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DNA Repair Deficiency in Neurodegeneration

Dennis Kjølhede Jeppesen[1], **Vilhelm A. Bohr**[2], and **Tinna Stevnsner**[1,*]

[1] Danish Centre for Molecular Gerontology and DanishAgingResearchCenter, University of Aarhus, Department of Molecular Biology, C. F. MoellersAllé 3, build. 1130, 8000 Aarhus C, Denmark

[2] Laboratory of Molecular Gerontology, National Institute on Aging, National Institute of Health, 251 Bayview Blvd., Suite 100, Baltimore, MD21224-8626, USA

Abstract

Deficiency in repair of nuclear and mitochondrial DNA damage has been linked to several neurodegenerative disorders. Many recent experimental results indicate that the post-mitotic neurons are particularly prone to accumulation of unrepaired DNA lesions potentially leading to progressive neurodegeneration. Nucleotide excision repair is the cellular pathway responsible for removing helix-distorting DNA damage and deficiency in such repair is found in a number of diseases with neurodegenerative phenotypes, including Xeroderma Pigmentosum and Cockayne syndrome. The main pathway for repairing oxidative base lesions is base excision repair, and such repair is crucial for neurons given their high rates of oxygen metabolism. Mismatch repair corrects base mispairs generated during replication and evidence indicates that oxidative DNA damage can cause this pathway to expand trinucleotide repeats, thereby causing Huntington's disease. Single-strand breaks are common DNA lesions and are associated with the neurodegenerative diseases, ataxia-oculomotor apraxia-1 and spinocerebellar ataxia with axonal neuropathy-1. DNA double-strand breaks are toxic lesions and two main pathways exist for their repair: homologous recombination and non-homologous end-joining. Ataxia telangiectasia and related disorders with defects in these pathways illustrate that such defects can lead to early childhood neurodegeneration. Aging is a risk factor for neurodegeneration and accumulation of oxidative mitochondrial DNA damage may be linked with the age-associated neurodegenerative disorders Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis. Mutation in the WRN protein leads to the premature aging disease Werner syndrome, a disorder that features neurodegeneration. In this article we review the evidence linking deficiencies in the DNA repair pathways with neurodegeneration.

Keywords

DNA repair; Genomic instability; Reactive oxidative species; Neurodegeneration; Aging; Mitochondria; Cockayne syndrome; Alzheimer's disease; Parkinson's disease; Werner syndrome

[*]Corresponding author: TinnaStevnsner, Danish Centre for Molecular Gerontology and Danish Aging Research Center, University of Aarhus, Department of Molecular Biology, C. F. MoellersAllé 3, build. 1130, DK-8000 Aarhus C, Denmark. Phone: +45 8942 2657. Fax: +45 8942 2650. tvs@mb.au.dk.

1. Introduction

Amongst the fundamental processes, crucial for viability of organisms, including humans, are appropriate cellular signaling responses to DNA damage and the ability to repair such damage. Our cells are constantly exposed to DNA damage caused by endogenous sources such as reactive oxygen species and exogenous sources such as mutagens and radiation. To protect against this damage all cells have various DNA repair pathways. The four major pathways for repairing damage to bases are nucleotide excision repair (NER), base excision repair (BER), mismatch repair (MMR) and double-strand break repair (DSBR) (Fig. 1). NER excises bulky helix-distorting DNA lesions and BER repairs damage to a single nucleotide base, whereas MMR corrects mismatches of the normalbases; such as failure to maintain normal Watson-Crick base pairing. Breakage of the DNA backbone also occurs, either in the form of a single-strand break (SSB) or a double-strand break (DSB). SSBs are handled by the BER pathway. The repair of DNA DSBs involves one of two mechanisms: non-homologous end-joining (NHEJ) or homologous recombination (HR). NHEJ directly joins the broken ends, whereas HR uses the intact sister chromatid as a template for repair. In addition, a type of repair termed direct reversal (DR) can reverse some forms of base damage without removing the base. Translesion DNA synthesis (TLS) uses specialized DNA polymerases to replicate past lesions in the DNA, which although more error-prone than BER, NER and MMR, may reduce the immediate danger of DSBs (Prakash and Prakash, 2002).

Deficiencies in DNA repair pathways can result in reduced stability of the cellular chromosomes which in turn can lead to mutagenesis, cellular dysfunction and aberrant phenotypes. Such genomic instability would be expected to potentially increase the risk of cancer, and indeed several hereditary DNA repair deficiency diseases (*e.g*. Xeroderma Pigmentosumare associated with increased cancer risk. Another major clinical feature of such deficiencies is neurological disease, and accordingly, DNA repair deficiencies are implicated in various diseases that feature progressive neurodegeneration. In the central nervous system (CNS), higher levels of DNA damage either due to increased exposure to damaging agentsand/or defective repair of DNA, can lead to pronounced neuropathology. The brain consists largely of non-proliferative neuronal cells and is therefore particularly vulnerable to defective DNA repair that would lead to “accumulation” (more accurately, a greater steady-state level) of unrepaired DNA lesions. These DNA lesions have been proposed to be the cause of the neuropathology observed in several neurodegenerative disorders.

Progressive neurodegeneration occurs when the loss of neuronal structure or function leads to a decline in the number of neurons due to apoptotic cell death. The most consistent risk factor for developing a progressive neurodegenerative disease is aging. With age often comes a decline in brain volume and function, which similarly to neurodegenerative disease can be attributable to the permanent loss of neurons (Brazel and Rao, 2004). The ”free radical theory of aging” hypothesizes that accumulation of unrepaired oxidative damage leads to the cellular decline and associated age-related deterioration (Harman, 1981). Considerable circumstantial evidence supports the role of oxidative damage in the aging process (Balaban et al., 2005; Bokov et al., 2004; Golden et al., 2002; Sinclair, 2005), and neurons have very high rates of oxygen metabolism. In view of this it has been suggested that deficiencies in the repair of oxidative DNA damage with aging, correlates with the cognitive decline and neurodegenerative diseases that are more prominent in the aged population(Weissman et al., 2007a). Mitochondria, the main cellular energy generators, are vital for proper neuronal function and survival, and their dysfunction have been linked to neurodegeneration. In addition, it has been suggested by the “mitochondrial theory of aging”

that accumulation of mitochondrial damage is the cause of the normal aging process (Harman, 1972).

In this review, we present an overview of the current understanding of the molecular basis for neuronal DNA repair deficiencies associated with neurodegeneration. This will be done by exploring the evidence gained from the study of both inherited and age-associated neurodegenerative diseases. Included are brief descriptions with illustrations of various pathways of DNA repair that we hope will be helpful to readers not already intimately familiar with these important cellular pathways.

2. Nucleotide excision repair deficiency

2.1. Nucleotide excision repair (NER)

Damage from ultraviolet (UV) radiation and reactive oxygen species can generate helix-distorting DNA lesions. The DNA repair process responsible for removing such lesions is the nucleotide excision repair (NER) pathway. NER is a highly conserved and versatile multistep pathway capable of repairing lesions such as UV-induced cyclobutane pyrimidine dimers and 6-4 photoproducts, intra-strand crosslinks (Niedernhofer et al., 2004), DNA-protein crosslinks (Nouspikel, 2008) and some DNA adducts caused by oxidative damage (D'Errico et al., 2006; Satoh et al., 1993). In human cells, recognition of these helix distortions leads to the removal of a short single-stranded DNA segment which holds the lesion (de Boer and Hoeijmakers, 2000). This creates a single-strand gap in the DNA which subsequently is filled during repair synthesis by a DNA polymerase using the undamaged strand as a template. NER can be divided into two subpathways, global genome NER (GG-NER) and transcription-coupled NER (TC-NER) that differ in the recognition of the DNA lesion, but subsequently uses the same excision mechanism (Fig. 2). GG-NER recognizes and repairs DNA lesions anywhere in the genome whereas TC-NER only resolves lesions in the actively transcribed strand of genes. Recent reviews describe GG-NER (Shuck et al., 2008) and TC-NER in detail (Fousteri and Mullenders, 2008). The NER pathway is active in the post-mitotic neurons though the activity is lower than in fibroblasts (Yamamoto et al., 2007). Two NER-associated disorders, Xeroderma Pigmentosum and Cockayne syndrome, both feature progressive neurodegeneration and will be discussed below.

2.2. Molecular mechanism of NER

For NER to be initiated the two prerequisites are: the presence of a lesion in the DNA, and a resulting helix-distorting disruption of the duplex DNA structure. For convenience, the NER pathway can be described as a process of five sequential steps:

- **i.** *damagerecognition* of the base lesion,
- **ii.** *local unwinding* of the DNA in the vicinity of the lesion,
- **iii.** *dualincision* of the DNA strand on the 3′ and 5′ side of the base damage site leading to the excision of a single-stranded lesion-containing oligonucleotide fragment,
- **iv.** *repairsynthesis* of DNA to fill the nucleotide gap,
- **v.** *DNAligation* to seal the nick, restoring covalent integrity.

The first step, recognition, differs between GG-NER and TC-NER.

- **i.** NER does not recognize the DNA lesion or its nature as such, but rather recognizes the distortion in the structure of the DNA double helix, caused by the lesion. In GG-NER, recognition of helix-distortion is facilitated by XPC, suggested by many studies to be the first protein factor to arrive at the lesion. XPC is complexed with HR23B (most often) or HR23A, two orthologs of the yeast protein Rad23, and also

CEN2 (Sugasawa et al., 1997; Sugasawa, 2006; Wood, 1999). XPC is a DNA binding protein that preferentially binds to damaged DNA with distorting structures that are substrates for NER (Wood, 1999). Poly-ubiquitination of XPC occurs upon DNA damage and this post-translational modification increases its affinity for DNA. The function of HR23B is not known but as it is an ortholog of Rad23 it is most likely involved in the ubiquitination of XPC. While not absolutely required, CEN2 is usually present and serves to stabilize the protein complex (Araki et al., 2001). The UV-induced cyclobutane pyrimidine dimersand 6-4 photoproductslesions cause little distortion of the helix by themselves. The DDB complex, consisting of the two subunits DDB1 and DDB2 (XPE), can facilitate recognition of such photo lesions by binding to the lesion and inducing a stronger distortion, thereby enhancing recognition by the XPC-HR23B-CEN2 complex (Sugasawa, 2006). The DDB complex is also part of the E3 ubiquitin ligase responsible for attaching ubiquitin monomers to XPC. In TC-NER, recognition is facilitated by CSB, CSA and XAB2. These are recruited to RNA polymerase II (RNA pol II) to stabilize it when the polymerase is stalled at a DNA lesion in the transcribed strand of a gene during active transcription (Laine and Egly, 2006; Tsutakawa and Cooper, 2000) and to recruit other NER proteins.

ii. For the local unwinding of the DNA duplex, the multi-subunit transcription factor TFIIH is recruited to the site of damage by either XPC (in GG-NER) or CSB and CSA (in TC-NER). XPG binds to TFIIH and stabilizes the complex (Ito et al., 2007). The XPB and XBD subunits of TFIIH are 3′-5′ and 5′-3′ DNA helicases, respectively, unwinding the DNA duplex in the immediate vicinity of the lesion (Winkler et al., 2000). The short stretches of single-stranded DNA (ssDNA) created by the unwinding facilitates binding of the XPA complex consisting of XPA and the ssDNA binding protein RPA. RPA and XPA stabilize the open structure (Missura et al., 2001; Patrick and Turchi, 2002).

iii. For the dual incisions, the heterodimeric XPF-ERCC1 endonuclease protein is recruited by XPA to incise the damaged strand 5′ to the lesion and then the endonuclease activity of XPG incises the damaged strand 3′ to the lesion (Staresincic et al., 2009). The incisions flanking the damaged site generate a single-stranded oligonucleotide fragment 27–30 nucleotides in length which includes the damaged base. The fragment is thus excised from the genome leaving behind a single-stranded gap. No additional specific factors appear to be needed for the excision in mammalian NER, at least invitro(Riedl et al., 2003).

iv. Repair synthesis to fill the gap is performed by DNA polymerase holoenzyme complexes, consisting of DNA polymerase δ and κ, or ε (Pol δ, κ, ε) and accessory proteins, using the undamaged strand as template. RPA appears to recruit the clamp loader RFC and the PCNA clamp to the repair site. Pol δ is then recruited by unmodified PCNA, the classical RFC1-RFC replication factor complex and p66. Pol ε recruitment is dependent on the CTF18-RFC clamp loader. Pol κ appears to be recruited by ubiquitinated PCNA and XRCC1. The clamp loader proteins, RFC1-RFC and CTF18-RFC, catalyze the loading of PCNA on to DNA so it can serve as a processivity factor in DNA synthesis by Pol δ, ε and κ (Ogi et al., 2010; Ogi and Lehmann, 2006). (v): To restore the integrity of the DNA backbone, the remaining nick in the DNA backbone is sealed by DNA ligase I (LIG1) during the S phase of the cell cycle, or by the DNA ligase IIIα (LIG3α)-XRCC1 complex throughout the cell cycle (Moser et al., 2007).

2.3. Xeroderma pigmentosum

Xeroderma Pigmentosum (XP) is an autosomal recessive hereditary disease characterized by marked photosensitivity, hyperpigmentation and a >1000-fold increased risk of skin cancer, mainly basal and squamous cell carcinomas (Kraemer et al., 1987). An additional feature of XP in about 30% of patients (Kraemer et al., 2007) is neurological abnormalities, referred to as XP neurological disease (Rapin et al., 2000; Robbins et al., 1991). Typical neurological symptoms include abnormal motor control, ataxia (uncoordinated movements), peripheral neuropathy, dementia, brain and spinal cord atrophy, microcephaly and sensorineural deafness (Kraemer et al., 1987; Robbins et al., 1991). The severity of the symptoms varies as does the age of diagnosis, and the disease is progressive with increasing severity of symptoms over time, including cognitive decline and dementia. Most of the symptoms in XP neurological disease have been attributed to progressive neurodegeneration by apoptotic neuronal cell death. This is supported at the histological level by the observation that loss of neurons occur in several different regions of the brain (Rapin et al., 2000).

In the late 1960s it was shown that cells from XP patients are defective in NER (Cleaver, 1968; Setlow et al., 1969). XP patients fall into seven complementation groups, XP-A to XP-G, corresponding to mutations in the NER genes *XPA-G* (Kraemer et al., 2007). An eighth group, XP-V, of patients does not have defective NER, but rather have mutated polymerase η (Masutani et al., 1999). The severity and nature of the symptoms is determined by the specific mutation and reflects the role of the protein in the NER process. XP complementation group A patients most frequently feature neurodegeneration (Hentati et al., 1992). Neurodegeneration may also occur in XP-B and XP-D patients (Hentati et al., 1992) and milder, typically adult onset, neurodegeneration can occur in XP-C and XP-F (Robbins et al., 1991; Sijbers et al., 1998). Neurodegeneration has not been reported so far in patients with the least severe form of the disorder, those from group XP-E (Rapic-Otrin et al., 2003). XPA, XPB, XPD and XPF are required for TC-NER while XPC and XPE (DDB2) are dispensable for this subpathway (Fig. 2). Thus it would seem that TC-NER is the most important pathway for protecting neurons while GG-NER deficiency (XP-C and XP-E patients) leads at most to mild neurodegeneration. This view is supported by the fact that GG-NER activity is attenuated in the post-mitotic neurons relative to mitotic cells while the TC-NER activity is the same (Nouspikel and Hanawalt, 2000). In the case of XP-F there is *in vitro* evidence that mutations in the XPF part of the XPF-ERRC1 endonuclease are responsible for at least part of the DNA repair defect and symptoms by causing cytoplasmic rather than nuclear cellular localization of XPF-ERCC1 (Ahmad et al., 2010). It was not possible, however, to predict the disease severity of XP-F patients by the level of cytoplasmic XPF-ERCC1.

As UV radiation does not reach the human brain and most chemical adducts cannot cross the blood-brain barrier, it has been hypothesized that the neurodegeneration in XP patients is caused by accumulation of endogenous DNA lesions that would normally be repaired by NER (Andrews et al., 1978). Oxidative damage is considered the main form of endogenous DNA lesion in the brain (Weissman et al., 2007a) and such lesions are mostly repaired by the BER pathway as discussed in Section 3. However, it has been shown that oxygen radicals can generate DNA lesions that are repaired by NER, *in vitro*(Yamamoto et al., 2007). One such class of oxidative lesions, 8,5′-cyclopurine-2′-deoxynucleosides (cyclopurines), have an extra, second bond between the base and the DNA backbone, and are generated specifically by hydroxyl radicals (•OH) (Brooks, 2007). Cyclopurines fulfill several criteria that can reasonably be applied to DNA lesions responsible for causing the progressive neurodegeneration in XP: they are substrates for NER, but not other DNA repair pathways (Brooks et al., 2000; Kuraoka et al., 2000), they are chemically stable (Brooks, 2007), they are endogenous lesions (Dizdaroglu et al., 2001; Randerath et al., 2001) and they may block transcription by RNA pol II (Brooks et al., 2000). It has not, however, been

determined whether cyclopurines accumulate in cells from XP patients (Brooks, 2007). Other potential neurodegenerative DNA lesions are the bulky propane-deoxyguanosine (PdG) adducts that are generated when lipid peroxidation products such as malodialdehyde react with DNA (Burcham, 1998). PdG lesions are endogenous (Marnett, 1999), repaired by NER (Johnson et al., 1997) and can block RNA pol II (Cline et al., 2004). However, PdG adducts are not as likely as cyclopurines to be stable over the period of time when neurodegeneration progresses in XP patients (Brooks, 2007).

Whatever the responsible DNA lesion, cyclopurine, PdG adduct or some as yet uncharacterized lesion, neurodegeneration is thought to partially result from the blocked transcription that occurs as lesions stall RNA pol II. This inactivation of genes could decrease the level of essential protein components of the neurons to the point that cell death becomes inevitable (Andrews et al., 1978) or the blockage could be a more direct trigger for apoptosis pathways due to the presence of stalled RNA pol II (Kohji et al., 1998; Ljungman and Lane, 2004). Also, there are multiple signaling pathways that result from the presence of lesions or stalled polymerase or repair complexes. It should be noted that many of the neurological symptoms in XP also feature in normal aging including peripheral neuropathy, dementia and hearing loss. This deterioration of neurological function has, in both aging and XP, been linked to a permanent loss of neurons that leaves the glial cell population largely unchanged. As such, XP neurological disease can be seen to resemble a form of accelerated aging of the nervous system.

2.4. Cockayne syndrome

Cockayne syndrome (CS) is a rare autosomal recessive disease featuring progressive childhood neurological impairment. The neurological symptoms include demyelination in the cerebral and cerebellar cortex, calcification in basal ganglia and cerebral cortex, neuronal loss, sensorineural hearing loss and decreased nerve conduction. Neurodegeneration is most pronounced in the cerebellum with severe loss of Purkinje and granule neurons and the second most affected areas of pathology is the basal ganglia nuclei and thalamus (Weidenheim et al., 2009). Other symptoms include cachectic dwarfism, retardation of growth and development after birth, and often photosensitivity and cataracts (Licht et al., 2003). The disease does not seem to confer an increased risk of cancer. The life expectancy of CS patients is 12.5 years, and as many of the disease features resemble normal aging, it has been classified as a premature aging syndrome. The cause of CS is in 62% of cases mutations in the *CSB* gene (CS-B patients) (Laugel et al., 2010), while most of the rest result from mutations in *CSA* (CS-A patients), though some XP-B, XP-D and XP-G patients can have a combined XP/CS phenotype (de Boer and Hoeijmakers, 2000; Rapin et al., 2000). The symptoms of CS-B patients cannot be distinguished from those of CS-A. The CSB and CSA proteins are active in TC-NER and in CS patients this pathway is defective for the repair of UV-induced cyclobutane pyrimidine dimers and 6-4 photoproducts lesions while the GG-NER pathway functions normally (Licht et al., 2003; Venema et al., 1990). Consequently, one of the hallmarks of CS-B cells is hypersensitivity to UV radiation-induced DNA damage in active genes. The 168 kDa CSB protein belongs to the SWI/SNF2 family of chromatin remodelers. The protein has an SNF2-like ATPase domain consisting of seven conserved motifs (I, Ia and II–VI) and the DNA-dependent ATPase activity is crucial for recovery from cellular UV-sensitivity, RNA synthesis restart after oxidative damage and chromatin remodeling (Stevnsner et al., 2008). CSB plays a key role in the initiation of TC-NER by recruiting the histone acetyltransferase p300 to the damaged site for chromatin remodeling and recruiting other NER proteins to the stalled RNA pol II (Fousteri et al., 2006). CSB association with RNA pol II and TFIIH forms the basis of several different models that have been suggested to explain the neurological symptoms in CS:

The “transcription defect” model proposes that the symptoms are caused by a subtle defect in transcription, and that the reduction in the process stems from mutations in the proteins involved. In support of this model are the findings that CSB associates with RNA pol II *in vivo*(van Gool et al., 1997) and stimulates elongation *in vitro*(Selby and Sancar, 1997), and the observation of reduction of transcription in CS-B cells *in vivo*(Balajee et al., 1997) and in CS-B and XP-B extracts *in vitro*(Dianov et al., 1997). CS symptoms are also often seen in XP-B and XP-D, and given that XPB and XPD are subunits of TFIIH, it is conceivable that mutations in these proteins could reduce transcription. The neurological symptoms are then in this model explained by high neuronal sensitivity to transcription defects, given that a high proportion of the neuronal (but not glial) genome is transcribed (Lein et al., 2007). This model, however, still leaves the severe white matter degeneracy in CS patients, unexplained.

The “recycling” model proposes that TFIIH shifts between two different conformations, transcription and repair, and that CSB is required to switch TFIIH back to transcription. CS symptoms would then occur when TFHII is stuck in repair conformation because of the mutated CSB, reducing transcription. CSA is part of an E3 ubiquitin ligase complex (Groisman et al., 2003). As CSB is ubiquitinated by the E3 complex and rapidly degraded by the proteasome (Groisman et al., 2006), CSA could be required for removal of CSB allowing TFHII to switch back to transcription mode. A variant of this model postulates that a stalled RNA pol II blocks transcription and impairs TC-NER by preventing the repair enzymes from gaining access to the DNA lesion. TC-NER cannot occur before RNA pol II has been removed (Svejstrup, 2002). Supporting this view is the fact that yeast deficient in RAD26 (CSB homolog) displays slower NER of the transcribed strand than the non-transcribed strand (Tijsterman and Brouwer, 1999), and finding a “footprint” of a stalled RNA pol II (Tornaletti et al., 1999). One way to resolve this blockage would be for RNA pol II to change conformation to reveal the DNA lesion, and there is *in vitro* evidence that CSB and TFIIH are vital for such remodeling activity (Sarker et al., 2005). A mutated CSB would then presumably impair this RNA pol II remodeling thereby contributing to CS pathology. Another way for the blockage to be resolved would be for CSB to remove stalled RNA pol II from the DNA altogether (Svejstrup, 2002), and mutated CSB would fail to do this. Yet another possibility is for RNA pol II to be ubiquitin-tagged for degradation, controlled by CSA and CSB (Bregman et al., 1996).

It is perhaps not likely that the pleiotropic nature of CS can be explained by just one of the above models, and several different mechanisms may give rise to the CS pathology. Also, like for XP neurological disease, symptom-causing DNA damage may potentially be oxidatively induced lesions. The brains of knockout $CSB^{-/-}$ mice are devoid of CSBand have been observed to contain higher endogenous levels of the cyclopurine (5′*S*)-8,5′-cyclo-2′-deoxyadenosine, which is a helix-distorting form of DNA lesion (Kirkali et al., 2009). Like the other cyclopurines, this moiety is a form of oxidative DNA damage that due to the presence of a C8-C′5 covalent bond requires resolution by the NER pathway. If such lesions are indeed accumulating in the brains of CS-B patients it implies a role for CSB in their repair *in vivo* either linked to transcription in TC-NER, globally in the genome by GG-NER, or both.

Lipid peroxidation has been implicated in numerous human diseases particularly many of which have disease progression associated with aging including cancer and atherosclerosis, and lipid peroxidation levels are increased in at least some cell types of aged humans and rats. Peroxidation of omega-3 and omega-6 polyunsaturated fatty acids can give rise to the major product *trans*-4-hydroxy-2-nonenal (HNE). While the primary targets of HNE in the cell are proteins and thiols, it can also, following oxidation, form an epoxide that readily reacts with DNA bases to form HNE-DNA adducts recognized by mammalian NER proteins (Chung et al., 2003). While toxic to both human wild-type and CSB-deficient cells, the

sensitivity to even low physiological levels of HNE was observed to be significantly greater for the CSB-deficient cells (Maddukuri et al., 2009). Induction of HNE-DNA adducts was found to inhibit transcription by T7 RNA polymerase as well as transcription by HeLa cell-free extracts. Interestingly, cells with a CSB ATPase motif II-mutant with no ATPase activity and presumably defective in TC-NER, were just as sensitive to HNE treatment as CSB-null cells. These data present the case for bulky HNE-DNA lesions as transcription inhibitors that block the progress of RNA pol II necessitating active CSB protein for their resolution by TC-NER.

As CSB interacts with proteins of the BER pathway, deficiency in this DNA repair pathway may also be involved in the CS phenotype, a possibility reviewed in Section 3.3. Such an involvement of the CSB protein may extend to the mitochondria as mutated *CSB* cells also appear to be deficient in mitochondrial BER and display dysfunctional mitochondria, as discussed in Section 7.3. In both the CS and XP diseases neurological tissue have pronounced susceptibility to the effects of NER deficiency, and there may be several reasons for this: neurons may suffer more DNA damage, neurons may also be more sensitive to changes in transcription, and both neurons and glial cells have lower NER activity than other cell types (Yamamoto et al., 2007). The answer to how a defective NER pathway might affect the neurons of the brain shielded as they are from the damaging effect of UV radiation may lie in the endogenously generated cyclopurines. These oxidative lesions are potent blocks for transcription as well as the progress of DNA polymerase δ and the translesion synthesis DNA polymerase η. Brain tissue is very rich in lipids with a particularly high content of the easily oxidized omega-3 and omega-6 polyunsaturated fatty acids while simultaneously having very high rates of oxygen metabolism and a low content of antioxidant enzymes (Barzilai, 2007). Thus compared to other cell types neurons may have to contend with a generation of lipid peroxidation-DNA products, such as PdG and HNE-DNA adducts, that is significantly greater that most tissues, and accordingly, may be highly vulnerable to a cellular NER deficiency. Relevant to this is the observed accumulation of HNE in the cerebrum of Alzheimer's, Parkinson's, Huntington's diseases and amyotrophic lateral sclerosis patients (Zarkovic, 2003). While these diseases are not associated with known defects in NER, the accumulation of HNE is considered a biomarker for oxidative stress. This highlights the potential great impact of oxidative damage in the pathology of many neurodegenerative disorders whether they are linked to a deficiency in NER or other pathways of DNA repair. It is worth keeping in mind, however, that it has so far not been possible to determine whether the neurodegeneration and apparent premature aging in CS are in fact primarily due to a NER deficiency, a transcription deficiency, or a result of a more complex array of defects in the neuronal cells.

3. Base excision repair deficiency

3.1. Base excision repair (BER)

DNA is inherently unstable due to spontaneous hydrolytic decay and due to modification by both endogenous and exogenous alkylating agents (Lindahl, 1993). In addition reactive oxygen species (ROS), such as the highly reactive hydroxyl radical ($^{\bullet}OH$), superoxide anion ($O_2^{\bullet-}$) and hydrogen peroxide (H_2O_2) are generated as a result of normal cellular metabolism. ROS is genotoxic and capable of damaging DNA by generating various oxidative DNA lesions with base or sugar damage (Evans et al., 2004; Lindahl, 1993). One such lesion, 7,8-dihydro-8-oxoguanine (8-oxo-dG) is a commonly used cellular biomarker to indicate the extent of oxidative stress (Klaunig and Kamendulis, 2004). A comprehensive description of the various types of oxidative DNA damage can be found in a recent review (Evans et al., 2004). Such DNA lesions can present mutagenic and/or cytotoxic challenges to the cell by blocking replication and transcription. The major pathway responsible for eliminating spontaneous hydrolytic, alkylation and oxidative DNA damage, and thereby

restoring genomic integrity, is base excision repair (BER). BER is an evolutionarily conserved DNA repair process responsible for correcting most common forms of DNA damage by recognizing, excising and replacing a broad spectrum of specific forms of DNA modifications (Hoeijmakers, 2001; Krokan et al., 2000). The BER pathway proteins are also involved in repair of DNA single-strand breaks as reviewed in Section 5. The following will describe the process of nuclear BER while mitochondrial BER (mtBER) will be discussed in Section 7.2.

3.2. Molecular mechanism of BER

BER is initiated by a distinct lesion-specific mono- or bifunctional DNA glycosylase and completed by either of two subpathways: short-patch BER (SP-BER) that replaces one nucleotide or long-patch BER (LP-BER) that replaces 2–13 nucleotides (Fig. 3) (Fan and Wilson, 2005; Fortini et al., 2003; Hegde et al., 2008; Sweasy et al., 2006; Wilson and Bohr, 2007). For convenience, the BER pathway can be described as a process of five sequential steps:

- **i.** *recognition and excision* of the inappropriate base moiety (*e.g.* 8-oxo-dG),
- **ii.** *incision* of the DNA backbone adjacent to the resulting abasic site,
- **iii.** *end processing* of the DNA termini to generate a 3′-hydroxyl group (3′-OH) and a 5′-phosphate moiety (5′-P),
- **iv.** *repair synthesis* to replace the missing nucleotide(s), and
- **v.** *DNAligation* to seal the remaining nick.

- **i.** The initiating step in BER is performed by a distinct DNA glycosylase which recognizes and excises a specific base substrate by catalyzing hydrolysis of the *N*-glycosylic bond (Dizdaroglu, 2005; Huffman et al., 2005; Stivers and Jiang, 2003). The result of this is an abasic (AP) site with an intact DNA phosphodiester backbone. DNA glycosylases can be either monofunctional or bifunctional. Monofunctional DNA glycosylases, such asUDG andMPG, have only the glycosylase activity. In contrast, bifunctional DNA glycosylases, such as 8-oxoguanine DNA glycosylase (OGG1), NTH1 and NEIL1, have an intrinsic 3′ AP lyase activity in addition to the glycosylase activity.
- **ii.** After excision of the substrate base, the next step is to incise the DNA backbone adjacent to the AP site. The major protein responsible for incision in mammalian BER is APE1 which incises the DNA backbone immediately 5′ to the AP site, leaving a 5′-deoxyribose-5-phosphate (5′-dRP) product (Demple and Sung, 2005; Wilson and Barsky, 2001). The bifunctional DNA glycosylases incise the DNA backbone immediately 3′ to the AP site via β- or βδ-elimination, leaving a DNA SSB with a 3′-phospho-α,β-unsaturated aldehyde (3′-PUA) or a 3′-phosphate (3′-P), respectively.
- **iii.** The third step in BER is end processing of obstructive 3′- and 5′-termini to generate the 3′-OH and 5′-P termini in the gap at the strand break, which is the normal substrate for a DNA polymerase. DNA polymerase β (Pol β) is responsible for removing the 5′-dRP moiety via its 5′-dRP lyase activity (Bennett et al., 1997a; Mol et al., 2000; Wilson, 1998), while APE1 removes the 3-PUA residue generated by β-elimination via its 3′-phosphodiesterase activity. The 3′-P moiety generated by βδ-elimination is a poor substrate for APE1 (Wilson, 2003), so *in vivo*, such blocking groups are excised primarily by the phosphatase activity of PNKP (Rasouli-Nia et al., 2004; Wiederhold et al., 2004). PNKP is also associated with

the resolution of 3′-TOP1-SSB obstructive termini in single-strand break repair (SSBR) (see Section 5.3).

iv. The next step, repair synthesis to replace nucleotide(s), can proceed by one of two subpathways, short-patch (SP) or long-patch (LP). The choice of pathway may depend on several factors (Horton et al., 2000). When the 5′-dRP intermediate can be efficiently removed by Pol β in the previous step (iii), SP-BER is usually favored (Sobol et al., 1996). LP-BER is utilized in cases where the 5′-moiety is refractory to the Pol β AP lyase activity (Gary et al., 1999), for example during repair of a reduced AP site. The majority of BER events is currently thought to proceed via the short-patch pathway (Almeida and Sobol, 2007). In SP-BER, Pol β performs repair synthesis to fill the single nucleotide gap. Pol β interacts with XRCC1, a scaffold protein involved in promoting SP-BER by recruiting other proteins (Gryk et al., 2002; Kubota et al., 1996). In LP-BER, the repair synthesis of 2–13 nucleotides is performed by Pol β, and/or Pol δ/ε coupled with the PCNA clamp in cooperation with the loading factor RFC (Fan and Wilson, 2005). The resulting 5′-flap structure formed during the repair synthesis is removed by the flap endonuclease, FEN1 (Fan and Wilson, 2005; Levin et al., 2004), the activity of which is stimulated by PCNA (Gary et al., 1997; Wu et al., 1996). Poly(ADP-ribose) polymerase-1 (PARP1) may help to facilitate LP-BER (Frouin et al., 2003; Prasad et al., 2001).

v. The final step in BER is ligation to seal the nick containing a 3′-OH terminus and a 5′-P terminus. In SP-BER the ligation is believed to be performed by the ligase activity of LIG3α present in a LIG3α-XRCC1 complex, where XRCC1 is believed to serve as a scaffold and to stabilize LIG3α*in vivo*(Caldecott et al., 1994; Caldecott et al., 1995; Cappelli et al., 1997). PARP1 is apredominantly nuclear enzyme that responds to oxidative DNA damage and facilitates DNA repair by BER. It associates with LIG3α and slightly enhances the ligase activity (Caldecott et al., 1996; Leppard et al., 2003; Schreiber et al., 2002). It is thought that PARP1 senses the DNA SSB created at BER intermediates, helping XRCC1 to recruit the end-processing enzymes used in step (iii) (Ziegler and Oei, 2001). Binding of the PARP1 to DNA breaks activates the protein to transiently modify itself and target proteins with branched chains of ADP-ribose units. PARP2 also associates with the LIG3α-XRCC1 complex and seems to be required for efficient BER (Schreiber et al., 2002). In LP-BER, ligation is performed by LIG1 (Levin et al., 2000). LIG1 is physically associated with PCNA (Levin et al., 2000; Montecucco et al., 1998) and this association may be critical for effective ligation (Levin et al., 2000). APE1 can associate with LIG1 and stimulate its activity when the DNA nick has a 5′-P terminus (Ranalli et al., 2002).

3.3. Association of BER deficiency with neurodegeneration and aging

The human brain represents only 2% of the body weight but it extracts aproximatey 50 % of the oxygen and 10% of the glucose from the arterial blood with glucose representingthe obligatory energy substrate utilized by the brain (Magistretti and Pellerin, 1996). Neurons, and particularly their mitochondria, have very high rates of oxygen metabolism due tothe high glucose requirement of neurons and the dependence on aerobic oxidation of glucose as their source of energy (Bell et al., 1993; Bruckner et al., 1999; Ly and Verstreken, 2006). Neurons are not only highly energetic but also long-lived. Combined with the low level of antioxidant enzymes in the brain, the type of DNA damage most likely to occur in the neuronal cells is ROS-induced oxidative DNA lesions(Nouspikel and Hanawalt, 2000; Viswanathan et al., 1999). In fact, the rate of ROS production in the CNS has been proposed to be inversely proportional to life-span in vertebrates(Barja, 2004a; Hinerfeld et al., 2004).

As it is believed that accumulation of oxidative DNA damage may lead to neurodegeneration (Barja, 2004b), and since BER is the major pathway for correcting this damage, it has been hypothesized that BER deficiencies may be a cause for neurodegenerative disorders(Yang et al., 2008). The BER pathway is known to be active in the neurons of the CNS. Induction of the BER proteins XRCC1, LIG3α and Pol β is seen in ischemically preconditioned rat brains, and the total BER capacity of nuclear extracts prepared from such brains is increased, most likely due to increased gene expression of these proteins (Li et al., 2007b). The increased ability to repair oxidative DNA base damage probably accounts for the attenuation of neuronal cell death observed in the ischemically preconditioned rat brains after reperfusion and consequent oxidative stress. In aged rats the activity of APE, the major enzyme responsible for incision of the DNA backbone in BER, is reduced in the frontal/parietal cortex, cerebellum, brainstem, midbrain and hypothalamus compared to young rats (Kisby et al., 2010). While APE activity declined with age, there was no change in the protein levels of APE, Pol β and LIG3 in the rat frontal/parietal cortex perhaps suggesting that the reduced APE activity could be due to altered post-translational modification. Interestingly, the decline in APE activity was significantly smaller in rats subjected to caloric restriction at all ages and brain regions. An overview of BER gene expression in the CNS can be found in various reviews (Weissman et al., 2007a; Wilson and Bohr, 2007). Fig. 4 summaries some of the studies (using mostly knockout animals and siRNA techniques) that have been performed to examine the link between BER and neurodegeneration. These studies provide evidence implicating BER in maintaining the genomic stability of neurons.

CS patients, as described in Section 2.4., are characterized by progressive neurological impairment and features resembling accelerated aging. CSB, the protein mutated in most patients with CS, may also be involved in BER. CSB-deficient cells seem to be deficient in BER of some oxidative lesions (Tuo et al., 2003), which could be due to either reduced transcription of the BER genes or a direct interaction of CSB with BER proteins. CSB mutant cells are defective in both the repair of 8-oxo-dG (Dianov et al., 1999) and 8-oxoA (Tuo et al., 2002) DNA base damage, indicating that CSB may be important for repair of these abundant lesions. The brains of $CSB^{-/-}$ mice accumulate endogenous oxidative formamidopyrimidine DNA lesions (FapyG and FapyA) (Muftuoglu et al., 2009). These lesions are the product of the imidazole ring-opened purines guanine and adenine, respectively, and NEIL1 is the DNA glycosylase responsible for their resolution by BER in both mice and humans. CSB was found to stimulate both the incision and AP lyase activity of NEIL1 on both FapyG and FapyA lesions *in vitro*, apparently not requiring the ATPase function of CSB. NEIL1 and CSB were found to co-localize *in vivo*, and additionally, endogenous NEIL1 and CSB could be co-immunoprecipitated(Muftuoglu et al., 2009). These results suggest that CSB can function in a complex with NEIL1 to resolve oxidative FapyG and FapyA lesions. The CSB protein has been shown to physically interact with the BER proteins PARP1 (Thorslund et al., 2005) and APE1 (Wong et al., 2007). PARP1 binds DNA SSBs, such as those generated during BER, and thereby becomes activated (see Section 5.1.). CSB is a substrate for PARP1 by interaction with the N-terminal part of CSB that lacks the ATPase domain, and PARP1-CSB complexes have been shown to relocate to sites of DNA damage *in vivo* after oxidative stress(Thorslund et al., 2005). The poly(ADP-ribosyl)ation of CSB by PARP1 (Thorslund et al., 2005) accelerates DNA repair (Flohr et al., 2003) suggesting that CSB functions in the PARP1 stimulation of BER. The interaction of CSB with APE1 stimulates incision of the DNA backbone by APE1 in a manner dependent on ATP (Wong et al., 2007). When functional CSB is absent the processing of 8-oxo-dG base modifications by the DNA glycosylase OGG1 appears to cause a strong transcriptional inactivation of the damaged gene (Khobta et al., 2009). Additional OGG1 deficiency can attenuate this effect making it likely that the SSB and AP site repair intermediates generated by OGG1 are the reason for gene inactivation. CSB is then

responsible for preventing such intermediates from causing transcriptional inactivation possibly by facilitating and enhancing transcriptional functions relating to the DNA repair process. This would be consistent with an association of CSB with RNA pol II, as described in Section 2.4.

The interactions of CSB with components of the BER pathway described here imply that impaired BER may contribute to the CS phenotype and that CSB may play a general role in processing of BER substrates. Further evidence linking the BER pathway to repair of neuronal DNA is found in studies looking at BER enzymes in aging neurons. These studies have generally found decreased BER activity and BER protein abundance with age (Xu et al., 2008). One study, using an *in vitro* UDG-initiated BER assay, found a large decline in nuclear BER activity in brain extracts from old mice compared with 6-day-old mice (Intano et al., 2003). Another study found a reduction in Pol β activity and protein abundance in brain nuclear extracts from old mice compared to young mice (Cabelof et al., 2002). It has been known for some time that oxidative DNA damage accumulates in the mammalian brain with aging (Hamilton et al., 2001; Hirano et al., 1996; Kaneko et al., 1996; Nakae et al., 2000; Sai et al., 1992; Shen et al., 2001). This accumulation is considered a possible cause for the progressive loss of neurons associated with aging (Barja, 2004b), and therefore potentially associates BER-deficiency with age-related neurodegeneration.

The BER proteins are also responsible for repairing DNA SSBs. Such breaks accumulate with age, lead to neuronal cell death, and deficient SSB repair can cause neurodegenerative diseases (see Section 5.), again linking BER deficiency with neurodegeneration. It is also possible that mtBER is more important for protection of neurons, as mitochondria are the primary source of endogenous ROS and mtBER deficiency has been implicated in various neurodegenerative disorders such as Alzheimer's disease.

4. Mismatch repair defects

4.1. Mismatch repair (MMR)

DNA mismatch repair (MMR) is a highly conserved pathway that removes base-base mismatches and insertion-deletion loops that arise during DNA replication and recombination, thereby improving the fidelity of replication 50–1000 fold (Hsieh and Yamane, 2008; Jiricny, 2006). Base-base mismatches are created when errors escape from the proofreading function of DNA polymerases. Insertion-deletion loops arise when primer and template strand in a microsatellite dissociate and re-anneal incorrectly, causing the number of microsatellite-repeat units in the template and in the newly synthesized strand to differ (Kunkel, 1993). Failure of MMR greatly elevates the rate of mutagenesis, increases genomic instability, and is associated with human cancers (Li, 2008). The human MMR system (Fig. 5) has recently been reconstituted with purified proteins, though many aspects remain unclear, and there are several different working models for mammalian MMR. Reviews are available for in depth discussion of MMR (Jiricny, 2006; Li, 2008).

4.2. Huntington's disease

Huntington's disease (HD) is an autosomal dominant progressive neurodegenerative disorder. The HD phenotype is characterized by loss of medium spiny neurons, cognitive deterioration and motor dysfunction, with onset of the disease usually in the fourth or fifth decade of life (van Dellen et al., 2005). The mutation in HD is a progressively expanding CAG repeat in the N-terminal coding region of the *HD* gene. CAG encodes glutamine in the normal gene product named huntingtin, whereas the mutant huntingtin has a growing polyglutamine tract that alters its interaction with huntingtin-binding proteins (Harjes and Wanker, 2003; Li and Li, 2004; Mirkin, 2007). The onset and severity of HD is determined by the length of the repeat. There is evidence to suggest that mutant huntingtin causes

mitochondrial dysfunction (Beal, 2005) and elevated mitochondrial DNA damage levels have been found in HD patients (Polidori et al., 1999). Surprisingly, it has been found that the MSH2-MSH3 complex that functions in MMR recognition causes the CAG expansion in HD (Kovtun and McMurray, 2001; Manley et al., 1999; Owen et al., 2005). *hHD*/*MSH2*$^{-/-}$ mice displayed abolition of CAG repeat expansion (Kovtun and McMurray, 2001; Manley et al., 1999) and loss of MSH3 abrogated the expansion in transgenic mice harboring the CAG tract in the *hHD* transgene (Owen et al., 2005). Loss of MSH6 did not prevent expansion (Owen et al., 2005). MSH2-MSH3 has strong repair specificity for small heteroduplex loops, but can also repair single base mismatches (Palombo et al., 1996). CAG can form a stable stem loop structure with a repeat unit of two GC pairs and a mismatched pair (Gacy et al., 1995), and such a heteroduplex loop might conceivably be recognized by MSH2-MSH3, but then fail to be excised in the MMR process (Moore et al., 1999). Since the CAG expansion in HD occurs in post-mitotic neurons (Kovtun et al., 2007), another mechanism is likely to be responsible. One model proposes that expansion occurs as a result of BER of oxidative damage: OGG1 excises an oxidized guanine (8-oxo-dG) to create a single strand nick followed by gap-filling synthesis by a polymerase. CAG repeat hairpins then form by strand displacement together with slippage during synthesis. Removal of the flap by FEN1 is inhibited as the 5′-end is inaccessible, while MSH2-MSH3 stabilizes its hairpin substrate, allowing the slipped-stranded intermediate to be converted to an expansion. This model is supported by several lines of evidence: 8-oxo-dG accumulation in the brain of HD mice correlates with degree of CAG expansion, and that expansion is suppressed by loss of OGG1 (Kovtun et al., 2007). Expansion is suppressed in *MSH2*$^{-/-}$ mice in the presence of OGG1 (Kovtun and McMurray, 2001) and in *OGG1*$^{-/-}$ mice in the presence of MSH2 (Kovtun et al., 2007), thus indicating that OGG1 and MSH2 physically or functionally interact together to cause expansion. A role for MMR in also repairing oxidative DNA damage is supported by the literature (Pitsikas et al., 2007). FEN1 have been shown to be inhibited by secondary structures at trinucleotide repeats (Spiro et al., 1999). A model that ties oxidation to expanding CAG repeats is consistent with the progressive nature of HD, and supported by evidence that age-dependent expansion occurs together with oxidative DNA damage accumulation in HD mice (Kovtun et al., 2007).

5. Single-strand break repair deficiency

5.1. Single-strand break repair (SSBR)

SSBs are some of the most common lesions found in chromosomal DNA and they can arise in two different ways: (i) indirectly, via enzymatic cleavage of the phosphodiester backbone. Cleavage occurs during BER of oxidative base damage generated by the attack of ROS (Connelly and Leach, 2004), and also during DNA topoisomerase I (TOP1) activity (Pommier et al., 2003). (ii) Directly, induced by the oxidative damage generated by the attack of ROS such as $^{\bullet}OH$, $O_2^{\bullet -}$ and H_2O_2, or by ionizing radiation. The repair of direct and indirect SSBs has been termed SSBR. In SSBR, PARP1 is believed to function as a SSB sensor that binds to the break and attracts the LIG3α-XRCC1 complex (Chalmers, 2004). After this, SSBR utilizes many of the same proteins, and follows essentially the same procedure, as BER (Fig. 3). SSBR has two subpathways, short-patch (SP) and long-patch (LP) similar to BER (Caldecott, 2003). Any SSB event leaving an intact 5′-P and 3′-OH group should be easily ligatable, but the DNA termini at SSBs frequently have altered 3′- and 5′ termini that will be obstructions to normal polymerization by Pol β and ligation by LIG3α. Examples of 3′-obstructive termini are 3′-topoisomerase I (3′-TOP1), 3′-phosphate (3′-P), 3′-phosphoglycolate (3′-PG) and 3′-unsaturated aldehyde (3′-PUA). Examples of 5′-obstructive termini are 5′-adenosine monophosphate (5′-AMP), 5′-hydroxyl (5′-OH), 5′-aldehyde (5′-Ade) and 5′-deoxyribose-5-phosphate (5′-dRP) (Wilson and Mattson, 2007).

Two neurodegenerative diseases characterized by cerebellar ataxia, ataxia-oculomotor apraxia-1 (AOA1) and spinocerebellar ataxia with axonal neuropathy-1 (SCAN1), have been found to be associated with defects in the repair of SSBs, specifically defects in the end processing of obstructive termini (Ahel et al., 2006; El-Khamisy et al., 2005). AOA1 and SCAN1 are both hereditary autosomal recessive diseases where the patients lack the non-neurological phenotypes of hypersensitivity to ionizing radiation, increased genetic instability and cancer incidence seen in a number of DNA repair disorders. This may imply that the nervous system is particularly sensitive to defects in the repair of DNA SSBs. Elucidating the molecular basis of these diseases offers insight into the mechanisms by which defective SSBR can cause neurodegeneration, and how the normal SSBR process helps to maintain the genetic integrity of post-mitotic neurons.

5.2. Ataxia-oculomotor apraxia-1

Ataxia-oculomotor apraxia-1 (AOA1) is an autosomal recessive neurodegenerative syndrome associated with progressive cerebellar atrophy, late axonal peripheral motor neuropathy, ataxia, oculomotor apraxia (limited eye movement control), and variable age of onset (1–16 years, mean age is 5) (Aicardi et al., 1988; Le Ber et al., 2003). AOA1 cells are sensitive to the SSB-inducing agents H_2O_2 and methyl methanesulfonate(Clements et al., 2004; Gueven et al., 2004). Accumulation of SSBs under conditions of oxidative stress has been reported and post-mortem brain sections from AOA1 patients display elevated levels of oxidative DNA damage(Hirano et al., 2007a)as did fibroblasts from a AOA1 patient (Harris et al., 2009) but evidence is conflicting. Recently it was reported that neither lymphoblastoid nor primary fibroblasts from AOA1 patients have reduced rates of SSBR (Reynolds et al., 2009) nor do AOA1-model*APTX*$^{-/-}$ mouse astrocytes (El-Khamisy et al., 2009).

AOA1 results from mutations in the gene (*APTX*) which encodes the protein aprataxin (Date et al., 2001; Moreira et al., 2001). The gene is a member of the histidine triad superfamily of nucleotide hydrolases and transferases (Brenner, 2002). The aprataxin protein (APTX) can remove 5′-AMP obstructive termini from DNA strand breaks in cell free assays (Ahel et al., 2006). APTX contains three conserved domains: an N-terminal forkhead associated domain that allows interaction with the XRCC1 scaffold protein part of the LIG3α-XRCC1 complex(Clements et al., 2004) that plays a crucial role in short-patch SSBR and BER of chromosomal DNA (Thompson and West, 2000; Whitehouse et al., 2001), a histidine triaddomain that possesses AMP-lysine hydrolysis activity (Ahel et al., 2006; Seidle et al., 2005) and a DNA-binding C_2H_2 zinc-finger motif (Date et al., 2001). APTX is recruited to DNA SSBs by XRCC1 (Hirano et al., 2007a). There it is believed to function as a nick sensor to scan the SSBs for the 5′-AMP obstructive termini that are intermediates in failed DNA ligase reactions when adenylation occurs prematurely, before a 3′-OH terminus is present (Ahel et al., 2006; Rass et al., 2008). When encountered such obstructions are resolved by excision of the AMP residues in a two-step catalytic reaction (Rass et al., 2008). This deadenylation restores the DNA 5′-P terminus that is necessary for the subsequent repair steps which are believed to mainly be by the short-patch pathway. This is consistent with the function of the three conserved domains and implicates APTX as having a direct role in DNA repair. Most of the disease-causing mutations that so far have been observed in AOA1 patients have been in the catalytic histidine triad domain. The zinc finger domain have been shown to provide stabilizing contacts that lock the enzyme onto its high affinity AMP-DNA target site, something that is necessary for efficient hydrolysis of the DNA adenylate (Rass et al., 2007a). Furthermore, it was shown that APTX can deadenylate DSBR intermediates in addition to BER/SSBR intermediates. APTX also interacts with PCNA, a LP-SSBR scaffold protein (Hirano et al., 2007a). But it has been an open question whether SSBR by the long-patch pathway plays a significant role in the post-mitotic neuronal cells. The main observations that suggest it does not are: long-patch repair seems to functions

mainly during the S-phase (Caldecott, 2001) and the LP-SSBR components (PCNA, Pol δ/ε, LIG1 and FEN1) all function during DNA replication. However, a recent study has further examined the involvement of SSBR in AOA1 cells (Reynolds et al., 2009). The presence of 5′-AMP termini caused a failure of short-patch SSBR at the final step of DNA ligation and accumulation of adenylated DNA SSBs in AOA1 lymphoblastoid extracts but not wild-type cells. The end-processing by PNKP and DNA repair synthesis by Pol β in the preceding repair steps did not appear to be affected by the presence of 5′-AMP and the absence of APTX in the AOA1 cells. Despite observing a failure of SP-SSBR, this study, however, did not observe reduced rates of chromosomal SSBR in AOA1 cells nor in quiescent primary *APTX*$^{-/-}$ mouse neural astrocytes. One explanation that may reconcile these findings is a channeling of adenylated DNA nicks into the long-patch SSBR pathway where the 5′-AMP termini in the absence of APTX presumably would be removed by the combination of Pol δ/ε repair synthesis and FEN1 endonuclease activities (Fig. 3). To examine this possibility, mouse quiescent *APTX*$^{-/-}$ astrocytes and wild-type astrocytes were treated with H_2O_2 or methyl methanesulfonate in the presence and absence of the Pol δ/ε inhibitor aphidicolin, and the level of SSBs assessed. This chemical inhibition of LP-SSBR reduced the rates of SSBR in the *APTX*$^{-/-}$ astrocytes but not the wild-type astrocytes suggesting that compensatory long-patch repair may explain the normal rates of chromosomal SSBR observed in AOA1 cells.

APTX may also process specific 3′-obstructive termini of SSBs in order restore them to the 3′-OH termini that are required for subsequent repair. This has been demonstrated by one study using *in vitro* assays to show 3′-phosphatase and 3′-PG hydrolase activities for APTX to resolve the 3′-P and 3′-PG obstructive termini, respectively (Takahashi et al., 2007). This study also confirmed that the C-terminal region (histidine triad and zinc finger domains) is responsible for the removal activity while the N-terminal region containing the forkhead associated domain allows interaction with XRCC1, which may enhance the catalytic activities. If AOA1 cells are indeed defective in SP-SBBR and APTX responsible for, or contribute to, processing of some 3′-obstructive SSB termini, this would represent a potential problem for efficient repair. LP-SSBR would be unable to compensate for the deficient short-patch repair as the 3′-OH required for DNA repair synthesis is unavailable. The findings presented above and the lack of a non-neurological phenotype in AOA1, suggests that APTX functions primarily in the repair of SSBs. However, it has been speculated that APTX may have a general proofreading function during ligation in DNA repair, given its ability to deadenylate both BER/SSBR and DSBR intermediates. This view is supported by its ability to associate with both the BER/SSBR scaffold XRCC1, and XRCC4, an indispensable protein in the NHEJ pathway of DSBR (Clements et al., 2004). Also indicative of a potential role for APTX in DSBR is the finding that MDC1, a protein that amplifies ATM-dependent DNA damage signaling in the DSB response, co-localizes and interacts with APTX after induction of DNA breaks (Becherel et al., 2010). MDC1 was found not to be required for SSBR suggesting that its interaction with APTX is in response to DSBs. However, in APTX-deficient cells the repair of ionizing radiation-induced DSBs was found to be normal but as suggested above this may indicate APTX involvement specifically in proofreading DNA ligation and resolution of abortive ligation events at DSBs and not a general role for APTX in DSBR. APTX is considered to be a nuclear protein, present in both the nucleoplasm and the nucleolus, and interestingly, APTX is associated with the nucleolar proteins nucleolin, nucleophosmin and UPF1, and also partially co-localizes with nucleolin (Becherel et al., 2006; Gueven et al., 2004). It is possible that this association serves to ensure effective and efficient processing of obstructive 3′- and 5′ DNA termini to prevent SSBs from reducing gene expression by stalling RNA polymerases at the sites of elevated transcription.

The accumulated data is thus suggestive of a potentially multifaceted cellular role for APTX. It is not yet clear which specific SSBs with obstructive termini, if any, are the neurodegenerative agents in AOA1 patients though 5′-AMP SSBs appear to be the most likely candidate. And while it appears that LP-SSBR can compensate for deficient SP-SSBR in *APTX*$^{-/-}$ mouse astrocytes it is by no means certain that this is the case for AOA1 neurons given that long-patch repair appears to be deficient in some types of terminally differentiated cells (Narciso et al., 2007).

5.3. Spinocerebellar ataxia with axonal neuropathy-1

Spinocerebellar ataxia with axonal neuropathy-1 (SCAN1) is a rare autosomal recessive neurodegenerative disease associated with progressive cerebellar atrophy and peripheral neuropathy, and with 15 years being the mean age of onset (Takashima et al., 2002). Similar to AOA1, the syndrome is not associated with genomic instability nor is there an increased predisposition to cancer.

SCAN1 is caused by a homozygous mutation in the *TDP1* gene resulting in the substitution of histidine 493 for an arginine residue (H493R) (Takashima et al., 2002). *TDP1* encodes tyrosyl-DNA phosphodiesterase 1 (TDP1), a member of the phospholipase D superfamily, and as such it contains two HKD motifs which interacts to form a single symmetrical active site. The symmetry of this active site is broken in the H493R SCAN1 mutation, resulting in a decrease of enzyme activity by about 25-fold (Interthal et al., 2005). TDP1 is involved in the repair of DNA strand breaks associated with various obstructive DNA termini.

During repair, replication, transcription, recombination and chromatin condensation, DNA topoisomerase I (TOP1) relaxes superhelical tension by nicking DNA followed by controlled rotation of the broken DNA strand around the intact strand and resealing of the nick (Champoux, 2001; Wang, 2002). During this process, reversible and transient 3′-TOP1-DNA intermediates known as TOP1 cleavage complexes (TOP1cc) are formed in which TOP1 is linked, by its active site tyrosine, to the 3′-teminus of the single-stranded nick. However the TOP1cc can become irreversibly “trapped” by endogenous DNA lesions such as base mismatches, DNA breaks or abasic sites that displace the 5′-OH terminus. The TOP1cc can also become unduly long lived due to enhanced binding of TOP1 to oxidative base lesions such as 8-oxo-dG(Lesher et al., 2002) and consequently SCAN1 cells are hypersensitive to the TOP1-inhibitor camptothecin (CPT) that prolong the half-life of TOP1cc (Interthal et al., 2005). The TOP1cc can then be converted into abortive 3′-TOP1-associated DNA SSBs (3′-TOP1-SSBs) by collision with the transcription machinery or proximity to endogenous or exogenous DNA lesions (Pommier et al., 2003) (Fig. 6). TDP1 is well documented to be the primary end-processing enzyme responsible for excision of the covalently linked 3′-TOP1-SSBs (Katyal et al., 2007; Plo et al., 2003; Pouliot et al., 1999; Yang et al., 1996) (Fig. 6). SCAN1 cells are defective for the repair of these SSBs and they have been found to accumulate in *TDP1*$^{-/-}$ mice(Katyal et al., 2007; Miao et al., 2006). The resolution activity of TDP1 leaves a 3′-P terminus that is converted to 3′-OH by the phosphatase action of PNKP. The kinase activity of PNKP phosphorylates the 5′-OH terminus, allowing gap filling by Pol β and finally the DNA nick is sealed by LIG3α aided by the XRCC1 scaffold.

SCAN1 cells have a reduced ability to repair H_2O_2-induced oxidative SSBs (Takashima et al., 2002). Human TDP1 has been shown to be able to repair oxidation-induced 3′-PG obstructive termini (El-Khamisy et al., 2005; Zhou et al., 2005). However, another study, using *in vitro* assays mimicking oxidative SSBs, suggests that APE1 could possibly be responsible for most of the 3′-PG-resolving activity in human cells (Parsons et al., 2004). It is also possible that APTX could be the major contributor to this activity, as it was reported to have a K_{cat} of 3′-PG hydrolase activity about 20-fold higher than APE1 (Takahashi et al.,

2007). APE1 is associated with removal of 3′-phospho-α,β-unsaturated aldehyde (3′-PUA) termini and endonucleolytic cleavage of AP sites. This would suggest that that TDP1 does not make a major contribution to resolving 3′-PG in SSBs. TDP1 does however appear to be required for end processing of PG-terminated 3′ overhangs on DNA DSBs as indicated by the complete inability of SCAN1 cell extract to resolve these substrates (Zhou et al., 2005). A similar result was found in a more recent study using cell extract from *TDP1*$^{-/-}$ mouse embryonic fibroblasts on protruding 3′-PG DSB substrates (Hawkins et al., 2009). In addition, these investigators found that the processing of 3′-PG on blunt-end DSB substrates was partially deficient in the absence of TDP1 indicating that other enzymes can resolve such blunt-ended substrates although less efficiency than TDP1. This potential role in DSBR is examined in more mechanistic detail in Section 6.5.

TDP1 also facilitates the repair of SSBs induced by ionizing radiation although the nature of these SSBs is unclear. They could be direct breaks, producing obstructive termini such as 3′-PG that TDP1 can resolve, or they could be TOP1-associated SSBs (Parsons et al., 2004). There is evidence linking TDP1 directly to components of the SSB multi-protein repair complex. Thus, yeast two-hybrid and co-immunoprecipitation experiments were used to show a direct interaction between TDP1 and LIG3α mediated by the N-terminal domain of TDP1, and the formation of a complex with LIG3α, XRCC1 and PNKP (El-Khamisy et al., 2005). This complex was found to repair model SSB substrates with 3′-tyrosyl termini. Further strengthening the link, another study showed co-immunoprecipitation of TDP1 with XRCC1 from a rodent cell extract (Plo et al., 2003). These findings are reconciled with the observation that LIG3α-XRCC1 stimulated TDP1 activity on TOP1-associated SSBs *in vitro* (El-Khamisy et al., 2007).

The N-terminal regions of the TDP1 orthologs from different species of lower eukaryotes are poorly conserved and vary substantially in length (Interthal et al., 2001). Budding yeast species lack the XRCC1 and LIG3α components of the human SSBR complex, possibly because only the much larger mammalian genome requires these factors to enhance the rate of SSBR to avoid accumulation of SSBs. The mammalian nervous system appears to be particularly vulnerable to the effect of a high steady-state level of SSBs. Given the above, it can be speculated that the large and crucial mammalian CNS requires TDP1 to be linked to the SSBR complex, thereby enhancing the ability to rapidly repair SSBs, particularly those associated with TOP1 activity. However, as TDP1 may also process obstructive DSB termini, it appears likely that the physiological role of TDP1, like APTX, is multifaceted.

5.4. Single-strand breaks, neurodegeneration and aging

AOA1 and SCAN1 are ataxias that lack the genomic instability and increased cancer incidence phenotypes seen with many DNA repair deficiency syndromes. Both are however, associated with particular defects in DNA SSBR, indicating the critical role such repair plays in protecting the nervous system against SSBs with 3′ and 5′-obstructive termini. The notion that both APTX and TDP1 probably are required for efficient *in vivo* SSBR in neural cells was underscored by the latest experiments on a double knockout *TDP1*$^{-/-}$/*APTX*$^{-/-}$ mouse model (El-Khamisy et al., 2009). The level of H_2O_2-induced SSBs were similar for single knockout *TDP1*$^{-/-}$ and *APTX*$^{-/-}$, and double knockout *TDP1*$^{-/-}$/*APTX*$^{-/-}$ quiescent primary astrocytes, but the global rate of chromosomal repair of these oxidatively induced SSBs was synergistically decreased in the double knockout compared to the single knockouts. A similar result was reported for cerebellar granule neurons. The rate of SSBR was likewise reduced synergistically in double knockouts after treatment with the alkylating agent methyl methanesulfonate. The additional deletion of *APTX*$^{-/-}$ did not affect the SSBR rate of*TDP1*$^{-/-}$ astrocytes treated with CPT probably because these SSBs are associated with 3′-TOP1 but not 5′-AMP obstructive terminus intermediates.

Neuronal cells are terminally differentiated post-mitotic cells that also have unusually high rates of oxygen metabolism compared to other non-dividing cells while also possessing a low level of antioxidant enzymes. This would be expected to lead to an increased accumulation of SSBs with obstructive termini, necessitating effective repair. The dependency of the neurons on SSBR is also increased by the high transcriptional demand of these cells (Flangas and Bowman, 1970; Morris and Geller, 1996; Sarkander and Uthoff, 1976; Sarkander and Dulce, 1978), and their limited cellular regenerative capacity compared to other terminally differentiated cells (Nouspikel and Hanawalt, 2002; Vierck et al., 2000; Yan, 2000). The failure to prevent the accumulation of SSBs in SSBR-deficient neurons can lead to stalled transcription as the break represents an impediment to RNA polymerase progression, particularly when an obstructive terminus is present (Zhou and Doetsch, 1994). Blocked transcription will eventually cause neuronal cell death by depriving the cell of vital transcripts, and perhaps also by more direct induction of apoptosis (Ljungman and Lane, 2004). It is also possible that merely a reduction in the level of transcription resulting from defective SSBR can contribute to neurodegeneration, as suggested by the progressive neurodegeneration in Cockayne syndrome that is associated with impaired transcription-coupled NER (see Section 2.4.). Another possibility is that a high steady-state level of unrepaired SSBs encourage depletion of NAD^+ and ATP in cells due to the continuously excessive activation of the SSB sensor PARP1 (Heeres and Hergenrother, 2007), thereby promoting the death of the highly ATP-dependent neuronal cells.

AOA1 features the loss of cerebellar Purkinje neurons (Sugawara et al., 2008) but no post-mortem studies on SCAN1 patients have been published so far. However, several observations make it appear likely that the SCAN1 disease also features loss of these neurons: TOP1 is particularly highly expressed in Purkinje neurons of adolescence human brain (Gorodetsky et al., 2007; Holden et al., 1997), the toxicity of the yeast SCAN1 TDP1 mutation is dependent on high levels of TOP1 (He et al., 2007) and several other ataxia syndromes (*e.g.* ataxia telangiectasia) feature neurodegeneration of cerebellar Purkinje cells.

The susceptibility of neurons to unrepaired SSBs compared to dividing cells, and the absence of increased genetic instability and cancer in AOA1 and SCAN1 patients are probably due to alternative processing in dividing cells (Fig. 7). In dividing cells that lack SSBR, the unrepaired SSBs are converted to DSBs when they collide with DNA replication forks during the S phase. Accurate and efficient DSBR is then performed by nuclease-dependent HR during DNA replication. For the 3′-obstructions, the XPF-ERCC1 complex is a possible nuclease and for the 5′-obstuctions FEN1 or EXO1 are candidates. The lack of HR in the post-mitotic neurons will lead to slow accumulation of unresolved 3′ and 5′-obstructive termini over the years, which would be expected to lead to increased levels of SSBs with age. Indeed, an age-related accumulation of DNA SSBs has been demonstrated in certain types of neurons that are not reduced in number during aging in the mouse brain (Rutten et al., 2007). These include cerebellar granule neurons, which were shown to be dependent on TDP1, as such cells derived from *TDP1*$^{-/-}$ mice displayed SCAN1-like DNA repair deficiencies (Katyal et al., 2007). They furthermore showed that loss of TDP1 resulted in gradual age-related cerebellar atrophy in mice. Deficient SSBR of oxidative damage has been linked to another ataxia disorder, ataxia with oculomotor apraxia 2 (AOA2), a disease caused by mutation in the helicase SETX but the role of this helicase is presently unclear(Rass et al., 2007b). These findings further strengthen the association between DNA damage, DNA repair defects, SSBs, neurodegeneration and aging.

6. Double-strand break repair deficiency

6.1. Double-strand break repair (DSBR)

One of the most toxic and mutagenic lesions is the DNA double-strand break (DSB), as chromosomal breakage may result in an extreme loss of genetic integrity. DSBs can be induced by exogenous sources, such as ionizing radiation and exposure to genotoxic compounds that directly or indirectly damage DNA. DSBs can also be induced by endogenous sources, such as the ROS generated by cellular metabolism, replication fork collapse during DNA replication and repair events, and during meiotic recombination. The result of DSBs in the nervous system is initiation of a defined signaling process leading to cell cycle arrest which allows repair or elimination of the damaged cell by apoptosis.

Two major mechanistically distinct pathways exist for DSB repair (DSBR) in mammalian cells: homologous recombination (HR) and non-homologous end-joining (NHEJ) (Fig. 8). HR allows the error-free repair of DSBs associated with DNA replication by using the other intact sister chromatid, which is in close proximity, as a template. This restricts HR to the late S to G2/M phase of the cell cycle when a sister chromatid is available in proliferating cells. In addition, HR is essential for the preservation of replication forks, telomere maintenance, and chromosome segregation in meiosis I. HR is known to be the predominant DSB repair pathway during the early proliferative stage of embryonic nervous system development (Orii et al., 2006). Recent detailed reviews describe error-free DNA DSBR via HR (Helleday et al., 2007; Lee and McKinnon, 2007; West, 2003; Wyman et al., 2004). NHEJ modifies and ligates the two DNA termini of a DSB, allowing for the error-prone repair of DSBs without the need for an undamaged template. NHEJ operates throughout the cell cycle and can repair differentiated cells. The mature nervous system consists largely of post-mitotic cells therefore NHEJ is the main pathway for repair of DNA DSBs in the post-natal brain. A detailed description of error-prone DNA DSBR via NHEJ can be found in recent reviews (Helleday et al., 2007; Lee and McKinnon, 2007; Lees-Miller and Meek, 2003; Lieber et al., 2003; O'Driscoll and Jeggo, 2006). The choice of which of the two pathways that becomes activated may be linked to the cell cycle or be regulated by the levels of available specific components of the two pathways (Rothkamm et al., 2003). The two pathways can cooperate in the repair of DSBs by being active simultaneously (Richardson and Jasin, 2000).

A variety of human syndromes resulting from defects in the molecular machinery that responds to DNA DSBs are characterized by neuropathology, some of them including progressive neurodegeneration. The following will focus on two neurodegenerative diseases, ataxia telangiectasia and ataxia telangiectasia-like disorder, resulting from a defective response to DNA DSBs. Furthermore, the DSB repair deficiency-associated disorder Nijmegen breakage syndrome, characterized by microcephaly, will be touched upon as it features a defect in the same molecular machinery.

6.2. Ataxia telangiectasia

Ataxia telangiectasia (AT) is a rare autosomal recessive neurodegenerative disease characterized by ataxic movements and telangiectasia (dilated blood vessels), resulting from mutations in the ataxia telangiectasia mutated (*ATM*) gene (Chun and Gatti, 2004; Gatti et al., 2001; McKinnon, 2004). The onset of AT is in early childhood and by age 2-3 years ataxia becomes visible, followed by progressive neurodegeneration such that by age 10 the patients are confined to a wheelchair (Chun and Gatti, 2004). Neurodegeneration of granule and Purkinje cells in the cerebellum is the hallmark of AT but other features include increased predisposition to lymphoid and breast cancer (Angele et al., 2003; Gumy-Pause et al., 2004; Thorstenson et al., 2003), immunodeficiency (Nowak-Wegrzyn et al., 2004),

sterility and extreme cellular and chromosomal sensitivity to ionizing radiation(McKinnon, 2004).

ATM is a member of the PIKK family of serine/threonine protein kinases (Shiloh, 2003). It autophosphorylates after DNA damage and plays a crucial role in the DNA DSB signaling cascade by phosphorylating a multitude of different proteins that all participate in the DSB response including DSBR proteins (Fig. 8). DNA DSBs in the nervous system initiate rapid signaling transduction processes which have been characterized, both from human neurological diseases and *in vivo* mouse models (Lee and McKinnon, 2007), and is similar to the process for cultured cells, described by numerous *in vitro* studies(Bakkenist and Kastan, 2003; Bakkenist and Kastan, 2004; Kastan and Bartek, 2004; Kobayashi et al., 2002). The DSB signal response involves a series of post-translational modifications that facilitate signal transduction via the protein-protein interactions of the MRN-ATM signaling pathway, resulting in cell cycle arrest to allow time for repair or apoptosis. Failure to activate ATM in response to DSBs is believed to attenuate repair and prevent apoptosis. This would then cause the damaged cells to escape apoptosis and remain in the maturing brain leading to neurodegeneration in AT as the cells later succumb to the damage and die (Lee et al., 2001).

The MRN complex is a DNA DSB sensor known to be required in both NHEJ and HR (Chen et al., 2001; Tauchi et al., 2002), whereas the requirement for ATM is less clear. ATM together with the MRN complex and Artemis was shown to participate in the repair of a subset of DSBs via the NHEJ pathway (Riballo et al., 2004). ATM together with the MRN complex may also function in DSBR via HR (Kobayashi, 2004; Morrison et al., 2000). However, one study found no observable effect of ATM deficiency in mouse embryos with inactivated HR (*XRCC2*$^{-/-}$ mice) (Orii et al., 2006). This would suggest that HR only requires ATM in some tissues or later in development. Alternatively, another ATM-related protein, ATR, could be functioning in place of ATM in the DNA DSB signaling during HR (Brown and Baltimore, 2003; Wang et al., 2004). Whreas it was generally thought that ATM was involved in DSBR and ATR in SSBR, it is now evident that functions of these two proteins overlap. ATM signaling in the nervous system seems to function predominantly in recently post-mitotic neural cells rather than proliferative precursor cells where the ATR or DNA-PK kinases may predominate (Lee et al., 2001; Orii et al., 2006). This would also indicate that ATM is involved in DNA DSB repair utilizing NHEJ, as HR is restricted to proliferative cells. ATM is required for DNA damage-induced apoptosis in the nervous system arising from LIG4 deficiency (Lee et al., 2000; Sekiguchi et al., 2001), indicating that ATM directly responds to endogenous DNA damage in the nervous system. When ATM is absent the level of ROS is increased and at least *in vitro*, treatment with antioxidants can increase the survival of Purkinje cells that does not express ATM(Biton et al., 2008). Reducing the ROS level by increasing the antioxidative capacity can reduce cerebellar atrophy in AT patients (Russo et al., 2009). In fact, very recent data shows that conditions of oxidative stress directly oxidize and activate ATM by the formation of disulfide-crosslinked ATM dimers in the absence of DSBs and the MRN complex (Guo et al., 2010). There is thus strong evidence that ATM is an important direct sensor of oxidative stress.

Recently, post-mortem examination of the brain tissue of AT patients revealed a dramatic age-dependent increase in cerebellar DSBs (Iourov et al., 2009). These breaks were not randomly distributed but instead accumulated at specific chromosomal loci, primarily chromosomal region 14q12. Interestingly, this locus contains two genes, *FOXG1B* and *NOVA1*, which are highly expressed in the cerebellum. Thus, the cerebellar-specific nature of the neurodegeneration in AT may be due to improper gene regulation in the presence of DSBs at defined chromosomal loci.

6.3. Ataxia telangiectasia-like disorder

Ataxia telangiectasia-like disorder (ATLD) (Stewart et al., 1999; Taylor et al., 2004) is a very rare disease in which the patient phenotype is similar to the AT phenotype in showing a progressive cerebellar ataxia, genomic instability and hypersensitivity to ionizing radiation. However, ATLD can be distinguished from AT by the absence of telangiectasia, normal immunoglobulin levels, and a later onset and slower progression of the disease. In addition, no increased predisposition to cancer has been observed so far in ATLD patients in contrast to AT patients. The disease is caused by mutations of MRE11, one of the proteins in the MRN complex (Fig. 8). MRE11 interacts with both of the other MRN components NBS1 and RAD50. Additionally, binding of the MRN complex to DNA is through the two DNA-binding motifs of MRE11. Disease-causing mutations generate a hypomorphic allele resulting in either a truncated protein or a full-length mutant. The result of the truncated protein is reduced levels of all three components of the MRN complex. The specific mutation present in cells from ATLD patients with full-length mutant protein determines the strength of interaction with NBS1 and RAD50; both weaker and stronger interactions have been observed (Taylor et al., 2004). Complete loss of function is embryonic lethal (Friedberg and Meira, 2006; Xiao and Weaver, 1997). A neuropathological study of a pair of male siblings with the same heterozygous mutations of the MRE11 gene found both cerebellar atrophy and the absence of MRE11 in the neurons of the cerebellar cortex, cerebral cortex, basal ganglia and midbrain (Oba et al., 2010). Cerebellar atrophy in the two siblings was already present at infancy as indicated by magnetic resonance imaging studies. The similarity of symptoms in AT and ATLD may suggest interrelationship between ATM and the MRN complex, and a connection between DNA DSBs and neurodegeneration.

6.4. Nijmegen breakage syndrome

Nijmegen breakage syndrome (NBS) (Carney et al., 1998; Digweed and Sperling, 2004) is a rare autosomal recessive disorder caused by hypomorphic mutations of NBS1, a component of the MRN complex (Fig. 8). In contrast to AT and ATLD, NBS is characterized by microcephaly. Otherwise, the extra-neurological symptoms are quite similar to AT, including the predisposition to cancer (Valerie and Povirk, 2003). The most common (>90%) mutation of NBS1, 657Δ5, leads to cells with a 26 kDa N-terminal protein fragment, which is not physically associated with the MRN complex as it lacks the C-terminal MRE11-binding domain (Maser et al., 2001; Varon et al., 1998). In the same cells a 70 kDa C-terminal fragment is produced by internal translation initiation within the NBS1 mRNA using an open reading frame generated by the 657Δ5 frameshift. This 70 kDa fragment contains the MRE11 binding domain and can interact with the other two components of the MRN complex, MRE11 and RAD50, with sufficient function to allow embryonic development (Maser et al., 2001). The C-terminal fragment also contains a conserved domain responsible for recruitment of ATM. Complete loss of function of NBS1 is embryonic lethal, as is complete loss of function of MRE11 or RAD50 (Friedberg and Meira, 2006; Xiao and Weaver, 1997). The requirement of human NBS1 for efficient HR and NHEJ was demonstrated in a study in which introduction of full length *NBS1* cDNA could restore repair proficiency in *NBS1*-deficient cells (Howlett et al., 2006).

6.5. Double-strand breaks, neurodegeneration and aging

The three syndromes, AT, ATLD and NBS all result from defective DSBR and share many characteristics, though they also differ in some aspects. The cause of the different clinical phenotypes between the syndromes is unclear. However, the hypomorphic nature of the MRE11 and NBS mutations could be responsible for some of the differences as the proteins are partly functional. It is intriguing that ATLD and NBS cause two different kinds of neuropathology, neurodegeneration and microcephaly, respectively, given that they both stem from mutations in components of the MRN complex. This suggests that despite their

presence in the same complex, MRE11 and NBS1 have distinct functions. One possible explanation would be for the mutations to differentially affect the DNA repair function and apoptotic function of the MRN complex. The MRE11 mutations would then interfere with the apoptotic function, leading to the subsequent neurodegeneration in ATLD patients, as cells containing DSBs erroneously are utilized in the development of the nervous system. Conversely, the NBS1 mutations probably interferes with the DNA repair function of the MRN complex causing hypersensitivity to DSBs but without affecting apoptosis, possibly resulting in the microcephaly of NBS patients due to the increased neuronal cell loss during development. This would be consistent with the interaction of NBS1 with γH2AX at sites of DSBs and the requirement of NBS1 for localization of activated ATM at sites of DSBs (Kitagawa et al., 2004; Lukas et al., 2003). Results from a recent study (Shull et al., 2009) on mice lend support to such an interpretation. The nervous system of $MRE11^{ATLD1/ATLD1}$ mice with truncated MRE11 protein displayed pronounced attenuation of ATM activation and subsequent resistance to apoptosis after damage induced by ionizing radiation. Mutant $NBS1^{\Delta B/\Delta B}$ mice with truncated NBS1 on the other hand, displayed a normal apoptotic response and a higher degree of ATM activation compared to the $MRE11^{ATLD1/ATLD1}$ mice after ionizing radiation treatment. Another protein linking potential deficiency in DSBR to neurodegeneration is the end processing enzyme TDP1 that can resolve protruding 3′-PG, and with less efficiency, blunt end 3′-PG DSB termini. This protein is known to be mutated in the ataxia disease SCAN1 and the processing of protruding 3′-PG is completely deficient in SCAN1 cells (see Section 5.3.). Even though TDP1 is an established protein in the repair of SSBs it has been observed to be more active at DSB termini (Raymond et al., 2005). The data on the reported sensitivity of TDP1-deficient cells to DNA damaging agents expected to produce large amounts of 3′-PG-DSB termini, is conflicting. Human SCAN1 cells do not seem to be particularly sensitive to ionizing radiation and a deficiency in the repair of DSBs in these cells were not found after such treatment (Katyal et al., 2007). Also, no defect in DSBR after IR was found in $TDP1^{-/-}$ and $TDP1^{-/-}/APTX^{-/-}$ mouse astrocytes as measured by the disappearance of DSB marker γH2AX foci (El-Khamisy et al., 2009). However, $TDP1^{-/-}$ mice are hypersensitive to the blunt end 3′-PG DSB inducing agent bleomycin (Hirano et al., 2007b). New data has been published on the interplay of TDP1 with the abundant Ku70/80 heterodimer and DNA-PK_{CS} components of the NHEJ pathway (Fig. 8) (Zhou et al., 2009). Ku70/80 and DNA-PK_{CS} are rapidly recruited to DNA ends and in the absence of ATP this was found to render both protruding and blunt 3′-PG termini highly refractory to TDP1. This inhibition was abrogated by addition of ATP to strongly restore TDP1 end processing of 3′-PG. This effect of ATP is most likely due to increased phosphorylation of DNA-PK_{CS} as previous work suggests that the autophosphorylation of DNA-PK_{CS} modulate the accessibility of DNA ends (Reddy et al., 2004). This rearrangement of DNA ends appears to be vital for allowing TDP1 and other factors to accomplish the processing necessary for eventual end joining. SCAN1 lymphoblastoid cells displayed chromosomal hypersensitivity to calicheamicin, which induces DSBs with obstructive 3′-termini on both strands, one protruding 3′-PG and one protruding 3′-P. End processing and resection in NHEJ may involve the exonuclease activities of WRN, FEN1 and Artemis, but such activity could be hindered by the presence of obstructive 3′-termini. The WRN exonuclease activity does not excise 3′-PG and 3′-P (Harrigan et al., 2007) and although the Artemis nuclease together with DNA-PK can process protruding 3′-PG, it does so only slowly and very inefficiently (Povirk et al., 2007). If a DSB is blocked by a 3′-PG in one end and a 3′-P in the other end, such a double block may then present a significant challenge. Thus, TDP1 may serve to process DSBs with 3′-obstructive termini on both strands that are blocks for the end processing exonuclease activities in NHEJ, and consequently the TDP1-deficient SCAN1 cells would lack this function.

DSBR is essential for neural homeostasis as defective DSBR can lead to severe neurodegeneration, particularly of granule and Purkinje cells in the cerebellum. Purkinje

cells are some of the largest neurons in the human brain, featuring an elaborate dendritic arbor and a large number of dendritic spines. Granule cells are tiny neurons, with cerebellar granule cells accounting for nearly half of the neurons in the CNS. Cerebellar granule cells send fibers through Purkinje cell dendritic arbors where they synapse onto the dendrites. Several features of Purkinje cells may explain why loss of these neurons is particularly prevalent in ataxia syndromes: high metabolic activity and levels of transcription, the dendritic tree complexity and the storage of relatively large amounts of Ca^{2+}. It can be speculated that DNA repair deficiency may impact Purkinje cells more because of Ca^{2+} involvement in signaling processes or greater susceptibility to disrupted Ca^{2+} homeostasis present in these cells.

It is clear that DSBR capability is critical for normal neurogenesis during development. This is illustrated by AT and ATLD where low or no ATM activation is believed to allow damaged cells to escape apoptosis and to incorporate into the developing brain, leading to neurodegeneration in early life(Lee et al., 2001; O'Driscoll and Jeggo, 2008). It is less clear, however, what role the DSBs arising spontaneously in the mature brain due to ROS generated by metabolic activity, might play in the neurodegeneration associated with aging. There is evidence to support ROS as the cause of unrepaired DNA DSBs in NHEJ-deficient neurons (Karanjawala et al., 2002). That unrepaired DSBs could contribute to aging is supported by studies showing accelerated aging in mice defective in NHEJ (Li et al., 2007a; Vogel et al., 1999). One study that analyzed DSBR in aging have found that cells from old mice contain more DSBs than cells from young mice (Singh et al., 2001). A role for DSBs in aging is also supported by studies of the premature aging syndrome, Werner syndrome (WS). WS is caused by a mutation inthe *WRN* gene that encodes a helicase believed to be involved in DSBR by both the HR and NHEJ pathways, as discussed in Section 8.2.2. There is also evidence that the efficiency and fidelity of NHEJ declines significantly during cellular senescence. A more than four-fold reduction in efficiency of end joining have been found in senescent cells and this process was furthermore associated with extended deletions (Seluanov et al., 2004). This decline and increasingly aberrant function may be hypothesized to contribute to age-related genomic instability and aging, as senescent cells are known to accumulate in older organisms (Choi et al., 2000; Ding et al., 2001). It is therefore plausible that unrepaired DNA DSBs contribute to the neurodegeneration associated with aging. However, as DNA SSBs are far more frequent than DSBs, although less toxic and mutagenic, it is also possible that the mature nervous system relies mainly on SSBR for neuronal homeostasis.

7. Mitochondrial dysfunction and DNA repair

7.1. Mitochondria and neurons

Mitochondria are membrane-enclosed organelles that generate most of the ATP supply in eukaryotic cells, including neurons. To generate ATP high-energy electrons must be transported through the electron transport chain at the inner mitochondrial membrane. This process leads to the generation of ROS when high energy electrons react with O_2 to form $O_2^{\bullet}$, which in turn leads to generation of H_2O_2 and $^{\bullet}OH$. While the mitochondria have various antioxidant enzymes to deactivate these highly reactive molecules they do not constitute a perfect defense. Therefore damage to DNA will inevitably occur and require repair. The mammalian brain consumes large amounts of oxygen due to its reliance on glucose for production of ATP and this energy production is largely dependent on the neuronal mitochondria. The density of mitochondria is particularly high at synapses to power the energy-intensive synaptic activities (Ly and Verstreken, 2006). The mitochondrial theory of aging presupposes that ROS generated during the lifespan damages DNA, proteins and lipids, and ultimately leads to the aging of the organism. The brain may be highly vulnerable to mitochondrial dysfunction with age due to its high energy demand with

concurrent production of ROS, the age-dependent decline of antioxidant defensive mechanisms, and the inability to generally replace lost post-mitotic neurons.

The generation of large amounts of ROS inevitably exposes the mitochondrial DNA (mtDNA) to high levels of oxidative stress. Mitochondria have their own circular genome with each mitochondrion containing approximately 4–10 DNA molecules, and this mtDNA is located in close proximity to the inner mitochondrial membrane. The location of the mtDNA and the lack of protective histones is believed to make this DNA particular vulnerable to oxidative damage (Ames et al., 1993). Consistent with this, levels of oxidative base damage in mtDNA are 2–3 fold higher compared to nuclear DNA (nDNA) (Hudson et al., 1998; Richter et al., 1988), and mtDNA damage is more extensive and persists longer than nDNA damage in human cells (Yakes and Van Houten, 1997). Mitochondrial DNA damage can lead to mitochondrial dysfunction and apoptosis (Kruman et al., 2004b; Linnane et al., 1989). The mitochondrial dysfunction will promote the production of ROS which in turn increase the level of mtDNA damage and conceivably creating a self-amplifying cycle of dysfunction until neuronal cell death occurs by apoptosis. The existence of such a “mitochondrial viscious cycle” is still being debated (Sanz et al., 2006). Accumulation of mtDNA damage in the brain is suggested to be inversely related to maximum mammalian life span (Barja and Herrero, 2000). The level of oxidative DNA lesions is increased in the aging human brain. Starting by middle age accumulation of DNA damage has been found in promoters of age-downregulated genes involved in mitochondrial and synaptic function leading to transcriptional repression (Lu et al., 2004). Such repression/silencing of genes could allow a cell to stay alive with persistent DNA lesions, although with reduced function. This may represent a worthwhile alternative to complete removal of an irreplaceable post-mitotic neuron by apoptosis. Whether damage to promoter regions leading to transcriptional repression also occurs in mtDNA as well as to nDNA involved in mitochodrial function is currently unknown and thus speculative. The transcriptional repression of genes within damaged regions of DNA is a potential contributor to the gradual cognitive decline seen with age. The importance of mitochondria suggest that mitochondrial dysfunction due to unrepaired neuronal mtDNA damage could be involved in the pathogenesis of age-related neurological diseases and there is indeed evidence for this in major neurodegenerative disorders (Lin and Beal, 2006), as discussed below.

7.2. Mitochondrial DNA repair pathways

A number of DNA repair activities and pathways that function in the nucleus have also been identified and characterized in mammalian mitochondria, though the proteins involved and details of the pathway can differ (Fig. 9). The absence of mtDNA NER in mammalian cell was suggested in 1974 (Clayton et al., 1974) and later confirmed by subsequent studies (LeDoux et al., 1992; Pascucci et al., 1997). Mammalian MMR activity for mtDNA has been reported though it may be different from the corresponding activity in the nucleus (Mason et al., 2003). Indeed, very recently, robust MMR activity was found in human mitochondria though key nuclear MMR factors were not detected (de Souza-Pinto et al., 2009). Specifically, evidence was found to suggest that the mitochondrial MMR pathway does not utilize MSH2 as the key mismatch-binding protein but rather the multifunctional YB-1 protein, thus making the nuclear and mitochondrial pathways distinct. There is some evidence for HR in mammalian mitochondria (Kajander et al., 2001; Thyagarajan et al., 1996), but this does not necessarily mean that HR repairs DSBs and there is conflicting reports on repair activity (Cullinane and Bohr, 1998; Cullinane et al., 2000; LeDoux et al., 1992). Some findings indicate that NHEJ may function in mammalian mitochondrial DSBR. Mitochondria seems capable of rejoining both cohesive and blunt-ended linearized plasmid DNA (Lakshmipathy and Campbell, 1999), and proteins that specifically bind to double-stranded DNA ends as well as substrates with 3′ or 5′ overhangs were identified in

mitochondrial extracts (Coffey et al., 1999). While some of the DSBR functions have been detected in mitochondria, the proteins, as discussed in the previous section, have not been detected in mitochondria.

No *in vivo* TLS activity in mitochondria have been shown so far, though human mitochondrial DNA polymerase γ can perform synthesis past benzo[a]pyrene adducts and insert a random nucleotide, *in vitro*(Graziewicz et al., 2004). DR activity has been shown to remove O^6-methyl-2′-deoxyguanosine (Myers et al., 1988) and O^6-ethyl-2′-deoxyguanosine (Satoh et al., 1988) from mammalian mtDNA, and consistent with this a study showed repair of methylation but not complex alkylation damage (LeDoux et al., 1992).

By far the most studied and well documented mammalian DNA repair pathway present in mitochondria is BER (mtBER). The mtBER proteins are not encoded by the mitochondrial genome; rather they are mitochondrial versions of nuclear-encoded proteins. Many DNA glycosylases have been found to have mitochondrial forms. OGG1β is a splice variant that localizes to the mitochondria, but has no glycosylase activity, while the OGG1α isomform possesses a strong nuclear localization signal but may in fact be responsible for excision activity at 8-oxo-dG in the mitochondria as well (Hashiguchi et al., 2004). MYH can excise adenine opposite 8-oxo-dG and it is currently unclear, which of the many human splice variants is the mitochondrial MYH (Ohtsubo et al., 2000). NTH1 can excise pyrimidine lesions, though the human NTH1 mainly localizes to the nucleus possibly due to a weak mitochondrial targeting sequence (Ikeda et al., 2002). UNG1, an isoform of UDG, can excise uracil and oxidized cytosines from DNA (Dizdaroglu et al., 1996; Nilsen et al., 1997). NEIL1 excises oxidatively modified pyrimidine bases (Jaruga et al., 2004; Vartanian et al., 2006). In addition, it is possible that MPG can repair alkylation base damage (LeDoux et al., 1993; Myers et al., 1988; Pettepher et al., 1991; Satoh et al., 1988). After excision of the base, the AP endonuclease APE1 performs incision of the abasic site (Tomkinson et al., 1988). The human DNA polymerase γ in mitochondria then performs gap-filling and processing of the termini (Kaguni, 2004). Finally, nick ligation is performed by the mitochondrial variant of DNA ligase III (LIG3β) encoded by the human *LIG3* gene (Lakshmipathy and Campbell, 1999), which unlike the nuclear variant does not seem to require XRCC1 (Lakshmipathy and Campbell, 2000). It now appears that the damage-sensing protein PARP1 is also present in the mitochondria and can be found in a complex with LIG3β and mtDNA (Rossi et al., 2009). It seems that many of the mtBER proteins are localized to the inner mitochondrial membrane and are therefore not freely soluble (Stuart et al., 2005). There have been several recent findings which indicate that mtBER also can occur by long patch repair DNA synthesis. Uracil and AP sites was found to be repaired via LP-BER by mitochondrial extracts free of nuclear BER proteins from human cells (Akbari et al., 2008). Two-deoxyribonolactone, a type of oxidized AP site, is known to be almost entirely repaired by LP-BER and dependent on the flap endonuclease activity of FEN1. Such repair activity has now been found in human mitochondrial extract along with FEN1 (Liu et al., 2008). TDP1, the enzyme responsible for resolution of TOP1cc and other 3′ obstructive termini (see Section 5.3.) is encoded by the nuclear *TDP1* gene, a fraction of which localizes to the mitochondria (Das et al., 2010). TDP1 appears to be required for efficient repair of oxidative mtDNA damage and mtBER/SSBR was found to be dependent on both TDP1 and LIG3β for resolution of 3′-TOP1 and 3′-PG obstructive termini. Bohr and coworkers have recently discovered that another end processing protein, APTX (see section 5.2.) is present in mitochondria (in press). One of the essential component of mitochondrial nucleoids, mitochondrial transcription factor A (TFAM) is important for transcription and replication in these organelles. The role of TFAM in mtBER has recently been examined and the results indicate that TFAM can modulate mtBER by binding DNA and by protein interactions. TFAM preferentially bound to DNA containing 8-oxo-dG *in vitro*, and lysates

from TFAM knockdown cells had higher 8-oxo-dG incision activity but increased mtDNA damage accumulation compared to the control cells (Canugovi et al., 2010).

7.3. Deficient mitochondrial BER in Cockayne syndrome

While the significance of mtDNA MMR, DSBR and DR in neurodegenerative processes is still unclear, there is substantial evidence, as described below, supporting a link to deficient mtDNA BER. Thus, the pathology of CS may in part be attributable to the role of CSB in the mtBER of oxidative base damage. Levels of the mitochondrial isoform of OGG1 in CSB-deficient cells are low as is the 8-oxo-dG incision activity (Stevnsner et al., 2002). Mutant $CSB^{m/m}$ mouse embryo fibroblasts exhibit hypersensitivity to the mitochondrial oxidant paraquat (de Waard et al., 2003). Mutant $CSB^{m/m}$ mice additionally contain increased levels of 8-oxo-dG in their mtDNA and the cellular hypersensitivity extends to another mitochondrial oxidant, menadione (Osenbroch et al., 2009). $CSB^{m/m}$ cells also display altered organization of respiratory complexes in the inner mitochondrial membrane and consistent with this are slow to recover from ATP depletion induced by menadione. Very recently two different groups have reported mitochondrial localization of CSB and further evidence of CSB involvement in mtBER. CSB was found in mitochondria complexed with mtDNA and mitochondrial OGG1upon oxidative stress (Kamenisch et al., 2010). In addition to increased CSB distribution after oxidative stress, reduced 8-oxo-dG, uracil and 5-hydroxy-uracil incision activities, linked to the mitochondrial inner membrane in CSB-deficient cells, was reported (Aamann et al., 2010). Altogether these findings strongly imply that CSB mutated cells have deficient mtBER as well as dysfunctional mitochondria. Deficient mtBER has also been linked to several age-associated neurodegenerative diseases as described below.

7.4. Alzheimer's disease

Alzheimer's disease (AD), a progressive neurodegenerative disease, is the most common age-associated severe dementia. The clinical symptoms of AD are progressive memory impairment, cognitive decline, and behavioral changes. At later stages of the disease, mobility and coordination ability is impaired with slowness, rigidity, tremors, and gait problems. Neuropathologically, AD is characterized by deposition of amyloid β-peptide (Aβ) plaques, intraneuronal neurofibrillary tangles, synaptic degeneration and neuronal death (Mattson, 2004). Aβ accumulates in mitochondria and can impair the function of electron transport enzymes (Caspersen et al., 2005), cause cellular calcium overload (Canevari et al., 2004) and may increase the level of H_2O_2 in the brain (Manczak et al., 2006), which is consistent with the finding that Aβ can cause oxidative stress such as lipid peroxidation (Bruce-Keller et al., 1998; Butterfield et al., 1994). The neurons lost in AD are the poorly myelinated projection neurons of the cerebral cortex, a population of cells that may be highly vulnerable to mitochondrial dysfunction due to their dependence on a high level of ATP production to enable energy-costly ion fluxes and axonal transport. The lack of myelin is associated with high metabolic demand, high oxygen consumption, and high baseline oxidative stress.

Brains from AD patients have elevated levels of oxidative base damage in both nDNA and mtDNA and interestingly, the mtDNA have approximately 10-fold higher levels than nDNA (Wang et al., 2005). Different brain regions show different levels of DNA damage and this pattern correlates with the pathology of AD brains, with the most affected regions having the highest level of DNA damage (Wang et al., 2005). AD brain cells have increased fragmentation of mtDNA, reduced mtDNA content and display evidence of apoptosis, indicating that mtDNA damage gives rise to the neuronal cell loss in AD (de la Monte et al., 2000). BER deficiency has been found in brain tissue from post mortem sporadic AD patients, with both an affected brain region (inferior parietal lobule) and the least affected

region (cerebellum) showing similar alteration in BER function (Weissman et al., 2007b). Specifically, in the inferior parietal lobule, reduced levels of the UDG and DNA polymerase β proteins were observed as well as reduced uracil incision, 8-oxodG incision and DNA repair synthesis. In the cerebellum, both UDG protein levels and uracil incision was found to be reduced as was 8-oxodG incision activity. DNA repair synthesis and Pol β protein levels were likewise significantly reduced although less so than for the inferior parietal lobule. Interestingly, this study also examined patients with the amnestic subtype of mild cognitive impairment, the earliest clinically detectable phase of AD. Samples from these subjects displayed a significant linear decline in uracil incision activity and DNA repair synthesis that was correlated with the severity of clinical symptoms. The finding that BER is impaired is not limited to neuropathological brain regions but extends to the cerebellum, a region with no neuronal cell death in AD, suggests that BER deficiency may be a general characteristic of human AD brains. Furthermore, this defect may be present at the earliest stage of AD as it was also found in amnestic mild cognitive impairment patients. It is likely that the BER deficiency in AD brains described above is even more pronounced when specifically measured in mitochondria, but it is important to note that this remains to be carefully investigated. One study have found decreased neuronal cytoplasmic levels of OGG1, the DNA glycosylase responsible for incision of 8-oxodG, in some AD brain regions (Iida et al., 2002). A more recent investigation adds further evidence for deficient BER in early AD, with reported significant decreases in nuclear and mitochondrial OGG1 activities in the neocortex of mild cognitive impairment patients similar to late-stage AD (Shao et al., 2008). The mtDNA damage in AD patients increases the production of ROS (Swerdlow et al., 1997) resulting in production of more mtDNA damage, and this combined with deficient mtBER may create an increasing cycle of destruction culminating in neuronal death. Polymorphisms in TFAM, a modulator of mtBER (see above), can influence the risk of sporadic late-onset AD (Zhang et al., 2011).

Mouse models of AD allow examination of the earlier stages of AD and its progression while the study of human AD is generally limited by the availability of post-mortem tissue samples. AD mice, unlike human AD patients, do not display neurodegeneration even though both Aβ plaques and neurofibrillary tangles accumulate. A possible explanation is suggested by recent findings. Transgenic mice with AD-like symptoms did not display a generally significant decrease in 8-oxodG, and uracil incision activity, and DNA repair synthesis by Pol β appeared normal in the symptomatic mice (Weissman et al., 2009). An investigation into in mtBER of the synaptic fraction from whole mouse brains during normal aging and in a model of AD found that significant age-related decline of BER capacity occur specifically at the synapses, due to a reduction in the level of BER proteins and reduced mitochondrial axonal transport(Gredilla et al., 2010). However, there was no difference in repair capacity between wild-type and AD-model mice in any age group. A difference in the mechanisms involved in progressions of disease pathology between species may therefore complicate the use of mouse models for research into human AD.

The presence of oxidative damage in the brains from AD patients with Aβ plaques and neurofibrillary tangles led to the hypothesis that such structures represented the main source of oxidative stress in AD brains. However, recent findings indicate that the role of Aβ peptides may be complex. Oxidative damage has been found in brains of individuals with mild cognitive impairment, a state preceding AD (Keller et al., 2005), and oxidative stress precedes Aβ plaque formation in the pathogenesis of AD. A newer, alternative hypothesis therefore proposes that while the Aβ peptides are initially produced as an antioxidant defense mechanism, the later deposition of aggregated Aβ plaques represent pro-oxidant structures. The presence of pro-oxidant Aβ plaques in specific areas of the brain combined with the general deficiency in repair of the oxidative base lesions in AD described above, potentially explains why cell death is limited to particular neuronal cell populations in the

AD brain. Also, the apparent absence of a BER deficiency in mouse AD brains may explain why neuronal cell death is absent even though Aβ plaques are present.

7.5. Parkinson's disease

Parkinson's disease (PD) is the second most prevalent neurodegenerative disease, affecting approximately 2% of the population over the age of 65 (de Rijk et al., 1997). PD is clinically characterized by tremor, muscular rigidity, bradykinesia, and pathologically by massive loss of dopaminergic neurons in the substantia nigra (SN). The loss of neurons is associated with Lewy bodies, inclusion bodies that contain aggregated α-synuclein protein in large amounts (Mouradian, 2002).

Several studies implicate DNA damage in PD neurodegeneration: oxidatively damagednDNA and mtDNA were found in SN neurons (Alam et al., 1997; Zhang et al., 1999), increased 8-oxo-dG was found in SN mitochondria of PD patients (Shimura-Miura et al., 1999), and the PD mitochondria produce more ROS and have more mtDNA damage than normal mitochondria (Swerdlow et al., 1996). DNA deletions can be caused by oxidative DNA damage (Dumont et al., 2000; Hayakawa et al., 1992) and several brain regions of PD patients display large numbers of mtDNA deletions (Gu et al., 2002), including the substantia nigra (Bender et al., 2006; Kraytsberg et al., 2006). mtDNA point mutations accumulate in SN neurons of PD brains (Cantuti-Castelvetri et al., 2005). The SN of PD patients also displays elevated expression of OGG1β (Fukae et al., 2005). These studies have led to the hypothesis that mtDNA lesions trigger the apoptosis of SN dopaminergic neurons in PD. Exposing neuroblastoma cells to a mitochondrial complex I inhibitor led to increased 8-oxo-dG levels in cells, many of which also displayed morphology characteristics of apoptosis and increased α-synuclein levels (Sherer et al., 2002). Transgenic mice with mutated α-synuclein displayed accumulation of oxidative mtDNA damage in brain cells that also featured increased levels of apoptotic markers (Tanaka et al., 2001). Mutation in α-synuclein have been associated with familial PD (Thomas and Beal, 2007) and altogether these results suggest that neuronal apoptosis induced by α-synuclein mutations is linked to mtDNA lesions.

The exact cause of the selective loss of dopaminergic neurons in PD remains unclear. But it is worth considering whether there are characteristics of dopaminergic neurons that may make them more vulnerable to defects in DNA repair. It has been put forth that these neuronal cells could be under oxidative stress because dopamine at physiological pH is easily oxidized to produce ROS(Izumi et al., 2005). Against this, it is argued that dopamine is normally stored in synaptic vesicles where the acidic conditions prevent auto-oxidation but it is also noted that under conditions of stress, such as exposure to glutamate, extravesicular dopamine will be present and therefore subject to oxidation(Izumi et al., 2009). The excitatory neurotransmitter glutamate has previously been implicated in PD (Choi, 1988)and it has been suggested that excessive stimulation of glutamate receptors on dopaminergic neurons may be involved in the progression of PD(Blandini et al., 1996; Rodriguez et al., 1998). There is recent evidence that dopaminergic neurons are more vulnerable to continuous exposure to low concentrations of glutamate than non-dopaminergic neurons (Izumi et al., 2009). This is intriguing in the context of DNA repair because low, transient, physiological levels of glutamate causes an influx of calcium in the neuron, which in turn induces damage to mitochondrial ROS production resulting in oxidative DNA damage (Yang et al., 2010). Such exposure to low and transient doses of glutamate was found to be followed by increased DNA repair activity and increased mRNA and protein levels of the essential BER protein APE1 resulting in rapid and efficient repair of neuronal DNA. In light of these findings, it seems possible that a prolonged or excessive stimulation of glutamate receptors in PD could cause a mitochondrial ROS production that exceeds the DNA repair capacity of the more vulnerable dopaminergc neurons. Or that any

potential deficiency in the repair of oxidative DNA damage in PD patients may adversely affect the capacity of the dopaminergic neurons to deal with the normal mitochondrial ROS production from glutamate receptor stimulation.

7.6. Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is the most common adult-onset motor neuron disease, and is characterized by progressive degeneration and death of neurons in the spinal cord, brain stem and cerebral cortex (Boillee et al., 2006). The disorder is clinically characterized by muscle weakness, fasciculations and atrophy that results from the denervation associated with the death of motor neurons. Approximately 90% of cases are sporadic (SALS) and the rest are familial (FALS). The protein ALS2 may protect neurons against oxidative stress, and a rare mutation in the *ALS2* gene can cause an inherited infantile/juvenile onset FALS (Hadano et al., 2001; Hadano et al., 2007). SALS patients exhibit mitochondrial dysfunction and higher levels of mtDNA point mutations in spinal cord cells (Wiedemann et al., 2002). Mutations in the Cu/Zn-superoxide dismutase 1 (SOD1) antioxidant enzyme that converts $O_2^{\bullet -}$ to H_2O_2 may be the cause of about 20% of FALS cases (Bruijn et al., 2004) and the SOD1 version from a mouse model of human FALS increases the vulnerability of mitochondria (Jaiswal and Keller, 2009). ALS patients have increased levels of 8-oxo-dG in the spinal cord (Kikuchi et al., 2002), as do transgenic SOD1 mice spinal cord motor neuron mtDNA (Warita et al., 2001). Both SSBs and DSBs of mtDNA were found in the motor neurons of SOD1 mutant mice, and the DSBs increased with age (Martin et al., 2007). The mtDNA repair enzyme DNA polymerase γ is decreased in SOD1 mutant mice spinal cord neurons (Murakami et al., 2007). Taken together, these results suggest that the motor neurons in ALS may have deficient mtDNA repair of oxidative lesions, and suffer from both mtDNA damage and mitochondrial dysfunction, potentially contributing to neurodegeneration.

8. RecQ helicase disorders

8.1. Human RecQ helicases

Helicases are ATP-hydrolysis powered motor proteins that separate the two complementary strands of nucleic acid duplexes. Humans posses five distinct DNA helicases of the RecQ family: WRN, BLM, RECQ1, RECQ4 and RECQ5 (van Brabant et al., 2000). Human RecQ helicases are active in replication, recombination, DNA repair and possibly transcription, chromatin structure regulation and telomere maintenance (Bohr, 2008). These functions provide the RecQ helicases with a key role in maintaining genomic integrity by protecting against deleterious changes to the DNA, and perhaps accordingly, mutations in these enzymes can cause rare diseases characterized by genomic instability (van Brabant et al., 2000). The RecQ helicases interact with various proteins of the DNA repair pathways as discussed in recent reviews (Brosh and Bohr, 2007; Cobb and Bjergbaek, 2006; Hanada and Hickson, 2007; Kusumoto et al., 2007; Ouyang et al., 2008; Sharma et al., 2006). Important cellular functions of human RecQ helicases are: unwinding of DNA duplexes by the 3′ to 5′ helicase activity (Sharma et al., 2006), strand annealing of complementary ssDNA molecules (Sharma et al., 2006), and in the case of WRN, 3′ to 5′ exonuclease activity (Huang et al., 1998; Kamath-Loeb et al., 1998; Shen et al., 1998). Mutations in three of the helicases, BLM, WRN and RECQ4, result in the disorders Bloom syndrome, Werner syndrome and Rothmund-Thomson syndrome, respectively. One of these diseases, Werner syndrome, features both progressive neurodegeneration and premature aging as discussed below.

8.2. Werner syndrome

8.2.1. Characteristics of Werner syndrome and the WRN protein—Werner syndrome (WS) is a rare autosomal recessive disease characterized by genetic instability, premature aging and elevated cancer risk (Epstein et al., 1966; Goto, 1997; Schellenberg, 2001). WS mimics many changes seen with normal aging such as wrinkling of the skin, graying of the hair, cataracts, diabetes, osteoporosis, and progressive neurodegeneration (Huang et al., 1998). From microarray studies it has been observed that transcriptional changes seen in WS closely resemble those seen in normal aging (Kyng et al., 2005). WS cells are characterized by high levels of chromosomal aberrations and hypersensitivity to some DNA damaging agents (Brosh and Bohr, 2007). The *WRN* gene encodes a 1432 amino acid protein with a 3′ to 5′ DNA helicase domain and a 3′ to 5′ exonuclease domain (Bohr et al., 2000). WS is caused by loss-of-function mutations in the *WRN* gene and both the helicase and exonuclease activities must be lost for the disease to develop (Huang et al., 2006). WRN has been shown to physically interact with proteins in several different DNA repair pathways including DSBR, BER/SSBR, MMR and DNA interstrand cross-link (ICL) repair, in addition to proteins involved in telomere maintenance (Brosh and Bohr, 2007; Saydam et al., 2007).

8.2.2. WRN in DSBR—WRN interacts with components of both the HR and NHEJ pathways of DSBR. For HR, WRN interaction with RAD52 either stimulates or inhibits the helicase activity depending on DNA structure, and increases the efficiency of strand annealing mediated by RAD52 (Baynton et al., 2003). This implicates WRN in the rescue of replication forks after DNA damage. WRN also interacts with BRCA1 (Cheng et al., 2006), and an interaction with the MRN complex through NSB1 stimulates the helicase activity (Cheng et al., 2004). RAD51 associates with WRN and RAD54 co-localizes strongly with WRN after replication arrest (Otterlei et al., 2006). In the NHEJ pathway, Ku70-80 heterodimer interaction with WRN strongly stimulates the 3′ to 5′ exonuclease activity (Cooper et al., 2000; Li and Comai, 2000) and DNA-PK_{CS} dependent phosphorylation of WRN regulates the helicase and exonuclease activities (Karmakar et al., 2002). Certain oxidative DNA lesions with OH groups at the C8 position in the major groove of DNA can block the exonuclease activity (Machwe et al., 2000). However, the presence of Ku70-80 can stimulate the WRN exonuclease to bypass these lesions (Bukowy et al., 2008). The interaction between Ku70-80 may therefore be important in the context of DSBs induced by both ionizing radiation and radiomimetic drugs, which are known to generate oxidatively induced base lesions in addition to DNA strand breaks. WRN thus appears to be an important accessory protein for increasing the fidelity of NHEJ. It is, however, not necessarily an essential component, as deficiency in core components of NHEJ causes hypersensitivity to ionizing radiation while the cells of WS patients appear to have only mildly increased sensitivity. It has been reported that the exonuclease activity of WRN is stimulated by the physical interaction with the LIG4-XRCC4-XLF complex, involved in NHEJ, and that this complex can ligate a substrate processed by the WRN exonuclease (Kusumoto et al., 2008). In light of the evidence for WRN activity in the DSBR pathways, the chromosomal aberrations seen in WS cells may partly result from unrepaired DSBs.

8.2.3. WRN in BER—WS cells are sensitive to DNA damaging agents repaired by the BER pathway (Blank et al., 2004; Harrigan et al., 2006) and accumulate 8-oxo-dG lesions (Von Kobbe et al., 2004b), indicating a role for WRN in BER. Furthermore, WRN is required for PARP1 ribosylation (von Kobbe et al., 2003), and physical interaction between WRN and PARP1 regulates the helicase and exonuclease activity of WRN (von Kobbe et al., 2004a), which implicates WRN in SSBR given that PARP1 is a sensor of SSBs. WRN may in fact be important in BER/SSBR as it interacts functionally with many of the proteins in these pathways. APE1 inhibits WRN helicase activity possibly to prevent undesired

unwinding of the BER intermediates before repair processing by downstream enzymes in the BER pathway (Ahn et al., 2004). WRN stimulates Pol β strand displacement synthesis (Harrigan et al., 2003). The FEN1 cleavage of the 5′ flap created by strand displacement synthesis is greatly stimulated (Brosh et al., 2001) and the NEIL1 DNA glycosylase is also stimulated by WRN (Das et al., 2007). WRN can protect non-dividing cells from oxidative DNA damage and depletion of the protein produce accelerated cellular senescence in normal fibroblasts (Szekely et al., 2005). Taken together these results indicate that the neurodegenerative and premature aging phenotype of WS patients may relate to oxidative damage and SSB accumulation.

8.2.4. WRN in MMR—It has been suggested by an earlier study showing deficient base-base mismatch and insertion-deletion loop repair in WS fibroblast cells, that WRN might have a role in MMR (Bennett et al., 1997b). WRN can physically interact with the MSH2-MSH6, MSH2-MSH3 and MLH1-PMS2 complexes involved in initiation of MMR (Saydam et al., 2007). The helicase activity of WRN was also found to be strongly stimulated by MSH2-MSH6 and MSH2-MSH3.

8.2.5. WRN in ICL repair—DNA ICLs are rare events formed by covalent binding of the complementary strands of the double helix that can prevent DNA strand separation and hence represent formidable blocks to replication and transcription. While they occur relatively infrequently, they are highly cyto- and genotoxic with an estimated 40 unrepaired ICLs being enough to induce cell death (Akkari et al., 2000). Accumulation of ICLs in the genome over time has been proposed to contribute to genomic instability and the aging process (Mitchell et al., 2003).

ICL repair in mammals is not yet well understood but may involve proteins from HR and the NER pathways as well as error-prone TLS polymerases (Hinz, 2010). When considering models for a mammalian ICL repair pathway, the current data argues for choice of subpathway and repair proteins that depend on cell cycle status (McHugh and Sarkar, 2006). In the DNA of non-replicating cells or outside of the S-phase, ICL repair is thought to rely primarily on NER proteins as well as TLS polymerase activity (Fig. 10A). In the context of actively replicating cells ICL repair appears significantly more complex involving coordination of the S-phase checkpoint, the Fanconi anemia (FA) pathway, TLS, NER and HR (Fig. 10B). Excellent reviews on ICL repair and the FA pathway have been published recently and are recommended for interested readers (Andreassen and Ren, 2009; de Winter and Joenje, 2009).

There is considerable evidence linking WRN to ICL repair. WS cells are more sensitive to ICL-inducing compounds than any other genotoxic compounds (Liu et al., 2009; Poot et al., 2001; Poot et al., 2002). Triggering of the intra-S checkpoint after exposure to DNA damaging agents is necessary to inhibit DNA synthesis and allow for repair. It has been reported that WRN is required for this S phase checkpoint as well as the damage signaling in response to ICL-induced DNA lesions (Cheng et al., 2008). The helicase but not exonuclease activity of WRN is required for the repair of at least some types of DNA ICLs *in vivo* (Cheng et al., 2006). This study also found evidence to suggest WRN cooperates with BRCA1 in the HR steps of ICL repair. The interaction of WRN with BRCA1 was found to increase in cells treated with ICL-inducing agents. WRN also participates in a complex with the ATR and RAD51 in response to ICL-induced replication arrest and interacts directly with RAD51 (Otterlei et al., 2006).

8.2.6. WRN in TLS—For TLS to bypass DNA lesions, it is necessary for the PCNA clamp to be activated by mono-ubiquitination by Rad18 (Lehmann, 2006). Very recently it has been suggested that WRN can participate in TLS through interaction with NBS1 of the

MRN complex (Kobayashi et al., 2010). DNA damage induced the dissociation of PCNA from WRN in an NBS1-dependent manner leading to the ubiquitination of PCNA. Furthermore, WS cells exhibited increase in spontaneous formation of Rad18 foci, an increase in the interaction between PCNA and Rad18 and spontaneous mono-ubiquitination of PCNA.

8.2.7. WRN in maintenance of telomeres—The ends of linear eukaryotic chromosomes have specialized nucleoprotein complexes called telomeres that function to protect against events that may lead to genome instability. During the normal aging process a progressive shortening of the telomeres is observed. Non-functional short telomeres are believed to contribute to the aging process. Fibroblast cells from WS patients have higher rates of telomere shortening than those of normal fibroblasts (Baird et al., 2004) and display symptoms of telomere dysfunction including premature senescence (Davis et al., 2003; Schulz et al., 1996). WRN interacts with telomeric DNA structures and telosome proteins, including TRF1 and TRF2, regulators of telomere length (Brosh and Bohr, 2007; Opresko et al., 2002). TRF2 stimulates the helicase activity of WRN (Machwe et al., 2004; Opresko et al., 2002) and it has been proposed that WRN plays a role in capping of the telomeres (Multani and Chang, 2007). TRF2 also binds to BER proteins, and both TRF1 and TRF2 interact with proteins that function in DSBR (Brosh and Bohr, 2007), possibly to recruit BER and DSBR to maintain the telomeres. It is worth noting that because of the high guanine content in telomeric DNA, the level of 8-oxo-dG base lesions is higher than in non-telomeric DNA, and the BER activity on this lesion is less effective in some telomere structures(Rhee et al., 2011). Very recently, an interesting study was published that links location (genomic vs. telomeric DNA) and chromosomal aberration frequencies with premature cellular senescence (Hagelstrom et al., 2010). In telomerase-negative WRN-deficient cells, the frequencies of telomeric but not genomic chromosomal abnormalities are significantly increased compared to control cells. It was furthermore predicted that in cells with increased telomeric chromosomal aberrations, the onset of replicative senescence will be dramatically accelerated, a factor that may be contributing to the accelerated aging observed in WS. These findings suggest that telomere dysfunction that activates apoptotic pathways may be involved in the neurodegenerative and premature aging phenotype of WS patients. Telomere dysfunction adversely affects many tissues including more quiescent systems and intriguingly, a very recent investigation has linked dysfunctional telomeres with impaired mitochondrial biogenesis and function as well as increased production of ROS (Sahin et al., 2011). Conceivably, this could have repercussions also for neuronal tissue.

8.2.8. Neurodegeneration in Werner syndrome—WS is often referred to as a segmental progeroid syndrome due to the phenotypic similarity to some symptoms of normal aging including progressive neurodegeneration. This similarity has prompted much research into the functions of the *WRN* gene as it may hold the promise of illuminating some of the cellular functions that can become deficient during the normal aging process. As described above, WRN is involved in many DNA metabolic pathways notably those involved in upholding the integrity of the genome. Failure to properly repair DNA is therefore a likely reason for the neurodegenerative symptoms seen in WS patients but what defective pathway(s) are responsible may be difficult to determine. Defective HR during neurogenesis may lead to damaged cells being incorporated into the brain, or alternatively, a defective NHEJ pathway results in DSBs in the mature non-dividing neurons. If BER/SSBR is compromised by a mutated WRN protein oxidative lesions will remain unrepaired with a rapidly rising steady-state level that resembles an accelerated form of the observed accumulation in normal aging brains. Finally, it is possible that the change in transcriptional pattern seen with this disease is simply not compatible with the high transcriptional demand of neurons. The study of the WS disorder has linked deficient DNA repair to the aging

phenotype but the question still remains whether such deficiency is a cause for aging *per se* or rather a reflection of increasing cellular dysfunction with age.

9. Conclusion

The neurodegenerative diseases examined in this review highlight the importance of DNA repair in maintaining genomic integrity in the CNS, and implicates DNA damage and DNA repair deficiency in the aging of the brain. Much work still needs to be done to better understand the role of DNA repair enzymes and pathways in neurons. In particular, it would be of great interest to determine and clarify if certain neuronal subpopulations are more vulnerable to the effects of DNA repair deficiencies given that some neurodegenerative disorders involve specific types of neurons. Neuronal DNA repair is one of the most exciting areas for future DNA repair investigations as understanding neurodegenerative processes will be of increasing concern in aging populations with the preservation of cognitive function as a key component of healthy aging. The study of the SSBR and DSBR syndromes so far may suggest that SSBs have the greater impact on the aging brain, but the extent to which the aging brain depends on the repair of the two types of strand breaks is not yet clear. Given the evidence that mitochondrial dysfunction is implicated in several common neurodegenerative diseases associated with aging, it will be of great interest to further investigate the nature and extent of neuronal mtDNA repair. More insight is also needed for potential future therapeutic strategies. While this review has presented evidence linking DNA repair defects and aging with neurodegeneration, we would like to end on a positive note by highlighting the fact that neurodegenerative disease is not an inevitable consequence of long life, not even in 115-year olds (den Dunnen et al., 2008).

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Abbreviations

3′-OH	3′-hydroxyl
3′-P	3′-phosphate
3′-PG	3′-phosphoglycolate
3′-PUA	3′-phospho-α,β-unsaturated aldehyde
3′-TOP1	3′-topoisomerase I
5′-Ade	5′-aldehyde
5′-AMP	5′-adenosine monophosphate
5′-dRP	5′-deoxyribose-5-phosphate
5′-OH	5′-hydroxyl
5′-P	5′-phosphate
8-oxo-dG	7,8-dihydro-8-oxoguanine
Aβ	amyloid β-peptide

AD	Alzheimer's disease
ALS	amyotrophic lateral sclerosis
AOA1	ataxia-oculomotor apraxia-1
AP	abasic
APTX	aprataxin
AT	ataxia telangiectasia
ATLD	ataxia telangiectasia-like disorder
ATM	ataxia telangiectasia mutated
BER	base excision repair
CNS	central nervous system
CS	Cockayne syndrome
DR	direct reversal
DSB	double-strand break
DSBR	double-strand break repair
GG-NER	global genome nucleotide excision repair
HD	Huntington's disease
HNE	*trans*-4-hydroxy-2-nonenal
H_2O_2	hydrogen peroxide
HR	homologous recombination
ICL	interstrand cross-link
LIG1	DNA ligase I
LIG3α	DNA ligase IIIα
LIG4	DNA Ligase IV
LP-BER	long-patch base excision repair
MMR	mismatch repair
mtBER	mitochondrial BER
mtDNA	mitochondrial DNA
NBS	Nijmegen breakage syndrome
nDNA	nuclear DNA
NER	nucleotide excision repair
NHEJ	non-homologous end-joining
OGG1	8-oxoguanine DNA glycosylase
PARP1	poly(ADP-ribose) polymerase-1
PD	Parkinson's disease
PdG	propane-deoxyguanosine
Pol β	DNA polymerase β

Pol δ/ε	DNA polymerase δ or ε
RNA pol II	RNA polymerase II
ROS	reactive oxygen species
SCAN1	spinocerebellar ataxia with axonal neuropathy-1
SN	substantia nigra
SOD1	superoxide dismutase 1
SP-BER	short-patch base excision repair
SSB	single-strand break
SSBR	single-strand break repair
ssDNA	single-stranded DNA
TC-NER	transcription-coupled nucleotide excision repair
TDP1	tyrosyl-DNA phosphodiesterase 1
TLS	Translesion DNA synthesis
TOP1	DNA topoisomerase I
TOP1cc	TOP1 cleavage complexes
UV	ultraviolet
WS	Werner syndrome
XP	Xeroderma Pigmentosum

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Article Highlights

- Neurological disease is a major symptom of genomic instability disorders
- Deficient DNA repair is linked to progressive neurodegeneration
- Several hereditary ataxia disorders are characterized by defective DNA repair
- Mitochondrial DNA damage is implicated in the age-associated Alzheimer's disease
- Neurodegeneration is a feature of the premature aging disorder Werner syndrome

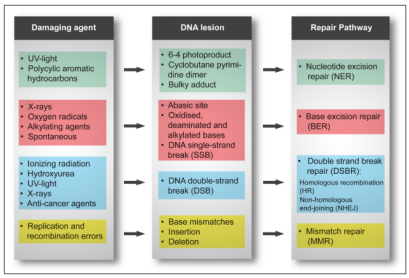


Fig. 1. DNA lesions and their repair by the four major DNA repair pathways in higher eukaryotes

Cells have multiple DNA repair pathways that provide the capacity to repair many different types of DNA lesions. The figure provides an overview of DNA damaging agents, the lesions they cause and the four main pathways responsible for removing and repairing the DNA lesions.

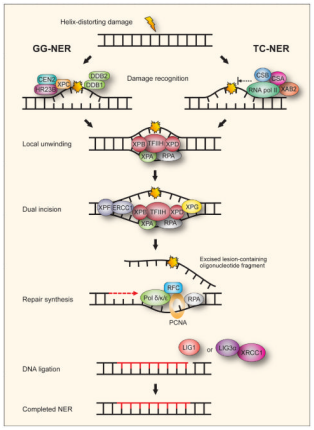


Fig. 2. The two subpathways of mammalian nucleotide excision repair

In global genome nucleotide excision repair (GG-NER) helix distorting DNA damage anywhere in the genome is recognized by the XPC-HR23B-CEN2 complex. The DDB complex consisting of the two subunits DDB1 and DDB2 (XPE) can facilitate recognition of lesions that by themselves cause little distortion of the helix. In transcription-coupled nucleotide excision repair (TC-NER) recognition is by the stalling of RNA pol II at DNA lesions on the transcribed strand of active genes facilitated by CSB, CSA and XAB2. Either XPC in GG-NER or CSB and CSA in TC-NER recruit TFIIH to the repair site followed by converging of the subpathways. The XPB and XBD subunits of TFIIH are DNA helicases that unwind the DNA in the immediate vicinity of the lesion. RPA and XPA bind to keep the DNA strands apart. For the dual incision, XPA recruits the XPF-ERCC1 endonuclease to incise the damaged DNA strand 5′ to the lesion while XPG incises 3′ to it. The lesion is thus excised in an oligonucleotide fragment leaving behind a single-strand gap. Repair synthesis is performed by DNA polymerase δ and κ, or ε (Pol δ/κ/ε) with the help of the accessory proteins RFC, PCNA and RPA. The remaining nick in the DNA backbone is sealed with ligation by either LIG1 or LIG3α-XRCC1.

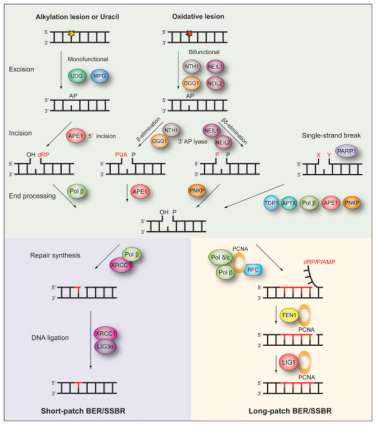


Fig. 3. The mammalian base excision repair and single-strand break repair pathways

Base excision repair (BER) is initiated by removal of the modified base by either a monofunctional or bifunctional DNA glycosylase to leave an abasic site (AP). If excision is by either one of the monofunctional DNA glycosylases UDG or MPG, the following incision of the DNA backbone 5′ to the AP site is by APE1. Excision by one of the bifunctional DNA glycosylases NTH1, OGG1, NEIL1 or NEIL2 is followed by incision 3′ to the AP site via β- or βδ-elimination facilitated by the intrinsic 3′ AP lyase activity of these enzymes. The resulting single-strand break will contain either a 3′ or 5′ obstructive termini. End processing is then performed by Pol β, APE1 or PNKP depending on the specific nature of the terminus. Single-strand breaks do not only occur as intermediates of BER but also by other means and can contain simultaneous 3′ and 5′ obstructive termini. PARP1 recognizes these breaks and the end processing may utilize the additional factors TDP1 and APTX. When end processing has produced the necessary 3′-OH and 5′-P termini the following BER and single-strand break repair (SSBR) steps diverge into two subpathways, short-patch and long-patch. In short-patch BER/SSBR repair synthesis of the single nucleotide gap is by Pol β aided by the XRCC1 scaffold, and subsequent ligation by LIG3α finishes the repair. In long-patch BER/SSBR repair synthesis of the 2–13 nucleotide gap is by Pol β, and/or Pol δ/ε aided by PCNA and RFC. A resulting 5′ flap is removed by FEN1 and the the final ligation step is by LIG1.

Gene/protein	Summary	References
MPG	Increased sensitivity to DNA-damaging agents in knockout mouse neuronal cells.	Kisby et al., 2004
UDG	Increased susceptibility to oxygen in knockout mouse primary cortical neurons.	Endres et al., 2004
	Depletion via siRNA promoted a DNA damage-associated apoptotic response in rat hippocampal neurons.	Kruman et al., 2004a
OGG1	Decrease in OGG1 expression in Alzheimer's disease hippocampal gyrus, superior and middle temporal gyri and inferior parietal lobule.	Lovell et al., 2000
APE1	Increased susceptibility to oxidative damage in neuronal cells with reduced APE1 expression	Vasko et al., 2005
	Relatively high expression of APE1 in plaque structures in the brain of Alzheimer's disease patients.	Tan et al., 1998
	Altered expression in amyotrophic lateral sclerosis patients.	Davydov et al., 2003; Kisby et al., 1997; Shaikh and Martin, 2002
Pol β	Defective neurogenesis characterized by apoptotic cell death in the knockout mouse developing CNS and PNS.	Sugo et al., 2000
XRCC1	Decreased expression following focal cerebral ischemia or cold-injury induced brain damage in CD1 mice	Fujimura et al., 1999; Fujimura et al., 2000
	Relatively high expression of XRRC1 in the temporal, parietal and occipital lobes of Down syndrome patients.	Fang-Kircher et al., 1999

Fig. 4.
Overview of studies linking BER and neurodegeneration.

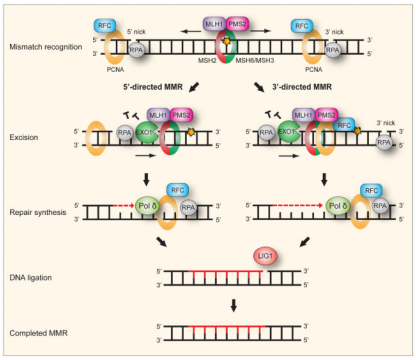


Fig. 5. Human mismatch repair

For convenience, the mechanism of human mismatch repair (MMR) can be seen as consisting of five consecutive steps: (i) Recognition and binding of a mismatch is by either a MSH2-MSH6 or MSH2-MSH3 heterodimeric ATPase complex. MSH2-MSH6 preferentially recognizes base-base mismatches and insertion deletion loops of 1–2 nucleotides while MSH2-MSH3 has preference for larger insertion-deletion loops. The mismatch-bound MSH2-MSH6 (or MSH2-MSH3) recruits the MLH1-PMS2 complex, a molecular matchmaker with weak ATPase activity, to form a ternary complex. The PCNA clamp recruits MMR proteins to the replication fork while the clamp loader RFC loads PCNA. A strand-specific nick or gap, which may reside either 5′ or 3′ to the mismatch, is sufficient to direct repair in 5′- and 3′-directed MMR, respectively. PCNA appears essential for 3′-directed but not 5′-directed MMR. (ii) Excision is apparently by the 5′ to 3′ exonuclease EXO1 in both 3′- and 5′-directed MMR. For 5′-directed MMR the excision is straightforward by the 5′ to 3′ exonuclease activity of EXO1. For 3′-directed MMR, the endonuclease function of PMS2 is activated by presence of the 3′ nick, and stimulated by RFC, PCNA and ATP, to introduce a necessary second nick 5′ to the mismatch. Excision can then follow by EXO1. RPA binds to protect the single-stranded DNA during the excision and to facilitate the following DNA repair synthesis. (iv) Repair synthesis is accurately performed by Pol δ. (v) Ligation of the remaining nicks after synthesis is by LIG1.

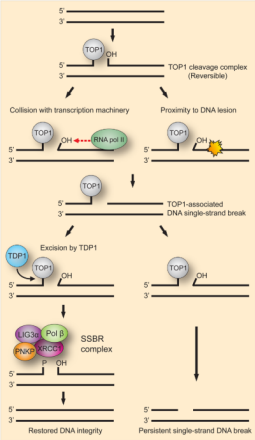


Fig. 6. Model for the generation of single-strand breaks from TOP1 cleavage complexes

During various processes of DNA metabolism the enzymatic activity of DNA topoisomerase I (TOP1) generates reversible 3′-TOP1-DNA intermediates known as TOP1 cleavage complexes. Such complexes can, however, become unduly long lived and collision with RNA pol II or the proximity of a DNA lesion creates a TOP1-associated DNA single-strand break. The enzyme responsible for cleaving the link between TOP1 and the 3′-teminus of the single-stranded break is TDP1. If excision is successful the remaining strand break can then be repaired by a SSBR complex consisting of PNKP, XRCC1, Pol β and LIG3α thereby restoring DNA integrity. If excision by TDP1 fails, a persistent DNA single-strand break will be generated.

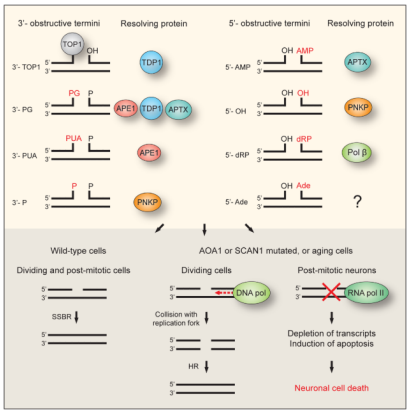


Fig. 7. Model for the differential impact of single-strand breaks on dividing cells and post-mitotic neurons caused by AOA1 or SCAN1 mutations, or aging

The upper part of the figure shows the various 3′- and 5′-obstructive termini and the proteins responsible for resolving them. The lower part of the figure shows the impact of single-strand breaks on wild-type, AOA1 and SCAN1 cells. In both dividing and post-mitotic wild-type cells efficient single-strand break repair (SSBR) will ensure resolution of the break. In dividing AOA1, SCAN1 or aging cells SSBR is deficient, but the single-strand breaks may be converted to double-strand breaks and subsequently repaired by homologous recombination (HR). In the post-mitotic neurons of AOA1 or SCAN1 patients, or aging individuals HR is not available and persistent unrepaired single-strand breaks in these cells lead to neuronal cell death.

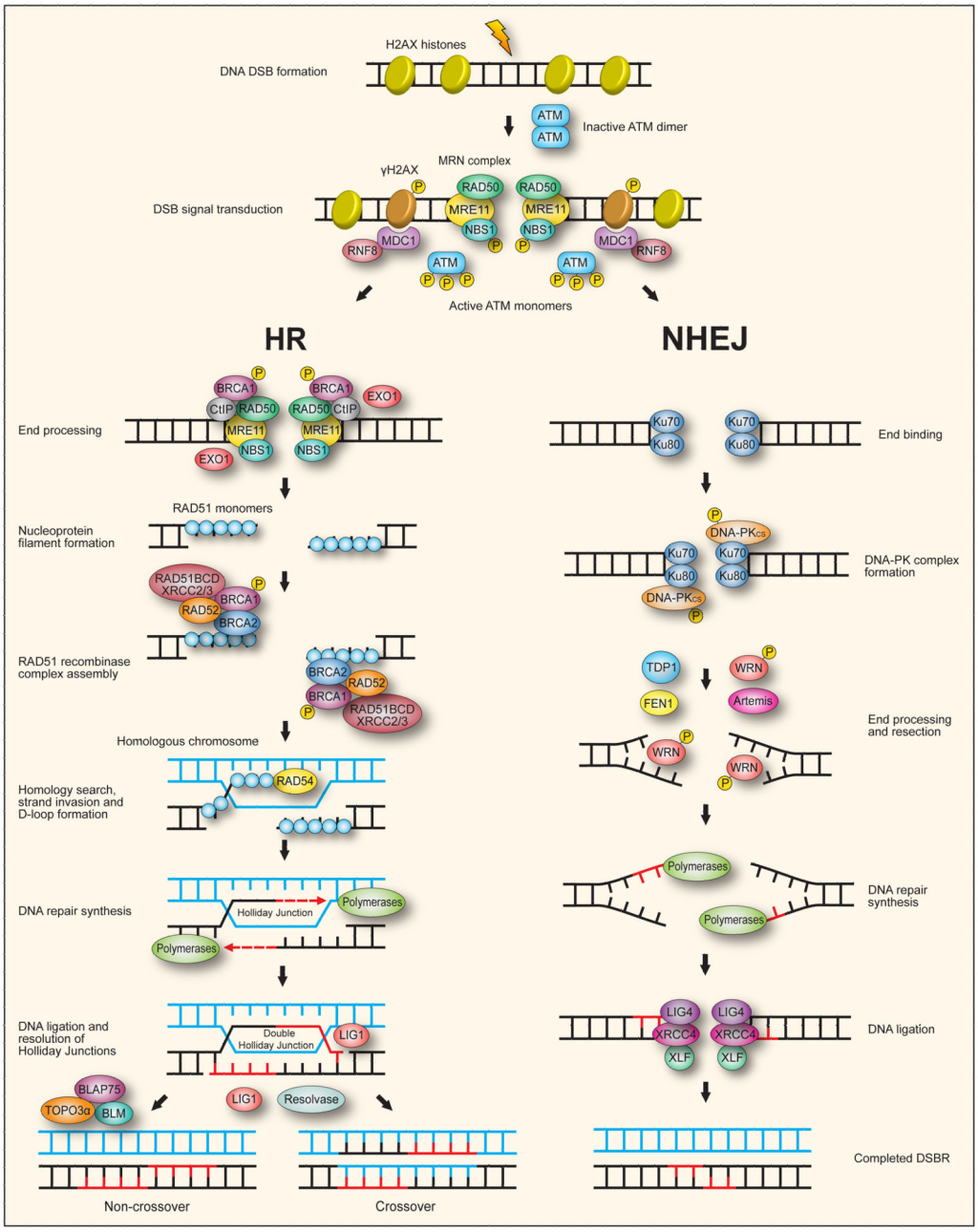
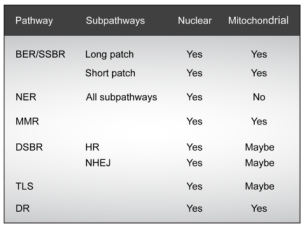


Fig. 8. The two major mammalian pathways for double-strand break repair

Repair of a DNA double-strand break (DSB) is usually accomplished by either homologous recombination (HR) when a homologous chromosome is available in the form of a sister chromatid, or by non-homologous end-joining (NHEJ) throughout the cell cycle. Following formation of a DSB, the MRE11-RAD50-NBS1 (MRN) complex is recruited to the break where it binds to the DNA ends through MRE11. A coiled-coil region of RAD50 reaches across the break and through coordination of a central Zn^{2+} ion, tethers the two broken DNA ends together. The serine/threonine protein kinase ATM is usually present as an inactive dimer but is recruited to the break site by NBS1. This causes ATM to autophosphorylate (P) and monomerize, activating the kinase. The activated ATM phosphorylates NBS1 and a multitude of other proteins that participates in the DNA DSB response, including BRCA1

and phosphorylation of nearby histone H2AX to generate γH2AX. The γH2AX at repair foci acts as a signal to recruit other repair proteins in order to assemble DSBR complexes. One such protein, MDC1, binds to γH2AX which recruits RNF8to the break site where it initiates an ubiquitylation cascade of histones H2A and H2AX causing chromatin restructuring and generation of binding sites for further protein factors. The HR pathway proceeds via the end processing of damaged DNA termini with initial nucleolytic 5′ resection performed by CtIP, a function dependent on CtIP recruitment of BRCA1. Further resection by EXO1 generates single DNA strands with 3′ overhangs upon which RAD51 monomers attach to form nucleoprotein filaments. A RAD51 recombinase complex is then assembled containing the accessory proteins BRCA1, BRCA2, RAD52 and the RAD51 paralogs: RAD51B/C/D and XRCC2/3. This recombinase complex, with the aid of an additional factor, RAD54, facilitates homology search and strand invasion of the homologous chromosome to form displacement loops (D-loops). DNA repair synthesis by DNA polymerase using the homologous strand as template extends the 3′ invading strand allowing branch migration of the Holliday junction, a cruciform intermediate. The repair synthesis allows capture of the other DNA end to create a double Holliday junction intermediate. DNA ligation by LIG1 seals the remaining nicks and resolution of the double Holliday junction by structure-specific endonucleases generate either non-crossover or crossover products depending on where the junctions are cut by the resolvase. The BLM RecQ helicase can cooperate with TOPO3α and BLAP75 to resolve DHJs with generation of exclusively non-crossover products.

The NHEJ pathway first involves binding of Ku70-80 heterodimer to the two DNA termini. This then recruits DNA-PK_{CS} to form the DNA-PK complex bringing the two DNA termini close together. Because of associated lesions not all DNA termini are readily ligatable and must be processed to generate the 5′-P and 3′-OH termini that are necessary for ligation. Autophosphorylation of DNA-PK_{CS} can make the obstructive termini accessible to end processing enzymes such as TDP1. DNA-PK_{CS} also mediates a regulatory phosphorylation of the WRN RecQ helicase. End processing and resection, while not fully understood, may involve the exonuclease activity of FEN1, WRN and Artemis. DNA polymerases then perform any necessary DNA repair synthesis. Finally, the DNA-PK complex, in a Ku70-80 mediated fashion, recruits the LIG4-XRCC4-XLF complex to perform the ligation of the DNA termini via the ligase activity of LIG4.



Pathway	Subpathways	Nuclear	Mitochondrial
BER/SSBR	Long patch	Yes	Yes
	Short patch	Yes	Yes
NER	All subpathways	Yes	No
MMR		Yes	Yes
DSBR	HR	Yes	Maybe
	NHEJ	Yes	Maybe
TLS		Yes	Maybe
DR		Yes	Yes

Fig. 9.
Overview of DNA repair pathways active in the nucleus and mitochondria of mammalian cells.

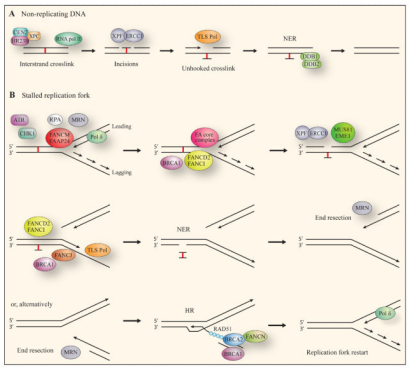


Fig. 10. Model for mammalian inter-strand crosslink repair

The ICL repair process is influenced by cell-cycle status. (A) In ICL repair in non-replicating cells the crosslink is recognized by the XPC-HR23B-CEN2 complex or RNA pol II. The XPF-ERCC1 complex makes incisions in the DNA on either side of the ICL leaving a gap in the opposing strand and the incised oligonucleotide still attached to the intact strand. TLS polymerases fill the gap while the flipped out crosslinked base is recognized by the DBB1-DDB2 complex, triggering the completion of repair by NER. (B) In actively replicating cells ICL repair at stalled replication forks is initiated when the arrested fork activates ATR and its downstream kinase CHK1. Facilitated by RPA and the MRN complex, ATR and CHK1 phosphorylates many proteins of the FA-BRCA network. The FANCM-FAAP24 complex enables access of other repair proteins, and subsequently becomes part of the FA core complex. The FA core complex monoubiquitylates the FANCD2-FANCI complex, which is then retained at the damaged region by BRCA1. The ICL is unhooked by XPF-ERCC1 and MUS81-EME1, leaving a DSB. The monoubiquitinated FANCD2-FANCI complex releases the replicative polymerase Pol δ and loads an error-prone TLS polymerase to perform bypass synthesis to repair the gap, possibly assisted by FANCJ. The crosslinked base is removed by NER. After 5′ end resection, possibly by the MRN complex, the BRCA2-FANCN-RAD51 complex initiates the reconstruction of the replication fork by HR.