Bacterial DNA repair genes and their eukaryotic homologues: 4. The role of nucleotide excision DNA repair (NER) system in mammalian cells*

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The eukaryotic cell encounters more than one million various kinds of DNA lesions per day. The nucleotide excision repair (NER) pathway is one of the most important repair mechanisms that removes a wide spectrum of different DNA lesions. NER operates through two sub pathways: global genome repair (GGR) and transcription-coupled repair (TCR). GGR repairs the DNA damage throughout the entire genome and is initiated by the HR23B/XPC complex, while the CSB protein-governed TCR process removes DNA lesions from the actively transcribed strand. The sequence of events and the role of particular NER proteins are currently being extensively discussed. NER proteins also participate in other cellular processes like replication, transcription, chromatin maintenance and protein turnover. Defects in NER underlay severe genetic disorders: xeroderma pigmentosum (XP), Cockayne syndrome (CS) and trichothiodystrophy (TTD).

Keywords: DNA damage, DNA repair, nucleotide excision repair, xeroderma pigmentosum, Cockayne syndrome, trichothiodystrophy

INTRODUCTION

The genetic material is under constant insult from various exo- and endogenous damaging agents which alter its coding properties. It is estimated that each cell encounters one million DNA damage incidents per day (Lodish, 2004). It has been suggested that a gradual accumulation of DNA damage during the cellular and organismal life-time contributes to normal aging and carcinogenesis (Harman, 1956; Olinski et al., 2007).

Living cells have developed a complex network of DNA repair mechanisms which collectively maintain genome integrity. Among the major DNA repair mechanisms are: nucleotide excision repair (NER), base excision repair (BER), mismatch repair (MMR) and recombination repair, which is a common term for two repair pathways: homologous recombination (HR) repair and non-homologous end joining (NHEJ) (for more details see accompanying review by Nowosielska, 2007). The first three mechanisms, i.e. NER, BER (for more details see ac-

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Abbreviations: CS A–B, Cockayne syndrome group A–B; CPD, cyclobutane pyrimidine dimers; DDB, DNA-binding protein; ERCC1, excision repair cross complementation group 1; GGR, global genome repair; hHR23, human homolog of yeast RAD23; NER, nucleotide excision repair; LIG 1, ligase 1; PCNA, proliferating cell nuclear antigen; POL δ/ε, polymerase delta/epsilon; RFC, replication factor C; RNA pol II, RNA polymerase II; RPA, replication protein A; TFIIH, transcription factor IIF; TCR, transcription-coupled repair; XP A–G, xeroderma pigmentosum group A–G.
companying review by Krwawicz et al. (2007) and MMR (for more details see accompanying review by Arczewska & Kusmierzek, 2007), are involved in the excision of the damaged or mispaired DNA bases, while the HR and NHEJ systems repair DNA double strand breaks (DSBs) (Hoeijmakers, 2001; Lindahl & Wood, 1999). An alternative to the BER mechanism, nucleotide excision repair (NER), is initiated by one of BER proteins, AP endonuclease 1 (APE1) which is able to incise the DNA strand 5’ to certain oxidized and subsequently fragmented DNA nucleotides (Ischenko & Saparbaev, 2002; Gros et al., 2004; Ishchenko et al., 2006). Additionally, a unique class of low-fidelity DNA polymerases can bypass DNA lesions in the process named translesion synthesis (TLS), enabling cell survival in the case of ineffective DNA repair (Lehmann et al., 2007).

More than 150 proteins are known to be involved in the DNA repair processes (Wood et al., 2005). All these proteins are the products of stability genes (caretakers) which protect the genetic material from the consequences of DNA damage and thereby prevent cancer and pre-mature aging diseases. Mutations in any of the DNA repair genes can result in genome instability (Lindahl & Wood, 1999; Hoeijmakers, 2001).

**NUCLEOTIDE EXCISION REPAIR**

Overview of NER reactions in eukaryotes

NER is a versatile multi-step DNA repair pathway that serves to remove a broad range of bulky, helix-distorting lesions. It is ubiquitous from simplest organisms such as mycoplasma to well developed ones like, mammals (Wang et al., 1994; Lehmann, 1995; Wood, 1997). The majority of environmental carcinogens, including UV irradiation, antitumor drugs (cis-platin) and food-borne genotoxins, form bulky DNA adducts which may block replication and transcription. Among other helix-distorting lesions, NER is responsible for the repair of UV light-induced photoproducts (e.g. cyclobutane pyrimidine dimers), lipid peroxidation-induced DNA adducts, cigarette smoke-induced benzo[a]pyrene DNA adducts, chemical carcinogen-induced 4-nitroquinoline and other DNA adducts (Kraemer et al., 2007a). NER is also involved in the removal of oxidative DNA lesions (Brooks, 2007; Johnson et al., 2004) and in *Escherichia coli*, single strand breaks (SSBs) (by UvrABC enzymes) (Truglio et al., 2006).

NER system was extensively studied in bacteria since 60-ties of 20th century. Damage recognition and consecutive steps of repair were recently described in depth by Van Houten and coworkers (2005) and Mellon (2005). This paper will focus exclusively on mammalian NER system, since sequence of events and the role of participating proteins is still extensively discussed.

NER process in mammals is carried out by a multi-protein complex referred to as the nucleotide excision repairosome, consisting of over 30 proteins which function in a stepwise manner (Table 1). The main stages of mammalian NER are: (1) DNA damage recognition, (2) assembly of the protein complex that carries out excision of damaged DNA, and finally, (3) synthesis and ligation of a stretch of DNA strand for gap filling (Park & Choi, 2006). The key event in eukaryotic NER is excision of an approximately 28-nucleotide (nt) DNA fragment containing the damaged site (Wood, 1997; Leibeling et al., 2006). In mammalian cells, NER consists of two distinct sub-pathways, namely global genome repair (GGR) and transcription-coupled repair (TCR), which are fundamentally identical except for the mode of the DNA damage recognition. In TCR, RNA polymerase II (RNA pol II) stalled at the damaged site constitutes the signal for the recruitment of DNA repair proteins, while in GGR, the DNA damage-induced helical distortion is recognized by a specific protein complex. Consistently, TCR specifically repairs transcription-blocking lesions in actively transcribed DNA regions. In contrast, GGR eliminates DNA lesions from the entire genome (Hanawalt, 2002; Gillet & Scharer, 2006; Saxowsky & Doetsch, 2006).

**Global genome repair (GGR)**

In GGR, the major DNA damage recognition factor is the XPC–hHR23 complex (Fig. 1). The transcription factor IIA (TFIIA), XPA and replication protein A (RPA) sequentially bind to the site of the damage to form a pre-incision complex. The two helicases XPB and XPD, which are parts of TFIIH, unwind the DNA double helix at the damaged site. The dual incision process is performed by endonuclease XPG and the XPF–ERCC1 complex, which hydrolyse phosphodiester bonds 2–8 nucleotides downstream and 15–24 nucleotides upstream of the damaged site. The resulting gap is filled in by DNA polymerases delta/epsilon (POL b/c) which require proliferating cell nuclear antigen (PCNA), RPA and replication factor C (RFC). Finally, the DNA fragments are ligated by DNA ligase I (LIG1) (Friedberg, 2001; Costa et al., 2003; Sancar & Reardon, 2004).

**Transcription-coupled repair (TCR)**

For the first time, TCR was described in mammalian cells by Bohr and co-workers and by Mellon and Hanawalt who observed that the removal of DNA lesions from the transcribed strands of active genes
is much more efficient than from the whole genome (Bohr et al., 1985; Mellon & Hanawalt, 1989). The TCR specifically repairs transcription-blocking lesions from the actively transcribed DNA regions. RNA polymerase (RNAP) stalled at the damaged site is the signal for the recruitment of TCR proteins (Fig. 2). The lesion is removed only in the presence of CSB in an ATP-dependent manner (Sarker et al., 2005; Laine & Egly, 2006a). Recent models of the TCR pathway propose that the CSB protein interacts with lesion-stalled RNAP and recruits other TCR factors to the damaged site (Sarasin & Stary, 2007). XPG has also been shown to bind cooperatively with CSB (Sarker et al., 2005). Subsequently TFIIH, RPA and XPA arrive at the site of the damage. It appears that TFIIH and XPA stabilize each other’s interactions with RNAP. A recent study suggests that an ATP-dependent activity of TFIIH is required to release the stalled RNAP (Laine & Egly, 2006a; 2006b). Afterwards, XPF is bound to the damaged site and the CSB-dependent incision

Figure 1. The mechanism of the global genome repair (GGR) subpathway of NER.
Table 1. Human nucleotide excision repair (NER) proteins

<table>
<thead>
<tr>
<th>NER factor</th>
<th>Function in NER</th>
<th>Gene</th>
<th>Chromosome location</th>
<th>Protein</th>
<th>Size (kDa)</th>
<th>accession number in NCBI Entrez</th>
<th>Saccharomyces cerevisiae homolog</th>
<th>E. coli NER factor</th>
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<td>HR23B</td>
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<td>Binds damaged DNA with XPC and recruits other NER proteins</td>
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<td>Binds damaged DNA with XPE in GGR and E3 ubiquitin ligase component of TCR</td>
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<td>XPE</td>
<td>48</td>
<td>NM 000107</td>
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<td>CSB</td>
<td>Stabilization and remodeling of DNA–RNAP interface and recruitment of other repair factors to damaged site in TCR</td>
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<td>10q11.23</td>
<td>CSB</td>
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<td>Rad26</td>
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<td>E3 ubiquitin ligase complex subunit in TCR, Assembly of TCR repairosome</td>
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process, performed by endonuclease XPG and XPF-ERCC1 complex, takes place. Functional CSB is also required for the assembly of the CSA–DDB1 E3–Ub ligase–CSN complex (Fousteri et al., 2006).

DNA damage recognition in GGR

Several proteins are involved in the DNA damage recognition step of GGR, among which the XPC–HR23B complex plays the major role. The human XPC is a 125 kDa protein, the function of which is restricted to GGR (van Hoffen et al., 1995). It is known to form a stable complex with a 58 kDa HR23B protein (human homolog of yeast RAD23 protein) at the damaged site. In this complex, XPC alone is responsible for the binding to the site of the damage, while HR23 stimulates XPC function and is required for the displacement of the complex in the next steps of GGR. HR23B can be substituted by HR23A, suggesting a functional redundancy of these two proteins (Sugasawa et al., 1998; You et al., 2003). The main role of the XPC–HR23B complex is the direct recognition and binding to the damaged DNA (small bubble) which causes a change of the DNA conformation and enables the recruitment of the entire repairosome to the damaged site (Batty & Wood, 2000; Yokoi et al., 2000). Earlier studies implied that the XPC–HR23B complex was also involved in the open complex formation and stabilization (Aboussekhra et al., 1995; Mu et al., 1997). Besides the XPC–HR23B complex, other proteins, namely XPA and XPE, may also be involved in the damage recognition process.

Another DNA damage sensor of GGR is the DNA damage binding (DDB) factor, a heterodimer consisting of subunits of 127 kDa (DDB1) and 48

Figure 2. The current view of the transcription-coupled repair (TCR) subpathway of NER.
DNA unwinding in GGR and TCR

The further steps of the NER pathway are similar in both GGR and TCR. The XPC–HR23B complex in GGR, and CSB protein in TCR, recruits other NER factors such as TFIIH, XPA, and RPA and XPF–ERCC1 in a sequential manner to the damaged site (Laine & Egly, 2006a; Park & Choi, 2006). It has been shown that, in GGR, the damage-recognition XPC–HR23B complex interacts with the p62 subunit of TFIIH to bring it to the site of the damage (Yokoi et al., 2000). TFIIH is a multi-protein complex which consists of ten subunits, including a 6 subunit core of XBP, XPD, p34, p44, p52 and p62, the CDK-activating kinase (CAK) complex (cyclin-dependent kinase CDK7, cyclin H, and the assembly factor MAT1) and TFB5 (Jaitovich-Groisman et al., 2001; Giglia-Mari et al., 2004).

In eukaryotes, TFIIH is functionally conserved and exhibits a dual role. It is involved in the initiation of RNAP transcription and participates in both NER subpathways (Flores, 1992; Drapkin et al., 1994; Schaeffer et al., 1993; Wang et al., 1994). The CDK complex of TFIIH phosphorylates the carboxy-terminal domain of RNAP during transcription initiation (Coin & Egly, 1998).

The XPB and XPD subunits of TFIIH are helicases which exhibit a DNA-dependent ATPase activity. The 89 kDa XPB enzyme catalyzes DNA unwinding in the 3′→5′ direction while the 80 kDa XPD enzyme functions in the opposite direction, i.e. 5′→3′ (Schaeffer et al., 1994; van Gool et al., 1997; Jaitovich-Groisman et al., 2001; Sugasawa et al., 2001). XPB appears to have a weaker helicase activity than XPD (Schaeffer et al., 1993) and is not involved directly in the unwinding and repair of damaged DNA. The XPB helicase unwinds an approximately 30-nt fragment of the DNA double helix around a lesion with the requirement of the XPB ATPase activity (Evans et al., 1997; Coin et al., 2007).

In TCR, these reactions probably lead to a partial release of stalled RNAP. Such incomplete release of RNAP has been observed in the absence of wild-type TFIIH or in the presence of mutated TFIIH, which indicates the importance of TFIIH helicase activity in the release of RNAP (Laine & Egly, 2006a).

The damage-recognition XPC–HR23B complex can also interact with XPA (You, 2003). It is a 36 kDa protein which is required for both GGR and TCR (Hanawalt, 1994; de Laat et al., 1999) and is known to interact with RPA, ERCC1 and TFIIH, as well as with the damaged DNA. An in vitro study shows that XPA protein preferentially binds to the damaged DNA through its central loop-rich domain (Ikegami et al., 1998). The zinc finger central region of XPA is also responsible for the binding of the
RPA70 subunit of RPA protein, while the N-terminal domain mediates a strong interaction with RPA32 (Lee & Hurwitz, 1990; Park & Sancar, 1994; Li et al., 1995; Ikegami et al., 1998; Stigter et al., 1998). Interestingly, the ERCC1-binding region of XPA forms a transient intra-molecular interaction with its DNA-binding region (Buchko et al., 2001).

RPA, also known as replication factor A (RFA) or human single-strand binding protein (HSSB), consists of three subunits: RPA14, RPA32 and RPA70 and has an ssDNA-binding activity which is responsible for the stabilization of the ssDNA intermediate produced by the helicase subunits of TFIIH (de Laat et al., 1998). Moreover, in the presence of XPA-minimal DNA binding domain (XPA-MBD), the RPA70 subunit has an affinity for the undamaged DNA strand opposite the DNA lesion. In this way, RPA may protect the intact DNA strand from the inadvertent nuclease attack (Lee et al., 2003). The interaction with ssDNA is mediated by the central domain of the 70 kDa subunit. Other regions of RPA are involved in interactions with its multiple protein partners. It has been shown that the ssDNA- and XPA-binding sites of RPA70 overlap partially, which implies that the stability of the XPA–RPA complex may be modulated by RPA–ssDNA interactions (Daughdrill et al., 2003).

Due to its affinity for ssDNA and the strong interaction with XPA, RPA plays an important role in the open complex formation and stabilization but also participates in the next steps of the NER pathway. In particular, it interacts with XPG and the XPF–ERCC1 complex, coordinating the function of these nucleases in the incision step.

**Dual incision in GGR and TCR**

Following DNA unwinding, sequential recruitment of the nucleases XPG and the XPF–ERCC1 complex leads to a dual incision in close proximity to the damaged site. XPG hydrolyses a phosphodiester bond 2–8 nt 3' to the damaged site (Habraken et al., 1993) while XPF–ERCC1 cuts 15-24 nt 5' to the lesion (Mu et al., 1995; Moggs et al., 1996).

XPG and XPF–ERCC1 are structure-specific nucleases which hydrolyse duplex substrates preferentially near the junction between the ssDNA and dsDNA (Sijbers et al., 1996). The XPF–ERCC1 and XPG binding to XPA (through ERCC1) and RPA (through XPF) proteins (Bessho et al., 1997) not only facilitates the correct positioning of these proteins at the damaged site but also stimulates the junction-cutting endonuclease activity of XPG and XPF–ERCC1 (Matsunaga et al., 1996; Bessho et al., 1997). In TCR, XPG seems to be recruited at an earlier step of the pathway and bind together with CSB to a stalled RNAP (Sarker et al., 2005).

XPG is a 133 kDa protein, a member of the FEN1 family of structure-specific endonucleases which incise a variety of DNA substrates, including bubbles, flap, splayed arms and stem-loops (Scherly et al., 1993; Harrington & Lieber, 1994; Cloud et al., 1995; Matsunaga et al., 1996). XPG possesses two highly conserved nuclease motifs separated by a spacer region which serves as a protein–protein interaction interface and determines the substrate specificity (Dundan-Sauthier et al., 2005).

Binding of XPG to the pre-incision complex induces a conformational change that is required for the recruitment of the XPF–ERCC1 complex, the last protein complex to join the incision complex.

XPF is a 115 kDa protein that forms a tight complex with the 38 kDa ERCC1 protein (Park et al., 1995). The strong interaction between the two proteins is mediated via the C-terminal helix-hairpin-helix domains of both proteins. XPF has a nuclease activity while a central region of ERCC1 is similar to the XPF nuclease domain but does not contain the residues crucial for the enzymatic activity (Choi et al., 2005). The XPF–ERCC1 heterodimer incises a variety of DNA substrates such as bubbles, stem-loop and flaps. The XPF and XPG nucleases require Mg2+ or Mn2+ but not ATP for the specific cleavage activity (Evans et al., 1997).

**DNA re-synthesis in GGR and TCR**

After incision of the damaged DNA, the resulting gap of about 30 nt is filled in by DNA polymerase δ (POLδ) or ε (POLε) and subsequently the DNA fragments are ligated by DNA ligase I (LIG1) (Wood et al., 2000).

Following dual incision, RPA remains bound to the ssDNA intermediates and is involved in the recruitment of PCNA and RPA to the repair synthesis site (Yuzhakov et al., 1999a; 1999b; Gomes & Burgers, 2001; Gomes et al., 2001; Riedl et al., 2003). The re-synthesis step by these polymerases occurs in a PCNA-dependent manner and with the requirement of RFC. RFC preferentially binds to the 3'-hydroxyl end of DNA primer and assembles PCNA onto the DNA template in an ATP-dependent manner (Fotedar et al., 1996; Waga & Stillman, 1998). In addition, XPG has also been shown to interact with PCNA and facilitate its loading to the repair synthesis site (Gary et al., 1997; Riedl et al., 2003). PCNA is a 37 kDa protein belonging to the DNA sliding clamp protein family (Wyman & Botchan, 1995) which forms a ring-shaped homo-trimeric sliding clamp that encircles DNA. The RFC–PCNA complex serves as a docking platform that links polymerase to the DNA template and initiates chain elongation (Lee & Hurwitz, 1990; Podust et al., 1994; Budd & Campbell, 1997; Wood & Shivji, 1997). PCNA also stabilizes the interaction
of polymerases with the DNA template (Ng et al., 1991). Furthermore, the interaction of polymerase with PCNA and RFC allows an accurate and efficient DNA synthesis (Waga & Stillman, 1998). Interestingly, POLδ but not POLε exhibits low processivity in the absence of PCNA (Burgers, 1991). Recently, a low-fidelity Y family DNA polymerase kapp (POLκ) was found to participate in the re-synthesis step of NER (Ogi & Lehmann, 2006).

Both POLδ and POLε belonging to the B family polymerases show an intrinsic proof-reading exonuclease activity (3′→5′) (Syvaoja et al., 1990; Syvaoja, 1990). Mammalian POLδ is a complex of four subunits: 125, 68, 50 and 12 kDa (Liu et al., 2000) while POLε consists of a large catalytic subunit of 261 kDa and three associated subunits of 59 kDa, 17 kDa and 12 kDa (Syvaoja & Linn, 1989; Li et al., 2000). Both replicative polymerases δ and ε are highly processive and can polymerize long DNA stretches without dissociating from the template and are stimulated by RPA and PCNA (Tan et al., 1986; Tsurimoto & Stillman, 1989).

RFC is a heteromeric protein complex composed of one large subunit, RFC145, and four small subunits: RFC40, RFC38, RFC37 and RFC36 (Uhlmann et al., 1996). The genes encoding these subunits share homology among themselves although each of them is necessary for the proper function of RFC (Bunz et al., 1993; Cullmann et al., 1995).

After the synthesis of a new DNA strand by DNA polymerase, the remaining nick is sealed by LIG1 to complete the repair. The enzyme binds to PCNA, encircles and partially unwinds nicked DNA and catalyzes the esterification of the 3′-hydroxyl and 5′-phosphoryl termini of the nick in DNA. The reaction also requires ATP and a diavalent cation. Human LIG1 is a 102 kDa monomer, composed of a highly conserved C-terminal domain with the active site and an N-terminal domain which contains the nuclear localization signal (NLS) and directs the enzyme to the sites of DNA replication (Modrich et al., 1973; Ranalli et al., 2002; Pascal et al., 2004).

**Regulation of NER proteins**

The activation of DNA repair towards damage response results in the promotion of protein–DNA and protein–protein interactions. The repair process is further modulated through phosphorylation, ubiquitylation and other post-translational modifications of the proteins engaged (Huang & D’Andrea, 2006).

**NER DEFICIENCY DISEASES**

The importance of the described DNA repair system is further highlighted by the fact that defects in some NER proteins cause severe genetic disorders: xeroderma pigmentosum (XP), Cockayne syndrome (CS) and trichothiodystrophy (TTD). To date, defects in 11 genes have been associated with these diseases, however, additional but as yet unidentified complementation groups may exist. Inherited mutations in these genes influence functions of the multi-protein complexes which play essential roles in both DNA repair and transcription.

Consistently with their genetic and molecular complexity, the phenotypes of these diseases are very diverse (Kraemer et al., 2007b).

In principle, two distinct phenotypes can be distinguished: (1) a >1000-fold increased UV light-induced skin cancer in XP, and (2) segmental progeria with a normal cancer incidence in CS and TTD. However, in some cases the symptoms of more than one of these diseases are observed simultaneously. On the other hand, defects in one gene may lead to different phenotypes, depending on the type and position of the mutation (e.g., defects in the XPD gene can lead either to XP, TTD or XP-CS, depending on the causative point mutation), making the genotype-phenotype relationship more complex (Andressoo et al., 2006).

**Xeroderma pigmentosum (XP)**

Xeroderma pigmentosum is a genetically diverse syndrome which falls into seven complementation groups: XP A–G which correspond to mutations in seven proteins, the key components of the NER system. An additional complementation group, XPV (XP variant), is caused by a mutation in the low-fidelity Y family DNA polymerase eta (POLη) which is responsible for error-free trans-lesion synthesis (TLS) past UV-induced DNA damage (Subba Rao, 2007).

Among XP patients severe photosensitivity and a >1000-fold increase in susceptibility to UV light-induced skin and eye cancer is observed. About 50% of the patients suffer from acute burning on minimal sun exposure and all develop freckle-like pigmentation on exposed skin. About 30% of XP patients additionally display progressive neurological disease characterized by sensorineural deafness, abnormal gait and cerebrum atrophy (Kraemer et al., 2007a); this subtype of XP is referred to as XP neurological disease (Brooks, 2007).

The phenotype is linked to the accumulation of mutations due to inefficient repair of DNA damage by the inactive NER system. The impaired repair of UV-induced DNA lesions is known to be responsible for elevated skin and eye cancer risk in XP patients (Friedberg, 2005). Recent studies indicate that the accumulation of certain types of endogenous oxidative bulky DNA lesions (including cyclo-
deoxyadenine and cyclo-deoxyguanine) in neurons of XP patients might account for their neurological abnormalities (Brooks, 2007). However, why not all XP patients display neurological abnormalities and why the disease affects only certain parts of XP patients brain, remains to be elucidated (Kraemer et al., 2007a).

Interestingly, the most severe proneness to skin cancer is observed in patients with mutations in genes, such as XPC, DDB1 or POL η, which are unique to GGR and do not participate in TCR (Subba Rao, 2007).

Cockayne syndrome (CS)

On the contrary, defects in proteins required for efficient TCR, namely CSA and CSB, are the cause of Cockayne syndrome (CS). Approximately 80% of CS cases are due to mutations in CSB and the remaining patients have a mutated CSA protein (Kleppa et al., 2007). CS is a rare autosomal recessive disorder characterized by postnatal physical and mental retardation, cachetic dwarfism, microcephaly, immature sexual development, features of premature aging, sensorineural deafness, white matter hypomyelination, central nervous system calcification, retinal and Purkinje’s cell degeneration. In contrast to XP, no increase in skin-cancer susceptibility is observed among CS patients (Subba Rao, 2007).

There is growing evidence that the features of premature aging in CS are linked to the accumulation of endogenous DNA damage in the genetic material of CS cells. Other defects, for instance defective transcriptional activation of nuclear hormone receptors by the TFIIH complex, may also play a role. The TCR defect in NER and the resulting RNAP blockage protect against cancer by triggering cell-cycle arrest and/or inducing apoptosis via both p53-dependent and independent pathways. On the other hand, an increased apoptosis rate in the nervous system is believed to be the cause of neurodegeneration in CS brain (Andressoo et al., 2006).

Trichothiodystrophy (TTD)

TTD is a clinically diverse syndrome characterized by severe neurological, somatic developmental and skeletal abnormalities. TTD patients share overlapping progeroid features with CS and XP ones but in addition show the hallmark sulfur-deficient brittle hair, postnatal growth failure, mental and physical retardation and ichthyosis. In contrast to XP, TTD is not a cancer-prone disease (Itin et al., 2001).

To date there is no evidence of progressive neurodegeneration in TTD patients and the neurological abnormalities seen in these patients seem to be due to impaired development and maturation of the nervous system. Dysmyelination of the cerebrum, congenital cataracts, prenatal development abnormalities and short stature appear to confirm the developmental cause of the observed phenotype (Kraemer et al., 2007a).

TTD patients carry mutations in XPD, XPB and TTDA, the three subunits of TFIIH, which, in addition to its role in NER, serves as a basal transcription factor for many genes implicated in normal organism development. It has been suggested that specific mutations in these genes affect the transcriptional rather than DNA repair functions of XPD, XPB and TTD proteins (Dubaele et al., 2003).

Combined NER disorders

The combined NER disorders, XP-CS and XP- TTD display both cancer predisposition and segmental progeria. The coexistence of cancer and progeria in these syndromes in spite of the absence of cancer in CS and TTD makes them interesting models for investigating connections between cancer and aging (Andressoo et al., 2006).

Mutations in XPB, XPD and ERCC5 may lead to combined symptoms of XP and TTD or CS, depending on the mutation type and position. Specific and limited point mutations in XPB and XPD are associated with XP-CS; in the majority of XP-CS patients XPG mutations were observed (Sarasin & Stary, 2007).

Why XP-CS patients are not protected from cancer similarly to CS patients remains unclear. However, it seems that a defect in XPD-XP-CS cells causes a genomic instability more severe than could be caused by UV only and as a result DNA lesions accumulate more quickly and, despite the elevated activity of gatekeepers, lead to cancerous transformation (Andressoo et al., 2006).

SUMMARY

NER is a complex system that serves as a prime example of how more than 30 proteins can cooperate in a common pathway to remove a wide range of DNA lesions. The further detailed research on NER genes can provide the better understanding of the molecular mechanisms involved in NER related diseases such as XP, CS and TTD and may show new preventional and therapeutic strategies especially in skin cancer and premature aging.

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