Nucleotide excision repair in aging & cancer

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Chapter 1

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Introduction

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"Some things should be simple. Even an end has a start"

An End Has A Start – Editors, 2007

DNA repair and p53 in aging and cancer – Guardians of genomic stability

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. Reason for 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: diet and obesity (30-35%), tobacco (25-30%), infections (15-20%), radiation, lack of physical activity and environmental pollutants or chemicals [1]. Exposure to these endogenous and exogenous factors causes or enhances abnormalities in the genetic material of cells [2]. These changes in the DNA or hereditary predisposition can result into 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 subsequently can cause diseases.

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.

In this thesis one of the most important and versatile DNA repair pathways, the Nucleotide Excision Repair (NER) pathway, is investigated in relation to carcinogenesis and mechanistic modes of action. Additionally, the role in carcinogenesis of the most frequently mutated gene in (human) cancer, the tumor suppressor p53, has been investigated. Several mouse models that have impaired DNA repair capacity and/or impaired p53 functionality were used to clarify the different roles of involved proteins in DNA repair, cancer predisposition and carcinogenesis. Additionally, these models can be used as an alternative improved model for carcinogenicity testing of compounds.

2. DNA damage

Genomic assaults are abundant due to environmental factors and continuously ongoing metabolic processes inside the cell [3]. Endogenous DNA damage occurs at an estimated frequency of approximately 20,000 – 50,000 lesions per cell per day in humans [4;5], 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 [6;7]. 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 [8]. 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 [7]. 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 kind are able to handle the lesions in an error-free way). Even though error-prone mechanisms do not result in restoration of 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 [9]. 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 [9].

In human, patients that are affected in these DNA repair or tumor suppressive pathways often suffer from increased or cancer susceptibility or other accelerated age-related phenotypes. Patients affected in the NER pathway for example suffer from severe cancer prone or premature aging syndromes depending on which protein is deficient in the pathway. DNA damage induced by sunlight (UV) or chemical exposure or the body's metabolism can't be repaired sufficiently and thereby causes tumor initiation and/or imbalanced cellular homeostasis. This thesis will focus on the functionality of the NER pathway and the additional role of impaired tumor suppression by loss of functionality of p53.

2.1 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 sources. 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 [10]. Exposure to numerous chemicals can result into helix-distorting bulky adducts, for example polycyclic aromatic hydrocarbons (present in cigarette smoke or charcoaled meat) [11] (Figure 1).

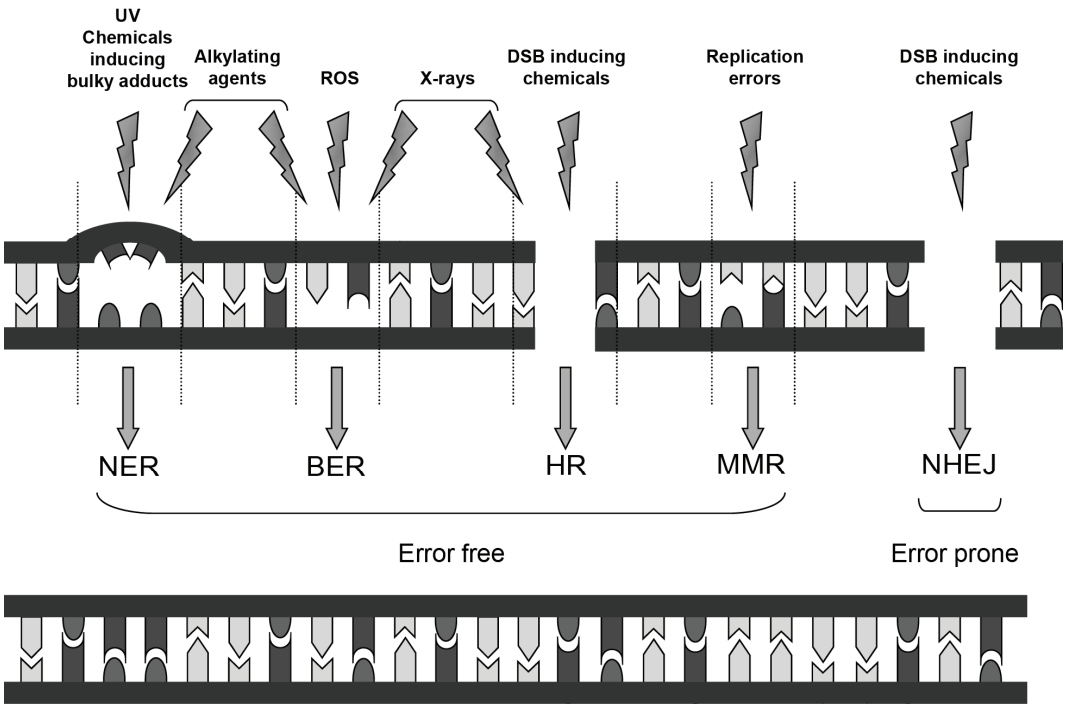

Figure 1. DNA repair pathways. Schematic overview of DNA repair pathways. Several types of induced DNA damage can trigger different repair pathways, which can repair the DNA in an error-free or an error-prone manner. NER (nucleotide excision repair), BER (base excision repair), HR (homologous recombination), MMR (mismatch repair), NHEJ (non-homologous end-joining)

2.1.1 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 [12]. However, UV induced helix-distorting lesions like 6-4PPs, are rapidly cleared by GG-NER [13]. 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.

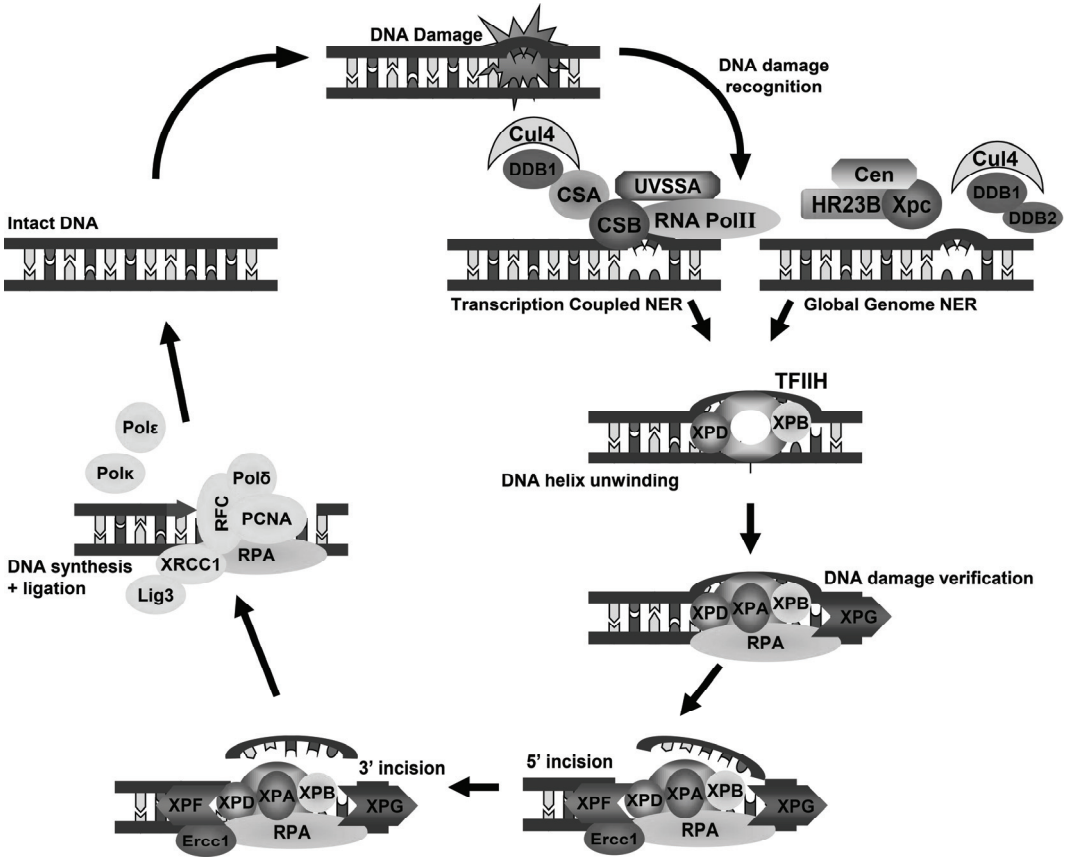

Figure 2. Schematic overview of the nucleotide excision repair (NER) pathway. Damaged DNA is recognized by either initial factors of the global genome repair (a.o. XPC) or transcription coupled repair (CSA and CSB), which constitute the two different repair pathways in NER. After DNA damage recognition 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.

2.1.2 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 [14]. 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 [15;16].

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 [17;18]. Centrin2 as well as hHR23B stabilize the heterotrimer complex, putatively by inhibiting polyubiquitination of XPC and hence preventing subsequent degradation by the 26S proteasome [17]. 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 [19-21]. 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 [22]. 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 [22].

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 [23]. 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 [24]. 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 [24;25]. Since affinity of the XPC-hHR23B to CPD sites is low, DDB2 is needed for efficient binding [25]. Upon ubiquitylation DDB2 is degraded by the 26S proteasome [24;26], hereby increasing binding affinity of XPC to the DNA as well as stimulating the interaction of XPC with hHR23B [18;27;28]. Degradation of UV-DDB enhances the binding of XPC-hHR23B to the DNA *in vitro* [23]. Timing of the programmed degradation of DDB2 determines the recruitment of XPC-hHR23B to the UV-damaged site [29].

The XPC protein contains several binding domains: a DNA binding domain, a hHR23B binding domain, centrin2 binding domain and a TFIIH binding domain [30]. 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 [7;30].

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 [31], while CSA does not [32]. CSA mainly interacts with CSB, XAB2 (XPA binding protein 2) and the p44 subunit of the TFIIH complex [33;34]. The function of CSA remains to be elucidated but seems to be implicated in TC-NER during elongation of the transcription process [35;36]. Both CSA and CSB are part of RNA PolII associated complexes, but for CSB additional functions are assigned outside NER [37].

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 [38;39]. But first, as in GG-NER, the TFIIH complex is recruited after damage recognition.

2.1.3 DNA helix unwinding

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 [40;41]. 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 [42] (Figure 2). The preincision complex further consists of the XPA, RPA and XPG proteins and is assembled around the damage site [43] (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 [44;45] 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 [46;47]. 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 [48;49].

2.1.4 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 [50]. XPG is responsible for the 3' incision and is putatively recruited by the TFIIH complex[43]. According to some studies presence of XPG appears to be necessary for ERCC1-XPF activity, which is responsible for carrying out the 5' incision [7;51]. 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[52].

XPG is expected to have additional stabilization features, it is able to interact with XPB, XPD and several other subunits of the TFIIH complex[7]. Since loss of XPG results in lethality a few weeks after birth [53] the protein might be involved in systemic and important additional mechanisms, like transcription[54;55]. Furthermore, XPG is believed to play a role in oxidative damage removal[56]. The ERCC1-XPF seems to be a multifunctional complex as well, since it is also involved in interstrand crosslink repair and homologous recombination [57;58].

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 [59]. XPG is thought to be involved in the recruitment of PCNA [52;59]. Resynthesis of DNA requires PCNA because of its ability to interact with DNA polymerases [59]. The way which and how these polymerases are involved in DNA resynthesis is not fully elucidated yet. 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 [60;61]. 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 [61]. Ligase 1 appears to be involved in the ligation step in proliferating cells only [61]. To date, the cross play of over 40 proteins in total is involved in NER to counteract DNA damage in the error free manner described above.

3. 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 [7]. 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 [7;62].

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 [4;7;8;11;62]. 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 [7;11;62]. 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 (of which deficiency causes TTD) 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. Since the focus of this thesis is the impact of deficiencies in NER on carcinogenesis, the XP syndrome will be discussed in more detail. The CS and TTD syndromes will not be discussed in detail in this thesis, but

more information and details can be obtained in the comprehensive review of NER by Cleaver et al [62].

3.1 Xeroderma pigmentosum

Xeroderma pigmentosum (XP), meaning parchment pigmented skin, was the first human causal NER-deficient disease identified [62]. 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 [63].

Early malignancies 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 [7]. Besides skin cancers, XP patients have a 10-20 fold increased risk of developing internal cancers [64]. The median 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 [65]. 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) [62]. XP-C and XP-F patients rarely develop neurological disorders [7;65]. 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 [7].

Most abundant XP variants in human are XP-A and XP-C (~50% of all XP cases) [66]. To investigate the involvement of these proteins on survival, aging and cancer development mouse models were created, mimicking existing NER mutations or deletions in humans. These mouse models are also crossed with the cancer prone p53 mouse model to investigate the role of NER and p53 in carcinogenesis.

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		

Table 1. Overview of most abundant XP features, including average age of onset or frequency of the specific feature in patients overall (indicated by %)

3.2 p53 in DNA repair and cell cycle arrest

p53 is the most mutated gene found in (human) cancers. Previous reports estimated that over 50% of the cancers have a mutation in the p53 gene; however, a more recent update even mentions p53 is mutated in 70% of the human cancers (15th p53 workshop 2010). In addition, p53 appears to be one of the key regulatory proteins in the cell and is connected to a broad variety of molecular mechanisms. The p53 was first identified as a cellular partner of an oncoprotein in the tumor Simian Virus, but was later dubbed as a tumor suppressor and designated as a transcription factor induced by stress, which can promote cell cycle arrest, apoptosis and senescence [67]. More recently, additional functions were added to the functional spectrum of p53, e.g. the regulation of metabolic pathways and cytokines that are required for embryo implantation [67]. One of the most pivotal roles of p53 is guarding the genome and tissue homeostasis.

The crucial event in the induction of the p53 pathway is the uncoupling of p53 from its key negative regulators, principally MDM2 and MDM4, which leads to the accumulation of stable active p53 (Figure 3). P53 induction in response to DNA damage is coordinated by the ataxia–telangiectasia mutated

(ATM) and ataxia–telangiectasia and Rad3-related (ATR) protein kinases, which mediate the rapid destruction of MDM2 and MDM4 [68;69].

ATM plays a crucial part in the immediate response to double-strand breaks, while replication stress and DNA crosslinking [70] is coordinated mainly through ATR, although interplay does exist. P53 also plays a role in regulating NER ([71;72].

P53 is stabilized and activated in response to a wide range of cellular stresses, including DNA damage and hyperproliferation [70;73]. Downstream p53 effects are possible by altering gene expression in several processes. Antiproliferative functions of p53 include cell cycle checkpoints, cellular senescence and apoptosis [7;70;74].

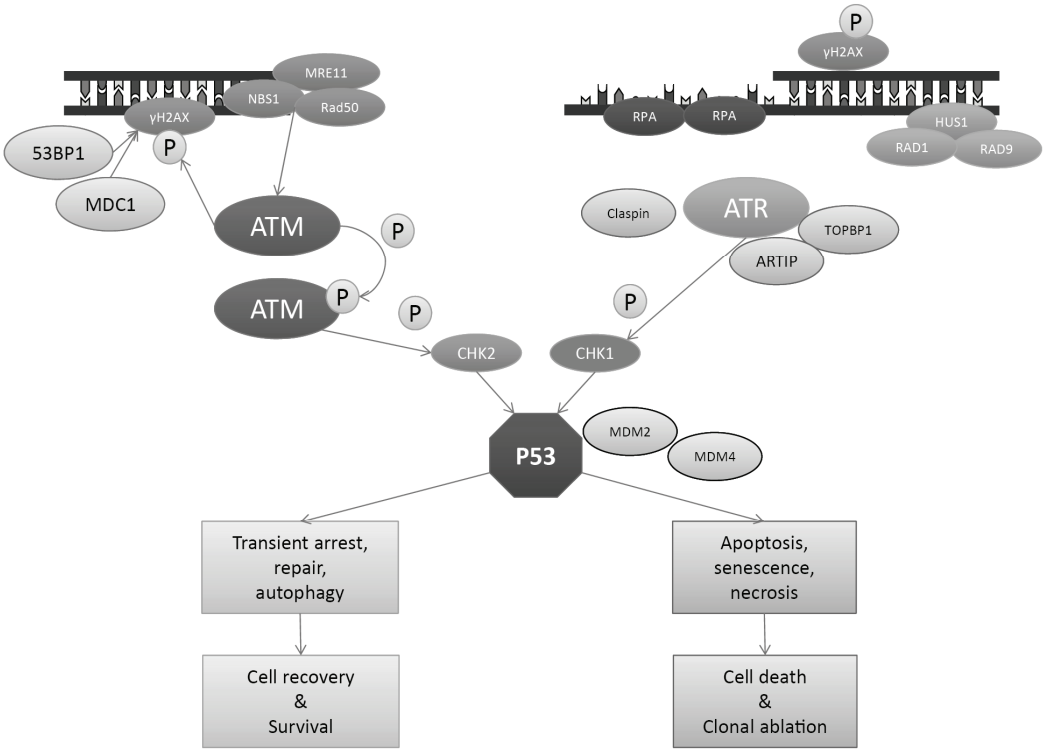

Figure 3. Schematic overview of DNA damage response and p53-signaling

Cell cycle checkpoints ensure the fidelity of cell division, verifying whether the processes at each phase of the cell cycle are accurately completed before progression into the following phase. Upon cellular stress cells can undergo growth arrest at these checkpoints, in which p53 regulation plays a key role. Cells can also enter a state of permanent cell cycle arrest, called senescence. Dysfunctional telomeres, DNA damage and excessive mitochondrial signaling are some of the causes that can induce senescence via p53 [74]. Apoptosis is another important effector function of downstream p53

regulation where cells are forced into cell death. In contrast to traumatic cell death (necrosis) apoptosis is a functional, programmed and overall beneficial process. Defective apoptotic routes can lead to a variety of diseases and complications, one of them being cancer development.

The protein's key role in tumor suppression and the fact that p53 has been implied in interacting with and regulation of NER made it very interesting to create mouse models that lack either functional NER and/or have diminished p53 functionality.

4. Cancer research - XP and p53 mouse models

4.1 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.

Mouse model	**Affected repair pathway**	**Enhanced spontaneous tumor response**	**Reference**	**Accelerated aging/developmental problems**	**Reference**
Xpa$^{-/-}$	GG-NER/TC-NER	Yes, liver	[81-83], this thesis	Shorter median life span, no pathology	This thesis, [82]
Xpb$^{-/-}$	NER/transcription	n.a.		Very early lethality (2-cell stage)	[120]
Xpc$^{-/-}$	GG-NER	Yes, lung	[82;102], this thesis	Shorter life span	This thesis, [82]
Xpd^{TTD}	NER/transcription	No	[121;122]	Shorter life span, aging and CR pathology	[121;122]
Xpd^{XPCS}	NER/transcription	n.d.			
Xpe (DDB2)$^{-/-}$	GG-NER	Yes, various	[28;123]		
Xpf$^{m/m}$	NER/ICL	n.a.		Very short life span, maximum 3 weeks	[124]
Xpg$^{-/-}$	TCR/transcription	n.a.		Very short life span, maximum 3 weeks	[125]
mHR23B$^{-/-}$	GG-NER	n.a.		Very short life span/embryonic lethality	[126]
Csa$^{-/-}$	TC-NER	No	[127]		
Csb$^{-/-}$	TCR/transcription	No	[128]	Normal life span, mild pathology	[128], unpublished results
Ercc1$^{-/-}$	NER/ICL	n.a.		Very short life span, maximum 4 weeks	[129;130]
Ercc1$^{\Delta 7/-}$	NER/ICL	No	van Steeg / Dollé	Short life span of 4–6 months	[130]

Table 2. Overview of spontaneous phenotypes of a selection of NER-deficient mouse models**.**
n.a.: not applicable, mouse models are too short lived to develop tumors, n.d.: not determined

Table 2 shows an overview of a selection of NER mouse models and their accompanying spontaneous phenotypes.Selected knockout mouse models (*Xpa* and *Xpc*) are described in more detail further below. These two models show a decreased lifespan in comparison to their concurrent wild type controls, but not as extreme as some other NER-deficient mouse models described in Table 2. Therefore the *Xpa* and *Xpc* mouse models survive long enough to study the effect of impaired NER on cancer development. Others, like *Xpb, Xpf, Xpg* and *Ercc1*-deficient models for example are too short lived to study carcinogenesis, but show signs of accelerated aging and are used to study this process.

4.1.1 *Xpa*-deficient mouse model

The first DNA repair defective models were the *Xpa*-deficient mouse models, generated by de Vries et al. [75] and independently by Nakane et al [76]. *Xpa*-deficient mice appeared more cancer prone compared to their heterozygote and wild type littermates when exposed to carcinogenic and genotoxic compounds [77-81]. As in humans, the mouse model exhibited a marked predisposition to skin cancer upon UV treatment of shaved dorsal skin [75].

Survival studies without directed exposure were performed initially in a mixed genetic background, *i.e.* C57BL/6J/Ola129[81] and C3H/heN strains[77] and in 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, but 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 heterozygote littermates of the same age. The lack of a congenic background for this and other mouse models made it harder to investigate the phenotype in these mice. Therefore, an *Xpa* mouse model in a congenic C57BL/6J background was investigated (this thesis) [82]. C57BL/6J mice showed a low baseline tumor response and appear therefore suitable for studying mutagenesis and tumorigenesis. In a congenic background a significant increase in liver tumors was also observed (10%). A small (but not significant) increase in lung tumors was also observed (6.6% of the *Xpa* mice) (this thesis) [82]. 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 (this thesis) [82].

Like human XP-A patients, *Xpa* mice appeared predisposed to skin cancer after UV light exposure to shaved dorsal skin of the mice [75;83]. 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 [84]. 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 [85-87]. *Xpa* mice were also predisposed to tumors of the cornea when exposed to UV radiation, see Table 3 [88].

Chemical exposure of *Xpa*$^{-/-}$ mice to 7,12-dimethyl-1,2-benz[a]anthracene (DMBA) also resulted in skin cancer [75]. 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) [81;89-91]. Other human carcinogens like Cyclosporin A and DES, although not directly mutagenic, showed to be carcinogenic in *Xpa* mice after 39 week exposure, but in contrast the low potent human carcinogen phenacetin did not result in a significant increase in tumors.

Mouse model	Treatment	Target	Enhanced tumor response*	References
Xpa	UV-B radiation	Skin, eye	Yes	[75;76]
	DMBA paint + TPA	Skin	Yes	[75;76]
	B[a]P gavage	Multiple, lymphomas	Yes	[92;94]
	B[a]P diet	Stomach, esophagus	Yes	[131]
	B[a]P intratracheal instillation	Lung	Yes	[91]
	AFB1 i.p. injection	Liver	Yes	[77]
	PhIP diet	Lung, lymphoma, small intestine	Yes	[132]
	4NQO drinking water	Tongue	Yes	[78]
	2-AAF diet	Liver, bladder, gall bladder	Yes	[79;133]
	CsA	Lymphoma	Yes	[134]
	DES	Osteosarcoma, lymphoma	Yes	[135]
	Wyeth 14.643	Liver	Yes	[133]
	DEHP	Liver	No	This thesis
	p-cres	Liver	Yes	Unpublished results
	Phenacetin	Kidney	No	[136]
Xpc	UV-B radiation	Skin	Yes	[95;97]
	2-AAF diet	Liver, bladder	Yes	[79]
	AAF i.p. injection	Liver, lung	Yes	[101]
	NOH-AAF i.p. injection	Liver, lung	Yes	[101]
	DEHP	Liver	No	This thesis
	p-cres	Liver	Yes	Unpublished results

Table 3. Overview of carcinogen exposure in the *Xpa* and *Xpc* mouse models.
* in comparison to the untreated controls

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 only after 12-13 weeks of exposure [79;92-94]. 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.

4.1.2 *Xpc*-deficient mouse model

Two independent *Xpc*-deficient mouse models were also created in the mid-nineties [95;96]. As the *Xpa* mouse model, this model is also 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 in *Xpc* and *Xpa*-deficient mouse models.
As in human XP-C patients, *Xpc* mice are highly predisposed to UV radiation-induced skin cancer (Table 3) [95;97-100]. Contrasting to $Xpa^{+/-}$ mice the heterozygous *Xpc* mice are more susceptible to UV-induced skin cancer when compared to their wild type littermates [99]. The haploinsufficient sensitivity could mean that XPC is a rate limiting factor in NER. Exposure studies with 2-AAF using *Xpc* mice showed a significant predisposition to liver and lung tumors compared to the heterozygous *Xpc* mice and wild types (Table 3) [7;101]. NER is believed to be the sole pathway to remove CPD and 6-4PP lesions, while for several other lesions different 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. Internal tumor incidence is therefore higher in XP mice than in human XP, since mice are not normally exposed to UV.

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, the wild type mice were not genetically related to the Xpc mice in this study [102]. The spontaneous survival characteristics of *Xpc*-deficient mouse model in a congenic C57BL/6J background together with their related wild type littermates were also investigated (this thesis). *Xpc* mice exhibited a significant decrease in survival, again showed a significant increase in lung and liver tumors and an increased mutation accumulation in these tissues compared to wild type mice (this thesis) [82]. 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 indicated that 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 (this thesis) [82]. Uehara *et al.* [103] 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. Compared to *Xpa* mice mutant frequency is higher in *Xpc* in liver, lung and spleen, just as the tumor incidence (this thesis) [82]. The additional mutation increase 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[103-109].
Exposures to B[*a*]P[110], 3,4-epoxy-1-butene (EB)[110], DMBA[111] and UV-B[112] 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* (this thesis).

4.1.3 *Xpa*p53* and *Xpc*p53*-deficient mouse models

Several p53 mouse models have been created over the last decades, many of which are accompanied by an increased response in tumor incidence and tumor onset. The *Trp53* knockout mouse develops normally but has an early spontaneous tumor response, on average 4-5 months of age [113;114]. The heterozygous knockout *Trp53* mouse, is also prone to low spontaneous (~50% of the animals after 18 months) and induced tumor formation [115]. Spontaneous tumor formation after 26 weeks in p53 heterozygote mice however is low (2.8% in males, 6% in females[115]). The heterozygote p53 model is, because of the relatively low spontaneous tumor incidence, suitable for detecting possible carcinogenic potency of compounds (up to 9 months of exposure). However, this model appeared to produce a high rate of false negative and false positive compounds in carcinogenicity testing [116].

A deficiency in either the *Xpa* or *Xpc* gene with the heterozygote state of *Trp53* in mice was combined to investigate carcinogenesis and additionally the potential use of these double mutants in carcinogenicity testing ([117], this thesis). DNA damage accumulation normally induces a p53 driven anti-proliferative response. The *XP*p53* double mutant mouse models would theoretically be able to accumulate more DNA damage, especially upon genotoxic exposure. We have shown that an increase in incidence and a shorter latency period for developing cancer is the result of genotoxic exposure, due to the diminished tumor suppressive capacity of p53. Therefore, the deficient *XP*p53* mouse models appear to be suitable for identifying carcinogens.

Previously, we have been able to demonstrate that *Xpa*p53* is a promising mouse model to test carcinogenic potency of compounds for humans [117;118]. Very high accuracy for predicting genotoxic carcinogenic compounds was established in a relatively short-term bioassay. However, exposure doses have to be adapted compared to the wild type situation to test compound carcinogenicity since *Xpa* deficiency leads to an increased sensitivity towards toxicity (this thesis). The *Xpc*p53* mouse model appears to be even more promising for predicting carcinogenicity of compounds ([119], this thesis). Since the XPC protein is dispensable for transcription coupled repair, the toxicity sensitivity is comparable to wild type, while the increased sensitivity towards genotoxic carcinogenic compounds remains. Additionally, several non-genotoxic carcinogens which are normally hard to distinguish from non-carcinogens other than in a two-year bioassay can be correctly assessed by the *Xpc*p53* model (this thesis).

5. Aim and Outline of this thesis

As mentioned in the introduction (**Chapter 1**), the role of DNA repair and tumor suppressor p53 in maintaining genomic stability is vital. Loss of function of DNA repair genes or the p53 gene has a substantial effect on cancer susceptibility. In this thesis the role of the highly versatile and essential DNA repair pathway, the Nucleotide Excision Repair (NER), has been investigated in regards to cancer development. NER-deficient mouse models have been created to mimic the human NER-deficiency, resulting in the highly cancer prone syndrome Xeroderma pigmentosum. Mouse models deficient for two key proteins in NER, XPA or XPC, have been investigated in this thesis. Extensive phenotyping studies have been performed in wild type mice, *Xpa* and *Xpc* mouse models. **Chapter 2** elaborates on the normal (wild type) survival and aging study. Here we investigated which parameters and processes are changed and regulated on pathological and transcriptional level during lifetime and could be

indicative for and contribute to age-related diseases like cancer, inflammation and cardiovascular disease.

The survival studies of both NER-deficient mouse models used for phenotyping these models, demonstrated that these mice are more cancer prone than the wild type mice, even without additional (carcinogenic) exposure (**Chapter 3**). Although being functional in the same DNA repair pathway, the two models exhibited a divergency in mutation induction and consequential tumor spectrum (**Chapter 3**). We accredited the XPC protein having an additional function outside NER, involved in oxidative damage prevention or repair. Therefore, we exposed both NER-deficient mouse models and wild type controls to pro-oxidants. This study indicated that *Xpc*-deficient mice are more sensitive to oxidative DNA damage, resulting in an increased mutational load and subsequent cancer risk (**Chapter 4**). Gene expression profiling revealed that *Xpc*$^{-/-}$ mice have a lower anti-oxidant response than *Xpa*$^{-/-}$ and wild type mice, supporting recent *in vitro* results by others and possibly explaining the sensitive response towards oxidative DNA damage and the increase in lung tumor response (**Chapter 3 + 4**).

Chapter 5 describes the effect on cancer susceptibility when NER-deficiency is combined with *p53* heterozygosity. The effect of increased DNA damage accumulation and deregulation in tumor suppressor response results in an increased cancer proneness, which could be applicable as a suitable alternative method for short-term carcinogenicity testing. The *Xpa*p53* and *Xpc*p53* mouse mouse models were compared to each other in regards to their cancer susceptibility, testing genotoxic as well as non-genotoxic carcinogens. Exposure to one of the genotoxic compounds, 2-AAF, resulted in a substantial increase in bladder tumors, which was also shown in heterozygous *p53* mice. We discovered that this exposure resulted in a novel route of expression of a functional p53 isoform, namely through the introduction of selective nonsense mutations in the 5' part of the murine *p53* gene (**Chapter 6**). All findings and general conclusions are described in **Chapter 7**.

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