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Tissue-specific accelerated aging in nucleotide excision repair deficiency

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Abstract

Nucleotide excision repair (NER) is a multi-step DNA repair mechanism that removes helix-distorting modified nucleotides from the genome. NER is divided into two subpathways depending on the location of DNA damage in the genome and how it is first detected. Global genome NER identifies and repairs DNA lesions throughout the genome. This subpathway of NER primarily protects against the accumulation of mutations in the genome. Transcription-coupled (TC) NER rapidly repairs lesions in the transcribed strand of DNA that block transcription by RNA polymerase II. TC-NER prevents cell death in response to stalled transcription. Defects in NER cause three distinct human diseases: xeroderma pigmentosum, Cockayne syndrome and trichothiodystrophy. Each of these syndromes is characterized by premature onset of pathologies that overlap with those associated with old age in humans. This reveals the contribution of DNA damage to multiple age-related diseases. Tissues affected include the skin, eye, bone marrow, nervous system and endocrine axis. This review emphasizes accelerated aging associated with xeroderma pigmentosum and discusses the cause of these pathologies, either mutation accumulation or cell death as a consequence of failure to repair DNA damage.

Keywords

skin cancer; photoaging; neurodegeneration; bone marrow failure; progeria

Nucleotide excision repair

Nucleotide excision repair (NER) is an evolutionarily conserved mechanism that removes DNA lesions that distort the double helix (Figure 1). NER is commonly divided into two subpathways that differ mechanistically only in how the damaged nucleotides are identified in the genome. Helix-distortion is recognized throughout the genome by XPC in the global genome subpathway of NER (GG-NER). HR23B or its homolog HR23A facilitates damage recognition by stabilizing XPC (Sugasawa et al., 1997). Many of the DNA lesions removed by NER are caused by environmental genotoxins, including polycyclic aromatic hydrocarbons, psoralens, aromatic amines and chemotherapeutic agents such as cisplatin and mitomycin C (Sancar, 1996). For example, NER is the only repair mechanism for 6–4 photoproducts and cyclobutane pyrimidine dimers caused by ultraviolet (UV) radiation in placental mammals (Friedberg et al., 2006). A second protein complex, DDB1-DDB2/XPE, specifically facilitates

the recognition of UV photolesions by XPC-HR23B (Sugasawa, 2006). DNA lesions that occur on the transcribed strand of a gene, which block transcription, are rapidly recognized and repaired by transcription-coupled NER (TC-NER). CSA, CSB and XAB2 facilitate TC-NER by stabilizing RNA polymerase II at or near the site of damage (Laine and Egly, 2006).

Once a lesion is identified, GG-NER and TC-NER use a common mechanism to excise the damage. The multi-protein basal transcription factor TFIIH is recruited to the damage site through interactions with XPC-HR23B or CSB and CSA. XPG binds TFIIH and is critical for the structural integrity of this multi-subunit complex (Ito et al., 2007). The XPB and XPD subunits of TFIIH are helicases that unwind the DNA on both sides of the lesion. XPA and RPA are then recruited to the site to stabilize this open repair intermediate (Patrick and Turchi, 2002). XPA facilitates the subsequent recruitment of XPF-ERCC1 nuclease, which incises the damaged strand of DNA 5' to the lesion. XPG makes the 3' incision. The lesion is therefore excised in a 26–29 base single-stranded oligonucleotide. This leaves a single-stranded gap, which is filled by the replication machinery (including polymerase δ and ε, PCNA, RPA and RFC) using the undamaged strand as a template. After DNA synthesis to fill the gap, DNA LigI or DNA Lig3-XRCC1 (Moser et al., 2007) restores the integrity of the backbone to complete the repair reaction.

Diseases caused by defective nucleotide excision repair

Inherited defects in NER cause three distinct human diseases. Xeroderma pigmentosum (XP) is characterized by photosensitivity, hyperpigmentation and ichthyosis (dry, scaly skin) in sun exposed areas, a 1000-fold increase in the risk of basal and squamous cell carcinomas and melanomas of the skin and eyes (Kraemer et al., 1984; Kraemer et al., 1987). Approximately 30% of XP patients develop progressive neurologic symptoms (Kraemer et al., 2007). There are seven complementation groups of XP (XP-A to –G) caused by defective NER, corresponding to mutations in the genes encoding *XPA*, *XPB*, *XPC*, *XPD*, *XPE*, *XPF* and *XPG*. The severity of symptoms in XP varies widely, with the age at diagnosis ranging from early infancy to adulthood, and for the most part correlates with the extent to which the mutation affects NER (Kraemer et al., 2007).

Cockayne syndrome (CS) is caused by mutations in *CSA*, *CSB*, *XPB*, *XPD* or *XPG*, leading to defective TC-NER. Symptoms include growth retardation, microcephaly, delayed psychomotor development, mental retardation, joint contractures, ataxia and abnormal gait, hypogonadism, muscle atrophy, cataracts, osteopenia, dental caries, cachexia, photosensitivity and a prematurely aged appearance (Nance and Berry, 1992). CS patients are not predisposed to cancer. Trichothiodystrophy (TTD), the third disease associated with defective NER, is identical to CS except the patients have additional cutaneous symptoms including brittle hair and nails and ichthyosis (dry, scaly skin). TTD is caused by mutations in *XPB*, *XPD* or *TTDA*, which encode subunits of TFIIH, resulting in destabilization or dysfunction of the transcription factor (Giglia-Mari et al., 2004). The cutaneous symptoms of TTD are caused by impaired transcription of skin-specific genes (de Boer et al., 1998).

Many symptoms of XP, CS and TTD are similar to those seen in very elderly people in the normal population. Thus defective NER may accelerate aging of several, but not all tissues (Table I). This review primarily focuses on premature aging associated with XP and caused by mutations in genes encoding core NER factors. For a discussion of aging and age-related diseases in CS, readers are referred to *Stevnsner* in this issue.

Skin

As we age, ours skin becomes more lax, causing wrinkling (Rabe et al., 2006). This is caused by progressive loss and disorganization of extracellular elastin and collagen fibers, reduction

in extracellular glycosaminoglycans, senescence of dermal fibroblasts and decreased vascularization, collectively leading to atrophy of both the epidermis and dermis (Kligman and Kligman, 1986; Rabe et al., 2006). Aging of the skin is dramatically accelerated and exacerbated by UV radiation. Thus sun-exposed areas of the skin invariably appear “older” than unexposed areas due to photoaging. Photoaged skin is characterized by poikiloderma (dyspigmentation), laxity, deep wrinkles, telangiectasias and a yellowed, leathery appearance (Rabe et al., 2006). Although sun exposure accelerates aging of the skin, histopathologic changes caused by photoaging differ from age-associated changes of unexposed skin. Photoaging causes dramatic elastosis (accumulation of thick, tangled, degraded elastin fibers), loss of collagen fibers, increased glycosaminoglycans, disorganization and atypia of keratinocytes, inflammation of the dermis (heliodermatitis), hyperplasia of dermal fibroblasts and loss of vascularization with telangiectatic changes (Kligman and Kligman, 1986; Rabe et al., 2006).

With aging, the incidence of raised, irregular skin lesions increases exponentially. In sun-protected areas, benign cherry angiomas are the only growths that occur as we age (Kligman and Kligman, 1986). In contrast, skin that is exposed to UV radiation is highly prone to multiple benign (seborrheic keratoses, actinic keratoses) and malignant growths (squamous cells carcinoma, basal cell carcinoma and melanoma) (Rabe et al., 2006). The two major risk factors for skin cancer are UV exposure and age (Lewis and Weinstock, 2007).

All XP patients are photosensitive and have cutaneous abnormalities in sun-exposed areas of the skin (Kraemer et al., 1987). In patients with severe XP, in which NER is virtually absent, acute sunburn occurs after very brief or indirect sun exposure. Thus even a limited cumulative UV exposure leads to premature onset of poikiloderma, telangiectasias, actinic keratoses (pre-cancerous dry scaly lesions) and cutaneous neoplasms. The mean age at onset of skin cancer in XP is 8 years of age (Kraemer et al., 1987). Non-sun exposed areas of the skin are not affected in XP patients. Therefore XP represents dramatically accelerated photoaging of the skin.

The fact that XP is such a faithful model of photoaging indicates that UV-induced DNA damage, typically repaired by NER, is largely responsible for the degenerative and proliferative changes associated with photoaging. Terrestrial sunlight contains UV-B (295–320 nm) and UV-A (320–400 nm) wavelengths. UV is absorbed by DNA, causing direct DNA damage, such as 6–4 photoproducts and cyclopyrimidine dimers (Friedberg et al., 2006). These wavelengths can also damage DNA indirectly through the production of reactive oxygen species, which cause oxidative lesions and single-strand breaks. Cutaneous neoplasms are largely restricted to patients of complementation groups XP-A, XP-C, XP-E and mild XP-F patients (Friedberg et al., 2006). Patients with CS due to defects in TC-NER, although photosensitive, are not cancer-prone. This indicates that GG-NER is primarily responsible for protecting against UV-induced mutagenesis. In the absence of GG-NER, mutations accumulate in UV-exposed areas of skin leading to skin cancer.

In contrast, TC-NER is primarily responsible for protecting against a cytotoxic response to DNA damage (Mitchell et al., 2003; Schumacher et al., 2008). In the absence of TC-NER, UV induces erythema and edema (acute sunburn), but not skin cancer. This differential protective effect of GG-NER and TC-NER is supported by studies in mouse models of XP. *Xpc*$^{-/-}$ mice, defective only in GG-NER, are susceptible to UV-B induced skin cancer, but not erythema or edema (Berg et al., 1998). *Xpa*$^{-/-}$ and *Ercc1*$^{\text{flox}/-}$;K5Cre mice (in which *Ercc1* is knocked-out only in the skin), defective in both GG-NER and TC-NER, are exquisitely susceptible to UV-B induced erythema and skin cancer (de Vries et al., 1995; Doig et al., 2006). Surprisingly, mice harboring disease-causing human mutations in *Csb* and *Xpd* are also susceptible to UV-induced skin cancer, unlike patients with CS and TTD (de Boer et al., 1999; van der Horst et al., 2002; van der Horst et al., 1997). This can be explained by the fact that in the absence of

TC-NER, excision of UV photolesions by GG-NER is more efficient in humans than in mice (van der Horst et al., 2002), reducing the risk of mutagenesis.

Eyes

Approximately 40% of XP patients have ocular disease (Kraemer et al., 1987). This is restricted to the conjuctiva, eyelids and cornea; tissues, which are exposed to UV radiation. Symptoms are progressive and include photophobia, conjunctival injection (caused by vasodilation and telangiectasias of the conjunctiva), loss of eyelashes, pingueculae and pterygia (non-malignant conjunctival growths), corneal opacity (leucoma) and ocular neoplasms (squamous cell carcinoma, basal cell carcinoma, melanoma and atypical fibroxanthoma) (Kraemer et al., 1987; Kraemer et al., 2007; Shao et al., 2007). The iris, lens and retina are shielded from UV radiation by the cornea and are therefore unaffected in XP.

The ocular disease seen in XP can occur in normal individuals, where the greatest risk factors are sun exposure and age. Therefore XP represents accelerated photoaging of the eyes. Ocular tumors, like skin cancer are caused by accumulation of UV-induced mutations in the epithelial cells of the conjunctiva, cornea and eyelids, or superficial mesenchymal cells. However, leucoma appears to be driven by a deficiency of limbic stem cells (Fernandes et al., 2004). Limbic stem cells are tissue-specific stem cells that replenish damaged corneal epithelia. Therefore some of the accelerated ocular aging seen in XP is due to either cell death or replicative senescence of stem cells as a consequence of failure to repair DNA damage.

Nervous system

Neurological disease can emerge at any age in XP from the first to fourth decade of life (Robbins et al., 2002) depending upon the severity of the NER defect (Robbins et al., 1991). Neurological symptoms are progressive and include loss of fine motor control, choreoathetosis, ataxia, unsteady gait, spasticity, rigidity, hyporeflexia, loss of hearing, laryngeal dystonia and dysarthria, dysphagia, dementia and a peripheral sensory axonal neuropathy (Hayashi et al., 2004; Robbins et al., 1991). Neuropathological findings include microcephaly, cerebral cortical atrophy with enlarged ventricles. This is caused by neurodegeneration in the cerebral cortex, basal ganglia, cerebellum, brain stem, corticospinal tract, cochlea, dorsal root ganglia and peripheral nerves (Hayashi et al., 2004; Robbins et al., 1991; Robbins et al., 2002). Loss of neurons is due to apoptotic cell death (Kohji et al., 1998), presumably as a consequence of failure to repair endogenous DNA damage. Myelination, or white matter is not affected (Hentati et al., 1992) nor are glial cells (Kohji et al., 1998). Accordingly, *in vitro* primary neurons from $Xpa^{-/-}$ mice are significantly more sensitive to genotoxic stress than astroglial cells (Kisby et al., 2004).

The fact that neurodegeneration is a common feature of XP implies that NER is crucial for maintaining neurons in humans. Because NER functions exclusively on the nuclear genome, this further implies that nuclear DNA damage, if not repaired, can drive neurodegeneration. Endogenous DNA lesions that are substrates for NER include abasic sites and alkylated bases (Sancar, 1996; Wood, 1996), as well as some oxidative lesions including urea, 7,8-dihydro-8-oxoguanine and 8,5’-cyclopurines (Bjelland and Seeberg, 2003; Brooks, 2007). The high penetrance of neurodegeneration in severe XP, suggests that NER must be the only mechanism for the removal of some of these endogenous lesions, making cyclopurines the best candidate causative lesions identified to date (Brooks, 2007). For a complete discussion of the contribution of oxidative stress to neurodegeneration, the reader is referred to *Englander* in this issue.

Neurodegeneration occurs most frequently in XP complementation group A (XP-A patients) (Hentati et al., 1992). Because XPA functions exclusively in NER, this demonstrates that

neurodegeneration is a direct consequence of loss of this DNA repair pathway. Neurologic disease can also occur in XP-B and XP-D patients. Milder, adult onset neurologic impairment can occur in XP-C and XP-F (Robbins et al., 1993; Sijbers et al., 1998), but has not been reported in XP-E(DDB2) patients (Rapic-Otrin et al., 2003). This indicates that TC-NER (requiring XPA, XPB, XPD and XPF among other proteins) is particularly important for neuronal protection, while GG-NER (requiring XPC and XPE) is less important for maintaining neurons. In accordance, GG-NER is decreased in human neurons relative to mitotically active cells, but TC-NER is sustained (Nouspikel and Hanawalt, 2000).

Surprisingly, in contrast to humans, neuropathology was not detected in $Xpa^{-/-}$ (de Vries et al., 1995; Nakane et al., 1995) or $Xpc^{-/-}$ mice (Cheo et al., 1997; Sands et al., 1995). However, under conditions of stress (traumatic brain injury), recovery is impaired in $Xpa^{-/-}$ mice (Wijnhoven et al., 2007), suggesting that there may be underlying deficits in the nervous system of these DNA repair-deficient mice, which are too subtle to observe directly. In general, mouse models of NER-deficiency syndromes (XP, CS or TTD) have milder neurologic disease than the patients they mimic (Niedernhofer, 2008), possibly because mice accumulate DNA damage more slowly than humans. Intercrossing mouse models of XP and CS ($Xpa^{-/-}$;$Csb^{-/-}$ or $Xpc^{-/-}$;$Csb^{-/-}$ mice) leads to a very severe phenotype with growth retardation, severely reduced lifespan and profound spontaneous neurodegeneration (Laposa et al., 2007; Murai et al., 2001; van der Pluijm et al., 2007). Neurologic symptoms include tremors, an abnormal gait, dystonia, poor balance and progressive ataxia beginning in the first week of life (Laposa et al., 2007; Murai et al., 2001; van der Pluijm et al., 2007). Neuronal proliferation is decreased, while apoptosis is increased in the cerebellum of these mice. This supports a critical role for CSB in protecting cells of the nervous system from a cytostatic and cytotoxic response to endogenous DNA damage. However in mice, unlike humans, this is not revealed until DNA damage levels are increased by simultaneously deleting NER.

Many of the neurologic symptoms seen in XP are also associated with old age in the normal population These include decreased fine motor control, unsteady gait, hyporeflexia, hearing loss, dementia and peripheral neuropathy. With aging, there is a progressive decrease in brain function and volume beginning in the 4^{th} decade of life (Brazel and Rao, 2004). Similar to XP, this decrease is attributed to loss of neurons, either through apoptotic cell death or failure to replace neurons, while glial cells are spared (Brazel and Rao, 2004). Therefore at the level of the whole organism, tissue and cell, many aspects of XP represents accelerated aging of the nervous system. Oxidative DNA damage accumulates with age in the central nervous system (Weissman et al., 2007). In XP patients missing NER, this oxidative DNA damage presumably accumulates more rapidly or is more likely to trigger cell death.

Other neurologic symptoms seen in XP are hallmark features of age-related neurodegenerative diseases. Both Parkinson's and XP patients may experience spasticity, rigidity, laryngeal dystonia and dysarthria, dysphagia and dementia. Cognitive decline is universal in Alzheimer's disease and in XP patients with neurodegeneration. Oxidative DNA damage is implicated in the pathogenesis of both of these neurodegenerative diseases (Weissman et al., 2007). Thus there may be some overlap in the mechanism of pathogenesis between XP and Parkinson's or Alzheimer's disease. This is an important consideration in terms of disease prevention or therapy.

Hematopoiesis

Our hematopoietic system has a remarkably robust proliferative capacity, capable of producing 10^{12} blood cells per day throughout our lifespan (Effros and Globerson, 2002). Despite this, there is evidence that hematopoietic function declines with age. A significant fraction of healthy individuals over the age of 70 are mildly cytopenic, in particular anemic (Salive et al., 1992).

Elderly individuals also have a reduced capacity to produce red blood cells in response to hypoxia (Udupa and Lipschitz, 1984) and neutrophils after endotoxin challenge (Timaffy, 1962). Age-associated loss of hematopoietic function is associated with decreased physical performance (Penninx et al., 2003) and increased risk of mortality (Wilkinson and Warren, 2003). Transplantation studies in mice indicate that the primary defect is loss of hematopoietic stem cell (HSC) function with age (Azuma et al., 2002; Liang et al., 2005).

Two very recent studies demonstrate that DNA repair mechanisms are critical for the preservation of HSC function with aging (Nijnik et al., 2007; Rossi et al., 2007). Specifically related to NER, Rossi *et al.* analyzed hematopoietic stem cells (HSCs) in a mouse model of TTD [Xpd^{TTD} mice (de Boer et al., 1998)]. The bone marrow of these mice remains normocellular until at least one year of age and the number of HSCs is preserved (Rossi et al., 2007). However, there is a progressive loss of bone marrow progenitor cells in these mice. Moreover, HSCs isolated from Xpd^{TTD} mice are impaired in their ability to repopulate the hematopoietic system of irradiated hosts in competitive bone marrow transplantation, relative to age-matched wild type mice. This directly demonstrates that HSC function is prematurely compromised in a model of TTD. Furthermore, $Ercc1^{-/-}$ mice undergo spontaneous bone marrow failure within their 4 wk lifespan (Prasher et al., 2005). Thus defects in at least two proteins required for NER accelerate aging of the hematopoietic system.

It is important to note that the Xpd^{TTD} and $Ercc1^{-/-}$ mice have defects in addition to decreased NER that influence their phenotypes (de Boer et al., 1998; McWhir et al., 1993; Weeda et al., 1997). Transcription is impaired in Xpd^{TTD} mice and DNA interstrand crosslink repair is defective in the absence of XPF-ERCC1 (McHugh et al., 2001; Niedernhofer et al., 2004), identical to what is seen in cells derived from patients that they model. Thus both animal models are exquisitely sensitive to genotoxic stress (de Boer et al., 2002; Niedernhofer et al., 2006). This sensitivity, or predisposition to a cytotoxic or cytostatic response to DNA damage, undoubtedly contributes to accelerated aging in these mice, including aging of the hematopoietic system. However, bone marrow failure was reported in an XP patient (Salob et al., 1992). Therefore NER may be important for maintaining hematopoietic function.

Accelerated aging of the hematopoietic system was also discovered in mice defective in nonhomologous end-joining of DNA double-strand breaks (Nijnik et al., 2007; Rossi et al., 2007), telomere maintenance (Rossi et al., 2007), the Fanconi anemia pathway of DNA interstrand crosslink repair (Carreau et al., 1999; Haneline et al., 1999; Navarro et al., 2006), mismatch repair (Reese et al., 2003), ATM (Ito et al., 2004) or RAD50 (Bender et al., 2002) [reviewed in (Niedernhofer, 2008)]. Many of the corresponding human genome instability disorders include prominent hematologic pathology (for a complete discussion of some of these diseases see *Hasty* in this issue). Therefore DNA damage clearly makes a substantial contribution to the loss of hematopoietic function associated with aging

Tissue-specific stem cells like HSCs are responsible for organ development, maintaining tissue homeostasis and regeneration after injury (Weissman, 2000). Preserving stem cells throughout the lifespan of an organism is therefore essential for maintaining tissue function and its ability to respond to stress (Rossi et al., 2007). Aging is defined as the loss of homeostatic reserve leading to degenerative changes and increased risk of morbidity and mortality (Kirkwood, 2005). Thus loss of tissue-specific stem cells is predicted to promote aging (Schlessinger and Van Zant, 2001; Van Zant and Liang, 2003). Genotoxic stress negatively affects HSCs and limbic stem cells of the eye, accelerating the onset of age-related disease. This is likely to extend to other tissue-specific stem cells (Sharpless and DePinho, 2007). The tissue-specific pattern of accelerated aging in XP, suggests that skin and neuronal stem cells are likely to be highly vulnerable to genotoxic stress.

Cancer

XP patients were reported to have an increased risk of non-cutaneous tumors (Kraemer et al., 1984), including astrocytoma, medulloblastoma and sarcomas of the brain, leukemia, pancreatic adenocarcinoma, testicular sarcoma, bronchogenic carcinoma and gastric cancer (Kraemer et al., 1987). In this study, the median age at onset of internal tumors in XP patients was in the third decade of life (ranging from the first to sixth decade). This is much later than the onset of skin cancer in XP, but much earlier than the onset of cancer in the normal population. Thus defective NER may accelerate the onset of the age-related disease cancer. The fact that there is no tissue-specificity to the predisposition to internal tumors in XP suggests that these malignancies could be caused by environmental exposures unique to individual patients rather than endogenous DNA damage.

Xpa$^{-/-}$ and *Xpc*$^{-/-}$ mice have a higher incidence and earlier onset of spontaneous, non-cutaneous tumors than wild type mice (Wijnhoven et al., 2007). *Xpa*$^{-/-}$ accumulate somatic mutations in liver as they age, but not in brain, and these mice have an increased incidence of spontaneous liver tumors (Giese et al., 1999). In contrast, mouse models of CS and TTD, with accelerated aging of multiple tissues, do not have an elevated spontaneous mutation frequency or an increased incidence of spontaneous internal tumors (Dolle et al., 2006). Thus mutations, arising from an NER defect, correlate with cancer but not aging, providing experimental evidence that mutations are not the driving force in aging (Mitchell et al., 2003; Schumacher et al., 2008)

XFE

In XP, accelerated aging is predominantly limited to the skin, eyes and nervous system and may be largely driven by environmental factors (UV exposure of skin and dietary or other factors that promote oxidative stress in the nervous system). However many proteins required for NER have additional functions, complicating interpretation of disease phenotypes. This is the case for XPB and XPD, which as subunits of TFIIH are required not only for NER but also for basal transcription. Another example is the nuclease XPF-ERCC1. Cells defective in XPF-ERCC1 are exquisitely sensitive to genotoxins that induced DNA interstrand crosslinks (ICLs) relative to other NER mutants (Niedernhofer et al., 2006). Thus XPF-ERCC1 is implicated in the repair of ICLs via a mechanism that is distinct from NER (McHugh et al., 2001; Niedernhofer et al., 2004). ICLs covalently link both strands of DNA together, preventing strand separation, transcription and replication, and therefore are extremely cytotoxic. Endogenous ICLs have not yet been detected *in vivo*, likely because the number of lesions required to kill a cell is below the limit of detection (Dronkert and Kanaar, 2001). However, there are numerous bifunctional electrophiles (*e.g.*, malondialdehyde) produced endogenously in millimolar quantities (Largilliere and Melancon, 1988), which modify nuclear DNA (Chaudhary et al., 1994; Rouzer et al., 1997) and form crosslinks *in vitro* under physiological conditions (Kasai et al., 1998; Niedernhofer et al., 2003). Many of these endogenous genotoxins are produced via fragmentation of membrane fatty acids by reactive oxygen species (Marnett, 2002).

Mutations in *XPF* can lead to either XP or a progeroid syndrome with dramatically accelerated aging of multiple tissues. XP-F patients typically have mild XP, with late onset of skin cancer and mild neurodegeneration (Sijbers et al., 1998). A mutation in *XPF* that severely affected XPF expression and its obligate binding partner ERCC1 caused accelerated aging of skin (not photoaging), nervous, cardiovascular, renal, hepatobiliary, hematopoietic and musculoskeletal systems (Niedernhofer et al., 2006). The neurologic symptoms in this single progeroid patient (hearing loss, tremors, ataxia and cerebral atrophy) are strikingly similar to the neurodegenerative disease in XP. Thus neurodegeneration in this patient may be caused by an

NER defect. However, many of the other symptoms, including hypertension, impaired kidney and liver function, anemia, sarcopenia and osteoporosis are not commonly associated with XP, particular in the first decade of life. Thus accelerated aging of the kidney, liver and musculoskeletal system in this progeroid syndrome are ascribed to defective repair of DNA interstrand crosslinks (Niedernhofer et al., 2006).

Endocrine

A mouse model of the progeroid syndrome caused by XPF-ERCC1 deficiency revealed profound endocrine changes as a consequence of impaired DNA repair (Niedernhofer et al., 2006). Virtually identical endocrine changes were discovered in mouse models of TTD and CS crossed into an *Xpa* nullizygous background to increase the level of endogenous DNA damage (van de Ven et al., 2006; van der Pluijm et al., 2007). *Ercc1*$^{-/-}$, *Xpd*$^{m/m}$;*Xpa*$^{-/-}$, and *Csb*$^{m/m}$;*Xpa*$^{-/-}$ mice show defects in the somatotroph, thyrotroph and lactotroph hormonal axes. This is driven not by a pituitary defect, but by decreased expression of numerous effectors of the growth hormone (GH) axis, most notably insulin-like growth factor-1 (IGF-1). These endocrine changes, regulated by insulin/IGF-1, are an evolutionarily conserved, systemic response to stress activated by genotoxins, DNA repair deficiency or old age (Niedernhofer et al., 2006; van der Pluijm et al., 2007). Therefore premature onset of these endocrine changes in DNA repair deficient mice can be considered accelerated aging.

Importantly, this stress response is not activated in *Xpa*$^{-/-}$ mice, which are prone to UV-induced skin cancer (photoaging) but not other age-related diseases typical of XP (*i.e.* neurodegeneration). Therefore these age-related endocrine changes are only detected in mice defective in DNA repair mechanisms that protect against cell death and as a consequence have prominent features of accelerated aging.

Premature onset of these age-related endocrine changes is commonly seen in patients with genome instability syndromes associated with prominent symptoms of accelerated aging. Circulating levels of GH and IGF-1 are decreased in patients with Werner's syndrome (Rubin and Reed, 1996), Fanconi anemia (Giri et al., 2007) and Rothmund-Thomson syndrome (Pujol et al., 2000). Furthermore, diabetes mellitus is common in Fanconi anemia (Giri et al., 2007) and ataxia telangiectasia (Bar et al., 1978). DNA repair pathways affected in these human syndromes protect against cytotoxic DNA lesions including stalled replication forks, DNA interstrand crosslinks and double-strand breaks. Therefore, aging of the endocrine system, like the nervous system, cornea and hematopoietic system is accelerated by cell death in response to genotoxic stress.

SUMMARY

Many aspects of XP parallel age-associated disease and pathology in the normal population. Photoaging of the skin and eyes, early onset cancer and neurodegeneration represent accelerated aging in XP. In addition, mice harboring mutations in genes encoding proteins required for NER display hematopoietic failure and endocrinopathies associated with advanced age in humans. Skin, ocular and internal tumors characteristic of XP are caused by loss of global genome-NER of DNA damage incurred from environmental exposures, leading to mutation accumulation. In contrast, neurodegeneration, bone marrow failure and age-associated endocrine changes are caused by failure of transcription-coupled NER or other DNA repair mechanisms to remove endogenous, cytotoxic DNA damage. Analysis of the accelerated degenerative changes in the bone marrow and eyes caused by defects in NER, indicate that loss of function of tissue-specific stem cells is a primary cause of accelerated aging in response to unrepaired DNA damage.

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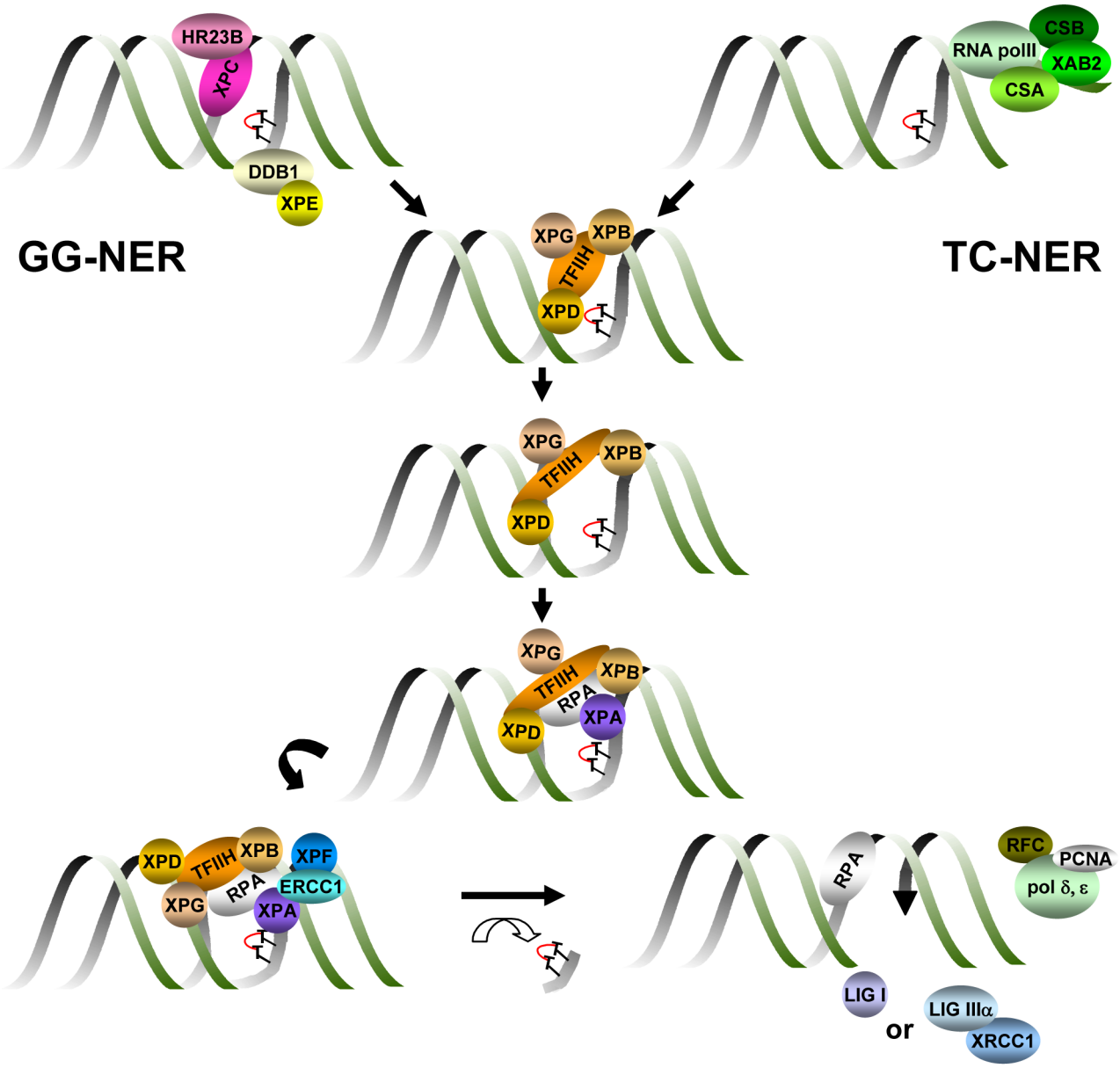

Figure 1. Schematic diagram of nucleotide excision repair

Helix-distorting DNA lesions, for example UV-induced cyclopyrimidine dimes T∩T) are recognized throughout the genome by the protein complex XPC-HR23B. Lesion recognition is facilitated by the DDB complex (DDB1 and XPE/DDB2) specifically in the case of DNA damage caused by UV radiation. DDB is part of the Cul4A complex, which ubiquitylates XPC, leading to its stable association with damaged DNA. This subpathway of NER is called global genome NER (GG-NER). Lesions on the transcribed strand of DNA, which block RNA polymerase II-mediated transcription, activate transcription-coupled NER (TC-NER). TC-NER is facilitated by CSB, CSA and XAB2. Either XPC in GG-NER or CSB and CSA in TC-NER recruit the transcription factor TFIIH to the site of damage. XPG stabilizes TFIIH. The XPB and XPD subunits of TFIIH are helicases that unwind the DNA around the lesion. XPA and RPA then bind and stabilize this unwound intermediate and recruit XPF-ERCC1. This endonuclease incises the damaged strand of DNA 5' to the lesion, while XPG makes the 3'

incision. The lesion is removed in a single-stranded oligonucleotide, leaving behind a gap, which is filled by the replication machinery comprised of polymerase δ and ε, PCNA, RPA and RFC. The DNA backbone is sealed by DNA Ligase I or DNA Ligase 3-XRCC1.

Table I

Tissue-specific accelerated aging associated with xeroderma pigmentosum.

Age-related pathology	Complementation groups affected	Pathway affected	Cause
Photoaging of the skin	XP-A, XP-C, XP-E and mild XP-F	GG-NER	Mutagenesis in keratinocytes and melanocytes
Photoaging of the eyes	XP-A others?	GG-NER in cancer TC-NER in leucoma	Ocular tumors: mutagenesis in epithelial cells of the cornea, eyelid and conjunctiva or soft tissue; Leucoma: loss or replicative senescence of limbic stem cells
Hematopoietic failure	*Xpd*$^{TTD/TTD}$ mice *Ercc1*$^{-/-}$ mice	TC-NER or interstrand crosslink repair	Replicative senescence of hematopoietic stem cells
Neuro-degeneration	XP-A, XP-B, XP-D, XP-F	TC-NER	Apoptosis of neurons
Endocrine changes	*Xpd*$^{m/m}$;*Xpa*$^{-/-}$, *Csb*$^{m/m}$;*Xpa*$^{-/-}$ and *Ercc1*$^{-/-}$	TC-NER or interstrand crosslink repair	Apoptosis
Multiple organs	Severe depletion of XPF	interstrand crosslink repair	Apoptosis