lived to develop tumors
n.d.: not determined

Table 2. Overview of spontaneous phenotypes of NER-deficient mouse models

background for this and other mouse models made it harder to investigate the underlying cause of the phenotypic responses in these mice. An *Xpa* mouse model in a pure genetic

C57BL/6J background more recently was investigated (Melis et al.,2008). C57BL/6J mice showed a low baseline tumor response and appear therefore suitable for studying mutagenesis and tumorigenesis. In a pure genetic background a significant increase in liver tumors was observed (10%). A small (but not significant) increase in lung tumors was also observed (6.6% of the *Xpa* mice) (Melis et al.,2008). Correspondingly, mutation accumulation in the C57BL/6J *Xpa* mice was significantly increased during survival compared to wild type mice in liver, implicating an *Xpa* repair defect and subsequent mutation induction in carcinogenesis (Melis et al.,2008).

Like human XP-A patients, *Xpa* mice appeared predisposed to skin cancer after UV light exposure to shaved dorsal skin of the mice (de Vries et al.,1995; Tanaka et al.,2001). Heterozygous *Xpa* mice did not show this cancer prone phenotype after UV exposure, not even when the *Xpa* mutation was crossed in in hairless mice (Berg et al.,1997). Skin cancer predisposition in XP mice might not only involve NER deficiency, but several reports indicate enhanced immunosuppression and impaired natural killer cell function are involved (Gaspari et al.,1993; Horio et al.,2001; Miyauchi-Hashimoto et al.,2001). *Xpa* mice were also predisposed to tumors of the cornea when exposed to UV radiation, see Table 3 (de Vries et al.,1998).

Chemical exposure of *Xpa* mice to 7,12-dimethyl-1,2-benz[a]anthracene (DMBA) also resulted in skin cancer (de Vries et al.,1995). Several chemical exposures in *Xpa* mice however shed some more light on the cancer development other than skin cancer, which in humans is the predominant tumor phenotype (Table 3). For example, oral treatment of *Xpa* deficient mice with genotoxic carcinogens like benzo[a]pyrene (B[a]P), 2-acetylaminofluorene (2-AAF), and 2-amino-1-methyl-6-phenylimidazo [4,5-b]-pyridine (PhIP) resulted in lung tumors and lymphomas (B[a]P), liver and bladder tumors (2-AAF) and intestinal adenomas plus lymphomas (PhIP) (de Vries et al.,1997b; van Steeg et al.,1998; van Steeg et al.,2000; Ide et al.,2000). Other human carcinogens like cyclosporin A (CsA) and diethylstilbestrol (DES), although not directly mutagenic, showed to be carcinogenic in *Xpa* mice after 39 week exposure, but in contrary the low potent human carcinogen phenacetin did not result in a significant increase in tumors.

LacZ and *Hprt* mutation measurements in *Xpa* mice after B[a]P and 2-AAF treatment showed a 2-3 fold increase in mutations compared to wild type mice after only 12-13 weeks of exposure (Hoogervorst et al.,2005; van Oostrom et al.,1999; Bol et al.,1998; de Vries et al.,1997b). This increase in mutational load in comparison to wild type indicates *Xpa* mice are more sensitive to mutation accumulation, which consequently corresponds to the increased cancer susceptibility of *Xpa* mice.

The increased sensitivity towards cancer development of *Xpa* mice made it possible to identify genotoxic carcinogens even more accurate and faster when combined with heterozygosity for p53. This latter mouse model could be beneficial in reducing and refining *in vivo* carcinogenicity testing of compounds.

6.2 *Xpc* deficient mouse model

Two independent *Xpc*-deficient mouse models were also created in the mid-nineties (Cheo et al.,1997; Sands et al.,1995). As the *Xpa* mouse model, this model 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. Hereby, differences between pathways can be investigated.

Mouse model	Treatment	Target	Enhanced tumor response*	References
Xpa	UV-B radiation	Skin	Yes	(de Vries et al.,1995; Nakane et al.,1995)
	DMBA paint + TPA	Skin	Yes	(de Vries et al.,1995; Nakane et al.,1995)
	B[a]P gavage	Multiple, lymphomas	Yes	(de Vries et al.,1997a; van Oostrom et al.,1999)
	B[a]P diet	Stomach, esophagus	Yes	(Hoogervorst et al.,2003)
	B[a]P intratracheal instillation	Lung	Yes	(Ide et al.,2000)
	AFB1 i.p. injection	Liver	Yes	(Takahashi et al.,2002)
	PhIP diet	Lymphoma, small intestine	No	(Klein et al.,2001)
	4NQO drinking water	Tongue	Yes	(Ide et al.,2001)
	2-AAF diet	Liver, bladder, gall bladder	Yes	(Hoogervorst et al.,2005; van Kreijl et al.,2001)
	CsA	Lymphoma	Yes	(van Kesteren et al.,2009)
	DES	Osteosarcoma, lymphoma	Yes	(McAnulty et al.,2005)
	Wy	Liver	Yes	(van Kreijl et al.,2001)
	DEHP	Liver	No	Unpublished results
	p-cres	Liver	Yes	Unpublished results
Xpc	UV-B radiation	Skin	Yes	(Sands et al.,1995; Berg et al.,1998)
	2-AAF diet	Liver, bladder	Yes	(Hoogervorst et al.,2005)
	AAF i.p. injection	Liver, lung	Yes	(Cheo et al.,1999)
	NOH-AAF i.p. injection	Liver, lung	Yes	(Cheo et al.,1999)
	DEHP	Liver	No	Unpublished results
	p-cres	Liver	Yes	Unpublished results
Xpe/ DDB2	UV-B radiation	Skin	Yes	(Itoh et al.,2004)
	DMBA paint	Skin	No	(Itoh et al.,2004)

* in comparison to the untreated controls
DEHP = Di(2-ethylhexyl) phthalate
AFB1 = Aflatoxin B1
4NQO = 4-Nitroquinoline 1-oxide
WY = Wyeth-14643
p-cres = p-cresidine
NOH-AAF = N-hydroxyacetylaminofluorene

Table 3. Tumor responses in *Xpa, Xpc* and *Xpe* mice upon exposure

As in human XP-C patients, *Xpc* mice are highly predisposed to UV radiation-induced skin cancer (Table 3) (Berg et al.,1998; Cheo et al.,1996; Cheo et al.,2000; Friedberg et al.,1999; Sands et al.,1995). Contrasting to $Xpa^{+/-}$ mice the heterozygous *Xpc* mice are more susceptible to UV-induced skin cancer (but only at approximately from 1 year old) when compared to their wild type littermates. The haploinsufficient sensitivity could mean that XPC is a rate limiting factor in NER and since XPC is involved in damage recognition might explain the difference with *Xpa* heterozygous mice. Exposure studies with 2-AAF using *Xpc* mice showed a significant predisposition to liver and lung tumors compared to the heterozygous *Xpc* and wild type mice (Table 3) (Cheo et al.,1999; Friedberg et al.,2006b). Internal tumor incidence is higher in XP mice than in human XP, since patients normally develop skin cancer at a faster rate and die of resulting metastatic complications. NER is believed to be the sole pathway to remove CPD and 6-4PP lesions, while for chemical carcinogenic exposure other repair mechanisms are also present in the cell. In human, other types of cancer generally do not develop fast enough and are possibly overshadowed by skin cancers in XP.

In a mixed genetic background (C57BL/6J/129) no decrease in survival was found in relation to wild type mice, even though *Xpc* mice showed an extremely high and significantly increased lung tumor incidence (100%). However, in this study the wild type mice were not genetically related to the *Xpc* mice (Hollander et al.,2005). The spontaneous survival characteristics of *Xpc* mice in a pure genetic C57BL/6J background together with their related wild type littermates were also investigated. *Xpc* mice showed a significant decrease in survival, again exhibited a significant increase in lung and liver tumors and an increased mutation accumulation in these tissues compared to wild type mice (Melis et al., 2008). Here, *Xpc* mice showed a divergent tumor spectrum from *Xpa* 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 (Melis et al.,2008). Uehara *et al.* have shown that enhanced spontaneous age-related mutation accumulation in *Xpc* mice is tissue dependent. Liver, lung, heart and spleen exhibited an increase in mutant frequency compared to wild type, while this difference was not visible in brain and small intestine. Mutant frequencies of liver, lung and spleen are higher in *Xpc* mice compared to *Xpa* mice, just as the tumor incidence in this study (Melis et al.,2008). The additional increase in mutational load in *Xpc* mice might be caused by increased sensitivity towards oxidative DNA damage. XPC functioning has been implied in other DNA repair pathways like base excision repair and non-homologous end joining or might be involved in redox homeostasis (D'Errico et al.,2006; Despras et al.,2007; Liu et al.,2010; Okamoto et al.,2008; Rezvani et al.,2010; Shimizu et al.,2003; Uehara et al.,2009).

Chemical exposures to B[a]P (Wickliffe et al.,2006), 3,4-epoxy-1-butene (EB) (Wickliffe et al.,2006), DMBA (Wijnhoven et al.,2001) and UV-B (Ikehata et al.,2007) also showed significantly enhanced mutant frequencies compared to wild type mice in several tissues. Direct comparisons to *Xpa* mice in these studies have not been made, however when *Xpa* and *Xpc* mice were exposed to pro-oxidants (DEHP and paraquat) for 39 weeks, *Xpc* again exhibited a higher mutant frequency than *Xpa*.

6.3 *Xpe* deficient mouse model

In 2004 and 2005 Itoh *et al.* and Yoon *et al.* independently generated a strain of $DDB2^{-/-}$ mice (Itoh,2006; Itoh et al.,2004; Yoon et al.,2005). The latter group reported that $DDB2^{-/-}$ mice

show a decrease in spontaneous survival (n=10) compared to wild type (Yoon et al.,2005). Also the heterozygous *DDB2*$^{+/-}$ mice showed a decreased lifespan, although not as severe as the *DDB2*$^{-/-}$ mice. Six out of 10 *DDB2*$^{-/-}$ mice harbored tumors at the end of life, while 3 out of 10 *DDB2*$^{+/-}$ mice were tumor bearing (Yoon et al.,2005). *DDB2*$^{-/-}$ mice additionally showed to be cancer prone upon UV-B exposure, resulting in a significant increase in skin tumors (Table 3) (Itoh,2006; Itoh et al.,2004; Yoon et al.,2005). DMBA treatment however did not enhance tumor incidence compared to wild type (Table 3) (Itoh,2006; Itoh et al.,2004). DDB2 deficiency is, due to these and other studies, since being classified as a XPE phenotype. Besides UV-B and DMBA exposure, other *in vivo* carcinogen exposures have not been reported in these models so far. DDB2 is well conserved between humans and mice and appears to function as a tumor suppressor, at least in part, by controlling p53-mediated apoptosis after UV-irradiation (Itoh et al.,2004).

7. Conclusion

DNA repair has proven to be of vital importance and protects or at least delays cancer development and several age-related diseases. DNA damage accumulation and consequent mutation accumulation is considered pathogenic. NER has been shown to be a highly versatile and important DNA repair pathway, removing helix distorting DNA damages. Mutations in the XP genes of NER in human can result in the severe syndrome Xeroderma pigmentosum, which is accompanied by a cancer predisposition and severe UV sensitivity. Mouse models mimicking this human syndrome are important to study cancer development and the consequences of persistent DNA damage. Novel functionality of DNA repair proteins and implications of their deficiency in mutagenesis, cell cycle regulation, carcinogenesis and aging were discovered using NER-deficient models. Besides mechanistic insight these models can be used as a refined model in carcinogenicity testing, especially in combination with p53 heterozygosity. The increased cancer susceptibility can be beneficial towards a decrease in the number of animals used and the duration of carcinogenicity testing.

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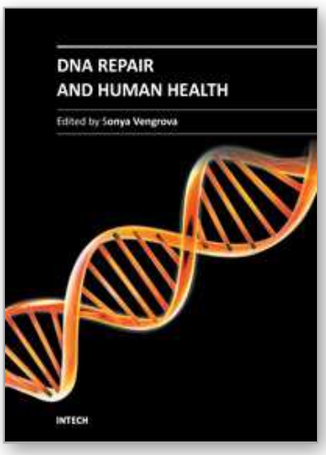

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Over the past decades, great advances have been made in understanding the cellular DNA repair pathways. At the same time, a wealth of descriptive knowledge of human diseases has been accumulated. Now, the basic research of the mechanisms of DNA repair is merging with clinical research, placing the action of the DNA repair pathways in the context of the whole organism. Such integrative approach enables understanding of the disease mechanisms and is invaluable in improving diagnostics and prevention, as well as designing better therapies. This book highlights the central role of DNA repair in human health and well-being. The reviews presented here, contain detailed descriptions of DNA repair pathways, as well as analysis of a large body of evidence addressing links between DNA damage repair and human health. They will be of interest to a broad audience, from molecular biologists working on DNA repair in any model system, to medical researchers.

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