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Lessons learned from DNA repair defective syndromes

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Abstract: Genomic instability is the driving force behind cancer development. Human syndromes with DNA repair deficiencies comprise unique opportunities to study the clinical consequences of faulty genome maintenance leading to premature aging and premature cancer development. These syndromes include chromosomal breakage syndromes with defects in DNA damage signal transduction and double-strand break repair, mismatch repair defective syndromes as well as nucleotide excision repair defective syndromes. The same genes that are severely affected in these model diseases may harbour more subtle variations in the 'healthy' normal population leading to genomic instability, cancer development, and accelerated aging at later stages of life. Thus, studying those syndromes and the molecular mechanisms behind can significantly contribute to our understanding of (skin) cancerogenesis as well as to the development of novel individualized preventive and therapeutic anticancer strategies. The establishment of centers of excellence for studying rare genetic model diseases may be helpful in this direction.

Key words: double-strand break repair – genetic recombination – genetic skin diseases – mismatch repair – nucleotide excision repair

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Introduction

The events of spontaneous mutation development are much too rare to account for the cancer risk in humans (1). Usually, multiple different gene mutations are necessary to allow for the malignant transformation of a cell. A cellular 'mutator phenotype' because of faulty genome maintenance and repair systems may be required for tumorigenesis. The genome of human cells as well as cells from many other procaryotes and eucaryotes contain mechanisms to protect themselves from endogenous or exogenous substances that damage cellular DNA (2). The DNA repair enzymes constantly scan the global genome to detect and remove DNA damage and damage to single nucleotides. To date, more than 130 DNA repair enzymes have been identified that secure genomic integrity (3). Direct reversion of the DNA damage, double-strand break (DSB) DNA repair via homologous or non-homologous recombination as well as the excision of the DNA damage account for the most relevant DNA repair mechanisms (4,5).

If, despite these repair mechanisms, the DNA damage persists, cells can make use of the special DNA polymerases that are able to bypass specific types of DNA damage (translesion synthesis) (2,3,6). One of the best studied polymerases is the 1999 identified *polymerase eta* that can bypass cyclobutane pyrimidine dimers (7–10). The consequences of a functional loss of *polymerase eta* are demonstrated by xeroderma pigmentosum variant (XPV) patients (MIM: 278750). These patients have a normal nucleotide excision repair (NER) capacity but accumulate DNA photoproduct-induced DNA mutations because of the alternative use of more error-prone polymerases. The loss of *polymerase eta* function in XPV patients leads to the same clinical XP symptoms found in other XP patients belonging to the complementation groups A to G who accumulate DNA mutations because of defects in NER of UV-induced DNA photoproducts (11,12).

Classical human models to support the hypothesis of multistep carcinogenesis, requiring a cellular mutator phenotype, are congenital genetic diseases with increased genomic instability which are characterized by enhanced tumor formation already in the youth (13). These syndromes include chromosomal breakage syndromes, mismatch repair (MMR) defective syndromes as well as NER defective syndromes. It is notable that the same genes that are involved in the development of these model diseases may also lead to genetic instability in normal individuals, for example, via polymorphic variants or acquired somatic mutations. This may ultimately affect cancer-proneness in 'healthy' individuals. Thus, the DNA repair genes may be viewed as tumor-suppressor genes. Clearly, the DNA repair systems that will be discussed below are not sharply demarcated against one another, but overlap and interact with

one another because of their complexity in many ways. For example, the MMR system is able to detect certain types of DNA damage which it is unable to repair. However, the activation and futile repair attempt of the MMR system often leads to programmed cell death (apoptosis) and the elimination of malignant cells (14). The efficacy of certain chemotherapeutic treatments (e.g. temozolomide treatment of melanoma patients) may depend on this path (15).

Chromosomal breakage syndromes

Double-strand breaks or single-strand DNA breaks which are located opposite to one another may develop endogenously during physiological processes (e.g. during replication or via reactive oxygen species) as well as because of exogenous noxae like ionizing irradiation or chemotherapeutics. Inefficient DNA damage signalling and recombinational repair of DNA breaks lead to enhanced chromosomal rearrangements (16). Such rearrangements are typically found in tumor cells. Following strand break formation, a complex cascade of events is initiated to slow down the cell cycle, and recruit DNA repair enzymes (17,18). Two different repair pathways, non-homologous end-joining (NHEJ) and homologous recombination repair (HRR), can be discerned for the repair of strand breaks (Fig. 1). After the replication, cells seem to prefer HRR because of the existence of a second identical chromatide. Otherwise, the more error-prone NHEJ pathway is utilized. The malfunction of either of these two systems already results in enhanced cellular genomic instability (18).

During HRR, the cut DNA strand interacts with the homologous DNA sequence of the sister chromatide (19–21). This sequence serves as a template to allow for an error-free religation of the DNA ends (Fig. 1). Interaction with the homologous sister DNA strand is initiated through the formation of 3′ overhangs. For that purpose, the 5′-3′ exonuclease activity of the *MRE11-RAD50-NBS1* protein complex is utilized (I). The *RAD52* protein binds to those 3′ overhangs (II). As *RAD52* competes with the *Ku* proteins of the NHEJ pathway in terms of binding to DNA ends, this step may determine, if HRR or NHEJ is initiated for strand break repair. *RAD52* interacts with *RAD51* which forms a nucleoprotein filament along the single strand (III). This *RAD51* filament catalyses the interaction with the homologous sister chromatide sequence (detection of the sister chromatide, strand invasion, and formation of a holliday junction) (IV). After the DNA synthesis and ligation resolvase proteins disintegrate the holliday junction (V) (22).

During NHEJ two DNA ends are religated without sequence verification or the necessity of a sequences homology (Fig. 1) (21,23,24). A heterodimer consisting of the *Ku* proteins *Ku70* and *Ku80* binds to the DNA ends to

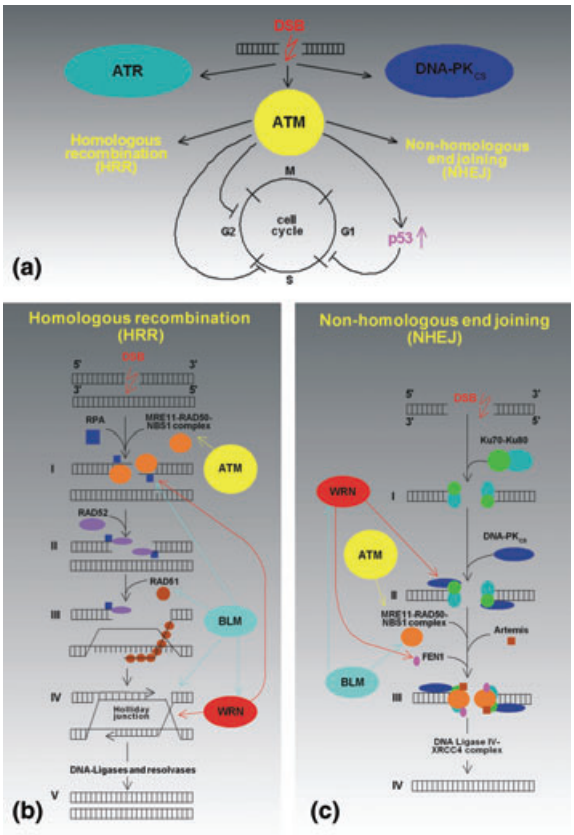

Figure 1. DNA damage-signalling and double-strand break (DSB) repair pathways. DSBs activate the phosphatidylinositol 3-kinase-like protein kinases ATR, DNA-PK$_{CS}$, and ATM which influences cell cycle control to prolong repair time (a). After S-phase, the homologous recombination pathway is preferentially activated. Here, the second chromatide is used as a template to allow for an error-free repair (b). During G1-phase, the error-prone non-homologous end-joining pathway is utilized. The two DNA ends are religated without any sequence verification, which usually leads to the loss or gain of a few bases (c). The two RecQ helicases *WRN* (*RECQL2*) and *BLM* (*RECQL3*) are indirectly involved in these repair pathways by interacting with different repair proteins. The *RECQL4* helicase seems to be involved in cell cycle regulation.

prevent degradation and possibly to converge the ends (I). Afterwards, the protein *DNA-PKcs* is recruited (II) as well as the *XRCC4-DNA ligase IV* protein complex. Usually, 3′ or 5′ DNA overhangs have to be processed prior to religation. This is accomplished by the *MRE11-RAD50-NBS1* protein complex, the *Artemis* protein, and the *FEN1* endonuclease (III). This step often leads to an insertion or deletion of a few bases which is the reason for the error proneness of NHEJ (22).

Several genetic diseases have been discerned with defects in DSB repair and recombination (25). Although very rare these syndromes are unique opportunities to learn about the clinical consequences of faulty DSB repair. In general, these syndromes are characterized by signs of premature aging, immunodeficiency and premature development of

neoplasias with hematologic neoplasias prevailing. Some syndromes also show skin abnormalities and skin cancer-proneness (Table 1). Patients with Ataxia telangiectasia (AT) (MIM: 208900) show progressive neuronal degeneration characterized by loss of Purkinje cells in the cerebellum and ataxia usually starting between the first and third year of life. AT is further characterized by telangiectasias in the face, a humoral and cellular immunodeficiency, and an increased sensitivity towards ionizing radiation. The cancer risk is 60–180 times higher than compared with normals. Treatment of AT patients is very difficult because of their extreme sensitivity to chemotherapeutics and radiation therapy. The defective gene in AT patients, *ATM* (AT mutated), plays a central role in the regulation of different signalling cascades including cell cycle control and DSB repair (25–29). The Nijmegen breakage syndrome (NBS) (MIM: 251260) is quite similar to AT, and was formerly viewed as a variant form of AT. NBS patients show no telangiectasias and, often exhibit café au lait macules, vitiligo, or altered eye pigmentations. Delineation from AT was possible after the identification of the defective gene, *NBS1* or *Nibrin*. *ATM* phosphorylates the *MRE11-RAD50-NBS1* protein complex which then initiates HRR (30–33). In some patients with AT-like disorders (MIM: 604391), mutations in the *MRE11* gene were identified (34,35). Three other syndromes have defects in RecQ helicases which interact with the known DSB repair enzymes. In the Bloom syndrome (MIM: 210900) the *BLM (RECQL3)* helicase defect leads to sun-sensitivity, skin rash, hyper- and hypopigmentations as well as an increased cancer risk. The tumors comprise the same spectrum as in the elderly, but the mean age of development is 24 years (25,29,36–38). A defect in the *WRN (RECQL2)* helicase leads to the Werner syndrome (MIM: 277700), the adult form of progeria. The clinical symptoms mainly include geriatric diseases which develop after puberty. Osteoporosis, atherosclerosis, cataracts, diabetes, and greying of the hair as well as tumor formation are common. Interestingly, these tumors include melanomas, but mainly UV-independent melanomas of the mucosae and acrolentiginous melanomas (25,39–43). In part of the Rothmund–Thomson syndrome patients (MIM: 268400) mutations in the *RECQL4* helicase have been identified. Of dermatological interest are photosensitivity and the development of acute facial erythema and swelling in the first months of life up to the age of two. This erythema spreads in the course of months or years over the buttocks and the flexor surfaces of the extremities, sparing the trunk, and develops into chronic poikiloderma with hyper- and hypopigmentation, telangiectasia and spot-like skin atrophy with life-long persistence (44). In addition to the increased risk of osteosarcoma, patients display an increased risk for non-melanoma skin cancer (45–47). The other three syndromes are caused by germ-line defects in three of the five known human RecQ helicases. This sub-family of DNA helicases is highly conserved in evolution. The helicases function at the interface of DNA replication, recombination, and repair (48). Through diverse functions in transcription, replication, maintenance of genome integrity, and interactions with a variety of other proteins, including MMR proteins and BRCA1, RecQ helicases suppress tumorigenesis and premature aging (49). The Bloom, Werner, and Rothmund–Thomson syndromes comprise developmental defects. Especially, the Bloom syndrome is characterized by proportional dwarfism. Mouse models suggest that the short stature is due to a uniform reduction of the number of body cells. In the early stages of the embryonic development, the number of cells that constitute the embryo was shown to be greatly decreased compared with the wild-type mice because of an increased rate of apoptosis (50). Finally, Fanconi anaemia (MIM: 227650) patients display a 15 000-times higher risk for acute myeloid leukaemia and suffer from progressive aplastic anaemia. Patients also have an increased squamous cell skin cancer risk (head and neck and anogenital region) (51,52). Chromosomal instability in blood lymphocytes after treatment with mitomycin C or diepoxybutane is diagnostic for Fanconi anaemia. There are at least 12 different complementation groups (*FANC-A* to *FANC-M*). The FA/BRCA pathway where all *FA* genes and the two *BRCA* genes are essentially involved is currently intensively investigated and seems to be involved in repair of DSBs, DNA crosslinks as well as UV-induced DNA photoproducts (53–55) (Table 1).

Mismatch repair defective syndromes

The most common error during cellular DNA replication is a false pairing of single nucleotides. Such a mispair of single bases occurs spontaneously every 10^3 to 10^4 base pairs (56). The second most common error during cellular replication is polymerase slippage at nucleotide repeats, for example GTGTGT. This results in microsatellite instability (i.e. a loss or gain of bases like a GT dinucleotide) which is a hallmark of the MMR deficiency. The MMR system may also detect incorrect base pairing opposite a damaged nucleotide, for example an oxidatively damaged nucleotide. This will not correct the damaged nucleotide, but will prevent a single base change mutation in the newly synthesized strand and induce DNA damage signalling, for example, leading to apoptosis. MMR is a multistep process with a variety of proteins involved (21,22) (Fig. 2). The proteins of the mutS (*hMSH2, hMSH3, hMSH6*) and mutL (*hMLH1, hMLH3, hPMS1, hPMS2*) gene families play central roles in the detection of falsely paired nucleotides (I) and verification of the newly incorrect synthesized strand (II).

Table 1. DNA repair defective syndromes: (skin) manifestations and affected genes

Syndrome	Benign (skin) lesions	Malignant (skin) lesions	Affected gene	References
Ataxia-telangiectasia (AT) MIM: 208900	Telangiectasias especially in the face, ataxia, infertility, humoral and cellular immunodeficiency, radiosensitivity	Various solid epithelial tumors, lymphomas, T-cell leukaemias	ATM *(Ataxia telangiectasia mutated)*	25–29
Nijmegen breakage syndrome (NBS) MIM: 251260	Café-au-lait macules, vitiligo and pigment deposition in the fundus of the eye, microcephaly, growth retardation, radiosensitivity, immunodeficiency	Lymphomas	NBS1 *(Nibrin)*	30–33
Bloom syndrome (BLM) MIM: 210900	Photosensitivity with facial erythema, circumscribed hyper- and hypopigmentation, growth retardation, immune defects, reduced fertility, diabetes mellitus	Osteosarcomas, Wilm's tumors of the kidney, tumor spectrum of the normal population with onset in early adulthood (20–25 years)	BLM *(RECQL3)*	25, 29, 36–38, 48–50
Werner syndrome (WRN) MIM: 277700	Greying of the hair, hair loss and skin atrophy, osteoporosis, small tissue calcifications, atherosclerosis, cataracts, type II diabetes mellitus	Melanomas (especially UV-independent melanomas of mucosal surfaces and acrolentiginous melanomas), soft tissue sarcomas, thyroid cancers, meningiomas, osteosarcomas	WRN *(RECQL2)*	25, 39, 40–43, 48–50
The Rothmund–Thomson syndrome (RTS) MIM: 268400	Photosensitivity, acute erythema and swelling, sometimes blistering, chronic phase with poikiloderma and hyper- and hypopigmentation, telangiectasia and spot-like skin atrophy, small stature, cataracts, skeletal defects	Non-melanocytic skin tumors, osteosarcomas	RECQL4	44–50
Fanconi anaemia (FA) MIM: 227650	Deformities of the skin, upper extremities, skeletal system, gastrointestinal tract, kidneys, heart and central nervous system, progressive anaemia, reduced fertility	Squamous cell carcinomas, acute myelogenous leukaemia	*FANC-A* to *FANC-M* (at least 12 different FA complementation groups)	51–55
Hereditary non-polyposis colorectal cancer (HNPCC) MIM: 120435	None	Colon cancer, other visceral tumors such as endometrial, ovarian, stomach, kidney, and small intestinal cancers	*hMSH1* *hMSH2* *hMSH6* *hMLH3* *hPMS1* *hPMS2*	59, 60
Muir–Torre syndrome MIM: 158320	Keratoacanthomas, sebaceous adenomas and epitheliomas mainly on the face	Sebaceous carcinomas, colon cancer, other visceral tumors such as endometrial, ovarian, stomach, kidney, and small intestinal cancers	*hMSH1* *hMSH2*	61–66

Table 1. Continued

Syndrome	Benign (skin) lesions	Malignant (skin) lesions	Affected gene	References
Turcot syndrome MIM: 276300	Meningiomas, pituitary gland adenomas, craniopharyngiomas	Medulloblastomas, gliomas, lymphomas, colon cancer, other visceral tumors such as endometrial, ovarian, stomach, kidney, and small intestinal cancers	*hMSH1* *hPMS2*	57, 58
Xeroderma pigmentosum (XP)	Sunburns, hyper- and hypopigmentation, atrophy in sun-exposed skin regions, xerosis, neurological symptoms	Basal cell carcinomas, squamous cell carcinomas, melanomas (UV-induced skin tumors) in childhood	*XPA* (MIM: 278700) *XPB* (MIM: 610651) *XPC* (MIM: 278720) *XPD* (MIM: 278730) *XPE* (MIM: 278740) *XPF* (MIM: 278760) *XPG* (MIM: 278780) *XPV* (MIM: 278750)	7–12, 73–75, 81, 82, 84–88
Cockayne syndrome (CS)	Sunburns, hyperpigmentation, physical and mental retardation, bird-like face	No increased (skin) cancer risk	*CSA* (MIM: 216400) *CSB* (MIM: 133540)	73, 74, 89, 90, 91, 95, 96, 97
Trichothiodystrophy (TTD) MIM: 601675	Sunburns, erythema, ichthyosis-like skin changes, nail and other neuroectodermal dysplasias, short, brittle sulfur-deficient hair (tiger-tail sign)	No increased (skin) cancer risk	*TTD-A* *XPB* *XPD*	73, 74, 83, 92, 93, 94, 98

This is followed by strand degradation via exonucleases and strand resynthesis (III).

Heterozygous germ line mutations in MMR genes do not result in clinical symptoms *per se*. However, a functional loss of the second allele of the affected MMR gene is present in familial occurring tumors. This results in a cellular mutator phenotype and malignant transformation is accelerated because of enhanced replication errors throughout the total genome. Interestingly, in non-familiar sebaceous gland tumors spontaneous somatic mutations of MMR genes in tumor cells can be found. The clinical consequences of an inherited MMR deficiency are mirrored by three diseases, the Hereditary-Nonpolyposis-Colorectal-Cancer (HNPCC) syndrome (MIM: 120435), the Muir–Torre syndrome (MIM: 158320), and the Turcot syndrome (MIM: 276300) (57,58). The latter two syndromes can be viewed as subtypes of HNPCC where patients either develop skin tumors (keratoacanthomas, sebaceous gland tumors) or brain tumors (glioblastomas), in addition to colorectal cancer (Table 1). The molecular reasons for this astonishing tissue specificity have yet to be established. The HNPCC, or the Lynch syndrome, is characterized by the so-called Amsterdam criteria: (i) three relatives with colorectal cancer one of whom being a first-degree relative; (ii) affected family members over at least two generations; (iii) at least one family member with colorectal cancer diagnosed before 50 years of age. For smaller families alternative, but less specific criteria exist (Amsterdam II, modified Amsterdam, or Bethesda criteria) (59,60). HNPCC type II families often develop other internal tumors including tumors of the endometrium, the ovary, the stomach, the kidney, and the small intestine. In 70–80% of all the affected individuals mutations in the *hMLH1, hMSH2, hMSH6,* and *hPMS2* MMR genes were identified (59). Further information, and, especially, guidelines for the clinical management of HNPCC patients can be found on the web (http://www.insight-group.org). The Muir–Torre syndrome patients are of special dermatological interest, because colorectal cancers are associated with sebaceous gland tumors in these individuals (61–63). The skin tumors predominately develop on the face, and include keratoacanthomas, sebaceous gland adenomas, epitheliomas and carcinomas (64–66). Microsatellite instability indicating an MMR defect, can also be identified in the skin tumor cells and mutations in the *hMSH2* and *hMLH1* genes were identified. Therefore, the possibility of the Muir–Torre syndrome should be considered in every patient with a benign or malignant sebaceous gland tumor (with the exception of sebaceous hyperplasia), and colon cancer should be excluded.

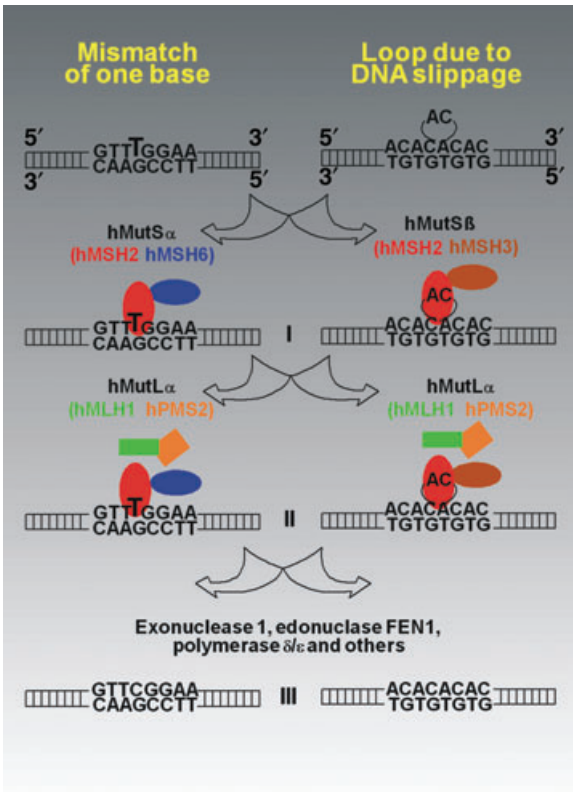

Figure 2. Mismatch repair pathway: mispairing of single bases and loops because of DNA slippage are predominately recognized by the hMutSα Protein dimer consisting of *hMSH2/6* and the hMutS*β* Protein dimer consisting of *hMSH2/3*.

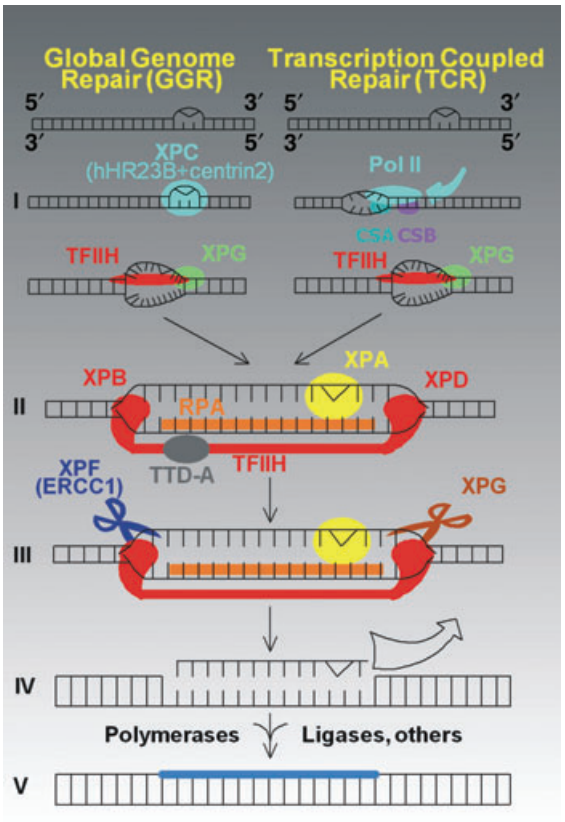

Figure 3. Nucleotide excision repair pathway: the *XPC* protein constantly scans the global genome for bulky DNA damage (GGR), the stalled polymerase II, together with the *CSA* and *CSB* proteins, initiate nucleotide excision repair in actively transcribed genes (TCR). *RPA*: replication protein A. TFIIH: transcription factor IIH, a multiprotein complex including the *XPB* and *XPD* helicases and *TTD-A* (~*TFB5*).

Nucleotide excision repair defective syndromes

Nucleotide excision repair is the most versatile and best-studied DNA repair system in humans (67). In general, bulky DNA damage that leads to a distortion of the DNA helix is substrate of NER (68,69). This includes UV-induced DNA lesions, like cyclobutane-pyrimidine dimers (CPD) or pyrimidine-(6–4)-pyrimidone photoproducts (6–4PP) as well as polycyclic aromatic carbohydrates found in tobacco smoke and crosslinking agents (68–70). Such crosslinking agents include chemotherapeutics like cisplatin. The NER principle can be found in multiple organisms of different hierarchies. Interestingly, in *Escherichia coli* bacteria only three proteins are needed to perform NER (71). This may demonstrate the astonishing evolution and specialization of this important DNA repair mechanism to maintain genomic integrity.

The NER process consists of multiple steps (72,73). Twenty to thirty different DNA repair enzymes contribute to this process in a defined sequence (74,75) (Fig. 3). At first the DNA damage has to be recognized. This is accomplished by the *XPC* protein complexed to *hHR23B* and *centrin2* in the global genome (I). Then, the DNA damage is demarcated with the help of *XPA* and the *XPB* and *XPD* helicases which are a part of the 10 proteins containing TFIIH transcription factor protein complex (II). The *XPG* and *XPF* endonucleases cut the lesion containing strand 3′ and 5′ to the damage, respectively (III). After the removal of a 27- to 29-bp oligonucleotide containing the damage (IV), the gap is filled by polymerases and ligases which use the complementary strand as a template (V). It is currently investigated whether the removed oligonucleotide is just degraded after transport into the cytoplasm or may induce UV-protective cell functions. It has been shown that small oligonucleotides with specific sequences are capable of inducing DNA repair as well as melanogenesis without UV exposure of the cells (76).

All the 7 xeroderma pigmentosum (XP) genes, *XPA* to *XPG* (MIM: 278700, 610651, 278720, 278730, 278740, 278760, 278780), are essentially involved in the NER cascade. The *XPC* protein recognizes the DNA damage

throughout the total genome, and initiates the global genome repair (GGR) subpathway of NER. The DNA damage in actively transcribed genes needs to be eliminated much faster. Here, the stalled RNA polymerase II leads to damage recognition and initiation of NER (77). This faster NER subpathway is called transcription coupled repair (TCR). During TCR, the *XPC* protein is dispensable (78). XP patients harbouring mutations in the *XPC* gene are still capable of repairing UV-induced DNA damage on actively transcribed genes. This may be one reason why XPC patients rarely develop neurological abnormalities in addition to their skin pathologies (79). The two Cockayne syndrome (CS) genes *CSA* (MIM: 216400) and *CSB* (MIM: 133540) seem to play an important role in the temporary removal of the stalled polymerase II to allow repair followed by the continuation of the transcription afterwards. Moreover, the two CS genes may play a general role in the handling of stalled polymerases during transcription (80). CS patients are defective in TCR but exhibit normal GGR (73). This may be one reason for the severe neurological abnormalities of some CS patients.

The clinical consequences of defective NER is vividly demonstrated by three NER-defective syndromes: XP, the CS, and the photosensitive form of trichothiodystrophy (TTD) (81). All diseases share increased sun-sensitivity and freckling in the sun-exposed skin areas as clinical symptoms (82). However, XP patients differ from CS and TTD patients with respect to their skin cancer-proneness (73,74). Six distinct clinical entities (XP, XP plus neurological abnormalities, CS, XP/CS complex, TTD, XP/TTD complex) and eleven causative genes (*XPA-XPG*, *pol eta*, *CSA*, *CSB*, *TTD-A*) can be distinguished. Especially, the *XPB* and *XPD* helicases which are a part of the TFIIH transcription factor complex functioning in both NER and transcription demonstrate the polypheneity of a gene. Mutations in these genes that modulate transcription lead to clinical CS and TTD symptoms, and mutations that modulate NER capacity lead to XP symptoms (83). Patients who suffer from XP exhibit severe sun-sensitivity, freckling and a 1000-fold increased skin cancer risk in sun-exposed areas (Table 1) (84). The median age of the first skin cancer is 8 years (compared with 60 years in healthy Caucasians) and include squamous and basal cell cancers as well as melanomas (85,86). Twenty per cent of all XP patients, mainly those belonging to complementation groups *XPA, XPB, XPD*, and *XPG*, exhibit progressive neurological abnormalities in addition to their XP symptoms (XP plus neurological abnormalities entity). The neurological symptoms include reduced deep tendon reflexes, deafness, and speaking and walking disability because of primary neuronal degradation (73,87,88). CS patients with defects in the *CSA* or *CSB* genes exhibit sun-sensitivity but no increased skin cancer risk (Table 1) (89). Other typical symptoms include growth retardation, cachexia, neurological, psychomotoric, and mental developmental delays, cataracts, retinopathy, deafness, dental caries, and a characteristic facies with a thin face, flat cheeks, and prominent tapering nose (bird-like face). Microcephaly and calcifications of the basal ganglia or elsewhere in the central nervous system occur commonly (90,91). Pathologically, neurological impairment correlates to a primary demyelinization of neurons. This contrasts the primary neuronal degeneration found in XP patients (73,74). TTD (MIM: 601675) patients also exhibit sun sensitivity but no increased skin cancer risk (Table 1). TTD is characteristically diagnosed by ichthyotic skin changes and short brittle hair. A sulfur deficiency in the hair matrix is the reason for the reduced hair strength (92). A typical tiger-tail hair pattern can be visualized under the polarizing microscope (alternating light and dark bands in the hair). Defects in three genes, *TTD-A* (93), *XPB* (94), and *XPD* (94), may result in TTD. All these three genes are subunits of the transcription factor IIH complex which has a dual function in transcription and NER (Fig. 3). Furthermore, there are patients who show combined symptoms of both XP and CS or XP and TTD. All XP/CS complex patients have mutations in XP genes, which demonstrates that certain functional losses in XP genes can also lead to CS symptoms (95–97). In 2001, two patients with XP/TTD complex were identified (98) who carried compound heterozygous mutations in the *XPD* gene. In recent years, a clear genotype-phenotype correlation in *XPD* was established. *XPD* mutations affecting NER alone cause XP, whereas, if transcription is also affected, TTD results (83).

Perspectives

It is apparent that a complex and overlapping network of highly specialized proteins exists which coordinate the signalling and processing of endogenous as well as exogenous-induced DNA damage. Which DNA repair system is preferentially activated not only depends on the type of DNA damage but also on the time point of damage detection during the cell cycle (54).

Cancer-proneness in XP but not in CS and TTD and progressive neurological symptoms

The main molecular difference between XP and CS patients is that CS patients only have a defect in TCR but not in GGR. DNA damage in the global genome can be repaired normally. XP patients with a defect in the *XPC* gene cannot repair damage in the global genome, but have normal TCR, resulting in skin cancer-proneness (78). Thus, defective NER in the global genome may eventually result in cancer. Another reason for XP cancer-proneness could be differences in the repair capacity of different types of

UV-induced DNA photoproducts. CS cells can repair 6–4 photoproducts normally but not cyclobutane pyrimidine dimers (99). This holds also true for TTD patient cells with a defect in the XPD gene (94). XP cells are defective in repair of both types of pyrimidine dimers. This would implicate that repair of 6–4 photoproducts may prevent cancer development. Finally, CS cells exhibit an increased rate of apoptosis because of TCR failure and blockage of transcription. Enhanced apoptosis of initially damaged cells would also prevent tumor cell development. These and other differences between XP and CS/TTD cells have to be further investigated in the future. The interesting question why XP patients are cancer-prone but CS or TTD patients are not has not been answered satisfactorily yet. Another pertinent question is the cause of the neurological abnormalities found in XP and CS (primary neuronal degeneration versus primary demyelinization). To date, progressive neurological symptoms represent the main hurdle in XP and CS patient care (100,101).

Disease susceptibility in heterozygous carriers of defective DNA repair genes

To date, heterozygous carriers of XP mutations are regarded as 'healthy'. The frequency of such clinically normal individuals (1:500) is much higher than XP patients (1:1 000 000). However, whether individuals who are heterozygous for a mutation in an XP gene are at increased risk of malignancy is not well understood. The only study to date of cancer risk in XP heterozygotes was published in 1979, before the XP genes were cloned (102). The study mentioned above was conducted on the pedigrees of XP families, and suggested that carriers of one mutated XP allele have an elevated incidence of skin cancer. Mice that have a homozygous knockout of the *XPC* gene have a markedly increased susceptibility to UV induction of skin cancer (103) and *XPC* heterozygous mice have an increased cancer susceptibility after prolonged UV exposure (104,105). However, the identification of heterozygous XP gene carriers in early phases of life was hampered by the lack of an easy-to-apply, reliable and high-throughput test system other than complete gene sequencing. Recently, at least for *XPC*, the level of *XPC* mRNA reduction was correlated with the number of defective *XPC* alleles. Heterozygous *XPC* gene mutation carriers exhibit ~66% and homozygous-diseased *XPC* patients exhibit ~33% of normal *XPC* mRNA expression. Thus, *XPC* mRNA levels may be evaluated as a marker of cancer susceptibility in carriers of mutations in the *XPC* gene who may then be thoroughly protected from UV exposure and followed by a dermatologist during life (106). This notion holds also true for other DNA repair enzymes involved in different repair pathways. For example, relatives of AT patients (obligate *AT* carriers) are more likely to develop breast cancer at an early age (107). It is estimated that 1% of the general population is *AT* carriers (108). In the population of Ashkenazi Jews, people with colorectal cancer were reported to be 2.76 times more likely to be carriers of a *BLM* mutation compared with disease-free controls (109). The observation that carriers of a single defective *BLM* allele are cancer-prone is supported by results from analyses of a transgenic mouse model (110).

Senescence

The link between DNA repair and senescence is currently intensively investigated by several groups. Cortopassi and Wang (111) were the first to show a positive correlation between DNA repair capacity and the lifespan of fibroblasts of several different species from mouse to man. Hart and Setlow (112) demonstrated that the rate of NER capacity is proportional to the logarithm of lifespan. In mice, DNA repair and transcription deficiency were related to premature aging (113). Cellular senescence is defined as loss of proliferative capacity. Recent concepts regard different forms of senescence as persistent DNA damage responses characterized by focalization of DNA damage response factors and DNA repair proteins in senescence-associated DNA damage foci. Senescence associated DNA damage foci mediate the signalling for the permanent growth arrest in the vicinity of different DNA lesions (114–116). Such DNA damage response factors mediating senescence include *ATM* or *ATR* (117). Both kinases play a critical role in early signal transmission after DNA damage (Fig. 1). Interestingly, the combination of psoralens plus UVA (PUVA) irradiation commonly used for the treatment of different skin disorders leads to accelerated skin aging. PUVA treatment leads to interstrand cross-links, which induce stalled replication forks which, by themselves, activate the *ATR* kinase. The group of Herrmann (117,118) found that PUVA induces premature cellular senescence in human dermal fibroblasts. This effect depends on *ATR*, which is essential to induce and to maintain the senescent cellular phenotype.

Mitochondrial repair

Most of the studies discussed only investigated nuclear DNA repair. However, a growing body of evidence is developing that even the repair of mitochondrial DNA is connected with congenital disorders, aging, photoaging, and carcinogenesis. The main function of mitochondria is the generation of energy for the cell via the respiratory chain which is located at the inner mitochondrial membrane. The mitochondrial DNA is a 16559-bp double-stranded circular molecule existing in about 4–10 copies per mitochondrion. A common 4977-bp deletion in the mtDNA is associated with congenital disorders like Kearns-Sayre syndrome, Alzheimer's disease, and diabetes, as wells as aging (119,120). For the repair of mitochondrial DNA damage,

several mechanisms, similar to nuclear DNA repair, exist. Base excision repair (BER) of oxidative DNA damage is the best characterized mechanism in mitochondria (121,122), but also MMR activities have been demonstrated in purified human mitochondria (123) as well as repair of DNA DSBs (121). Interestingly, there is no efficient repair of UV-induced CPDs in mtDNA (124) and NER has so far not been detected (121). However, Stevnsner et al. (125) found a reduced repair capacity of 8oxoG in mitochondrial extracts of *CSB*-deficient cells. The *CSB* protein is a component of NER. Trifunovic et al. (126) investigated homozygous knock in mice expressing a proof reading deficient *polymerase* γ which is involved in all the repair processes of mitochondria. Clinically, these mutant mice exhibit an aging phenotype characterized by progeroid symptoms, like weight loss, kyphosis, osteoporosis, alopecia and s.c. fat reduction.

DNA repair gene variants and cancer susceptibility/individualized cancer prevention

The knowledge gained by studying NER defective syndromes can be transferred to the normal population. Subtle modulations of DNA repair, for example via polymorphisms, may result in increased cancer susceptibility in normals. For example, a reduced NER capacity has been found in patients with lung cancer, head-and-neck squamous cell cancer, and patients with basal cell carcinomas using host cell reactivation (127–129). Wei et al. (130) recently demonstrated that reduced DNA repair capacity is an independent risk factor for the development of cutaneous melanoma in the general population. We found that a functional relevant *XPC* polymorphism was associated with a 2-fold increased melanoma risk in the normal population (131). Normal fibroblasts harbouring this *XPC* polymorphism roughly showed a 50% reduction in their NER capability (132). Other studies identified a 10% reduction of DNA repair capacities in patients with basal cell carcinoma (133), a 25% reduction in patients with lung cancer (134), and a 30% reduction in patients with head and neck squamous cell cancer (127) compared with healthy controls. This reduction in DNA damage repair function may explain the association of these polymorphisms with the development of different cancers. In the future, genetic profiles of cancer risks will have to be constructed to develop risk models incorporating the combinations of many polymorphisms in many repair genes at once. Such a profile can serve as a molecular marker for an individual cancer risk assessment in addition to the relatively unspecific phenotypic risk markers used in the clinic nowadays (135).

DNA repair gene variants and efficacy of cancer treatments/individualized cancer therapy

In addition to serving as markers for cancer predisposition, DNA repair genes may also have great implications in the therapeutic outcome of certain cancer treatments. Several different mechanisms of chemoresistance have been described, such as alterations in drug transport, an increase in drug detoxification, an induction of cellular protective agents, or an increased DNA repair of drug induced DNA damage (136). For example, cisplatin sensitivity has been linked to defective NER, with altered levels of *XPA* protein in testicular germ cell tumors (137) and of *XPG* protein in the mouse leukaemia line L1220 (138). Cisplatin resistant cells exhibit enhanced NER. Recently it was shown that a novel alkylating anticancer agent, ectainascidin 743 (Et743), subverts normal NER by generating lethal DNA breaks during transcription coupled NER (139). NER-defective XP cells were resistant to this chemotherapeutic agent. It was found that cisplatin resistant ovarian carcinoma cells with increased NER were sensitive to killing by Et743. The authors suggested that the evaluation of the Et743 treatment for cisplatin-resistant tumors and monitoring XP and other NER factors in tumor samples might help guide the choice of chemotherapeutic agents (139). However, the assessment of different melanoma cell lines resistant to cisplatin, fotemustine, vindesine, or etoposide revealed no altered NER of UV-induced DNA photoproducts (14). This is in accordance with recent literature in pharmacogenetics, which suggests that genetic polymorphisms in genes involved in drug metabolism, drug targets and DNA repair may contribute significantly to the variability of individual drug response (140,141).

New therapeutic strategies/DNA repair creams

Finally, new therapeutic approaches may be developed. In the last few years a delivery system has been studied that utilizes the packaging of repair enzymes into liposomes that can be applied to the skin as a hydrogel lotion on a regular basis. This technique could deliver any repair enzyme at a defined concentration and frequency to epidermal skin cells, which offers a new dimension in topical dermatotherapy (142). In the first prospective pilot study, the efficacy of a *T4 endonuclease* liposomal therapy was investigated in 30 XP patients. A 68% and 30% reduction in the development of actinic keratoses and basal cell cancers, respectively, was demonstrated in XP patients who applied the repair cream. The authors conclude that improved DNA repair inhibits tumor promotion as well as tumor progression (143). Currently, this treatment is investigated for its efficacy in skin cancer prevention in renal transplant patients. Stege et al. (144) investigated the efficacy of a second liposomal encapsulated repair enzyme, photolyase. The enzyme specifically binds to cyclobutane-pyrimidine dimers. If the enzyme is photoreactivated with visible light (300–800 nm), it can separate the dimer into the original monomers (direct reversion). Nineteen healthy volunteers were treated with a photolyase containing liposomal lotion.

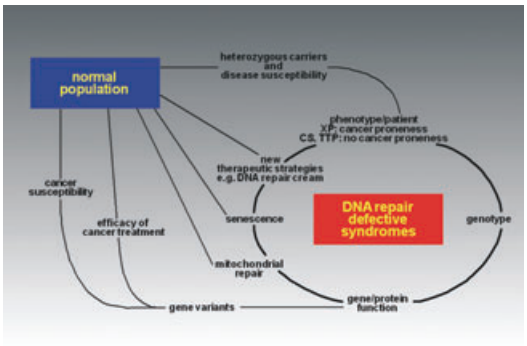

Figure 4. Perspectives of studying DNA repair defective syndromes.

This treatment reduced the content of cyclobutane-pyrimidine dimers in UVB-irradiated skin of the probands up to 45%. In addition, the extent of UVB-induced skin erythema was reduced (144).

Thus, clinical and molecular studies of DNA repair defective syndromes may have great implications for oncology, and lead to novel approaches for cancer prevention, genetic susceptibility testing, cancer diagnostics, and more individualized therapeutic strategies (Fig. 4). The establishment of centers of excellence for studying the whole variety of rare genetic syndromes with DNA repair defects may be very helpful in this direction. This would parallel other genetic diseases like ichthyoses (145) or porphyrias (146,147) where specialized centres were very helpful, especially with respect to molecular-genetic laboratory diagnostics.

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