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Base Excision Repair, Aging and Health Span

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Abstract

DNA damage and mutagenesis are suggested to contribute to aging through their ability to mediate cellular dysfunction. The base excision repair (BER) pathway ameliorates a large number of DNA lesions that arise spontaneously. Many of these lesions are reported to increase with age. Oxidized guanine, repaired largely via base excision repair, is particularly well studied and shown to increase with age. Spontaneous mutant frequencies also increase with age which suggests that mutagenesis may contribute to aging. It is widely accepted that genetic instability contributes to age-related occurrences of cancer and potentially other age-related pathologies. BER activity decreases with age in multiple tissues. The specific BER protein that appears to limit activity varies among tissues. DNA polymerase-β is reduced in brain from aged mice and rats while AP endonuclease is reduced in spermatogenic cells obtained from old mice. The differences in proteins that appear to limit BER activity among tissues may represent true tissue-specific differences in activity or may be due to differences in techniques, environmental conditions or other unidentified differences among the experimental approaches. Much remains to be addressed concerning the potential role of BER in aging and age-related health span.

Keywords

base excision repair; aging; DNA damage; mutagenesis; health span

1. Introduction

Long before cellular responses to DNA damage were elucidated, Alexander proposed the DNA damage theory of aging (Alexander, 1967). According to this theory, an accumulation of DNA damage (i.e. an alteration in the normal three dimensional molecular structure of DNA) leads to cellular dysfunction and thereby aging. We now know that DNA damage results in a plethora of responses including inhibition of transcription, inhibition of replication, impairment of cell cycle progression, transcriptional mutagenesis, senescence, cell death and other processes (Andreassen et al., 2006; Campisi and d'Adda di Fagagna, 2007; Essers et al., 2006; Kao et al., 2005). Failla (Failla, 1958) and Szilard (Szilard, 1959) proposed what is known as the Somatic

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Mutation Theory of Aging. According to this theory a gradual accumulation of mutations (i.e. fixed and heritable changes in DNA sequence) in somatic cells occurs with increased age that in turn leads to cellular dysfunction and is manifest as aging. DNA damage and mutagenesis are distinct but intimately linked processes. Because of this, it has been difficult to determine whether DNA damage or mutagenesis or both play a major role in aging. Transgenic and knockout mice are now being used to more directly test the roles of DNA repair, DNA damage and mutagenesis in aging.

In contrast, genetic instability is now commonly accepted as an important mechanism in the etiology of cancer, an age-related pathology. In addition, genetic instability in gametes is a human health concern with advanced parental age for women and men. Advanced maternal age is associated with chromosomal aneuploidies in offspring (Caron et al., 1999), while several autosomal dominant disorders are associated with increased paternal age and *de novo* germline mutations (Crow, 2000). Thus, there are clear associations between genetic instability, age and decreased health span.

Because they function to ameliorate DNA damage and minimize mutagenesis, there are multiple DNA repair pathways that may be important in aging including, nucleotide excision repair (see paper by Laura Niedernhofer, this volume), double-strand break repair (see paper by Paul Hasty, this volume), and others. Nuclear and mitochondrial genetic integrity may both play important roles in aging, thus it is important to consider mechanisms that function to maintain genetic integrity in these organelles (see paper by LeDoux, this volume for mitochondrial DNA repair). The DNA base excision repair (BER) pathway is responsible for ameliorating many types of spontaneous DNA damage (i.e. DNA damage that occurs as a result of normal cellular metabolism without known or intentional exposure to agents that damage DNA). Spontaneous DNA damage and mutagenesis are the most likely sources of genetic instability in aging and age-related diseases. Therefore, BER has the potential to have a major effect in sustaining genetic integrity and preventing aging and age-related diseases involving genetic instability. Below we summarize the status of BER in aging and age-associated health span in mammals.

2. BER pathways

2.1. Overview of pathway

BER is a mechanism whereby cells repair one nucleotide lesions derived from base damage emanating from reactive oxygen species, irradiation, genotoxic chemicals, spontaneous deamination or from naturally occurring abasic (AP) sites (Almeida and Sobol, 2007; Dianov et al., 2001; Hitomi et al., 2007). Because they are formed as repair intermediates in the BER pathway, AP sites and single-strand breaks (SSBs) that require end processing, can be repaired through this pathway. Briefly, BER involves damage recognition by a DNA glycosylase followed by removal of the damaged base (Fig. 1). An AP site is left from the action of the DNA glycosylase, and apurinic/apyrimidinic endonuclease, APE1, incises the strand at the 5'hosphate, leaving a 5'deoxyribosephosphate (5' dRP) group and 3' hydroxyl (3'OH) group. If the DNA glycoslyase is bifunctional, it also has an intrinsic AP-lyase activity and can incise the deoxyribosephosphate backbone itself. The ends created by bifunctional DNA glycosylases must be processed to produce a 3'OH and 5' phosphate before nucleotide insertion by an appropriate DNA polymerase. Repair synthesis replaces the excised DNA and ligation seals the phosphodiester backbone.

2.2 DNA glycosylases and damage recognition

DNA glycosylases recognize and initiate repair for a multitude of lesions in DNA resulting from deamination, spontaneous or enzyme-invoked (Sousa et al., 2007), alkylation and

oxidation. In general, aberrant bases distort the DNA helix and are recognized by specific DNA glycosylases (Hitomi et al., 2007). Compared to the damage recognition proteins for other excision repair pathways, DNA glycosylases display limited substrate specificity and tend to show a preference for purine or pyrimidine bases (Hazra et al., 2007). Monofunctional DNA glycosylases hydrolyze the *N*-glycosidic bond linking the base to the ribose moiety, thereby excising the base and leaving an AP site for further processing by the enzyme APE1. Bifunctional DNA glycosylases have an AP lyase activity in addition to their glycosylase activity and in general excise oxidized bases. A biologically important feature of DNA glycosylases is a redundancy in substrate specificity (Fig 2). Because of this redundancy single DNA glycosylase knockouts in mice typically have very mild consequences.

Exocyclic amine groups of the nucleotide bases are subject to spontaneous, and, as recently reported for immunoglobulin class switching, enzyme-invoked deamination. The resulting purine bases, hypoxanthine and xanthine from guanine and adenine, respectively, are excised by the monofunctional methyl-purine DNA glycosylases, MPG (Miao et al., 1998). Deamination of pyrimidine bases in the DNA creates uracil from cytosine, and more alarmingly, the normal base thymine from 5-methyl-cytosine. At least 4 classes of uracil DNA glycosylases have evolved to counteract this highly mutagenic event. Human UNG1, targeted to the mitochondria, and the nuclear UNG2 act on G/U mispairs. Additionally UNG1/2 can act post-replicatively to remove misincorporated UMP. Thymine DNA glycosylase, TDG, (Cortazar et al., 2007) recognizes U in the context of CpG/GpU pairing, and excises mispaired thymine residues in the context of TpG/GpC resulting from 5-methylcytosine deamination. TDG removes thymine solely on the basis of mispairing and is highly regulated with multiple protein associations reported (Baba et al., 2005; Cortazar et al., 2007; Dianov et al., 2001; Mohan et al., 2007; Parikh et al., 1999; Pearl, 2000; Steinacher and Schar, 2005; Takahashi et al., 2005). Similar to TDG, the MBD4 glycosylase recognizes U or T mispairs in the CpG context (Hendrich et al., 1999). The single-strand selective monfunctional uracil DNA glycosylase (SMUG) excises U from G/U mispairs and is active against a subset of oxidized uracil residues: 5-hydroxyuracil (hoU), 5-hydroxymethyluracil (hmU) and 5-formyluracil (fU) (Matsubara et al., 2004). SMUG also removes 5-fluoro uracil residues (An et al., 2007; Baker et al., 2002). Recent reports suggest the highly efficient UNG2 is adapted for replicating DNA while SMUG might be more important in chromatin interactions (Pettersen et al., 2007).

Alkylating agents attack base nitrogens which lead to 7-methylguanine and 3- methyladenine as the most abundant lesions while 3-methylguanine and 7-methyladenine typically represent minor lesions (Chakravarti et al., 1991; Fortini et al., 2003a). The N-methylpurine DNA glycosylase, MPG, also known as alkylpurine DNA glycosylase, ANPG, is a monofunctional DNA glycosylase that is able to repair these lesions and 1, N^6 ethenoadenine, hypoxanthine and xanthine (Chakravarti et al., 1991; Engelward et al., 1997) BER is the major route for removal of most alkylation damage. MPG associates with methylated DNA-binding domain 1, MBD1, a transcriptional repressor. MBD1-MPG binds methlyated promoters. Dissociation of the complex frees MPG to act as a DNA glycosylase (Watanabe et al., 2003). MPG associates with PCNA, APE1 (Xia et al., 2005), and XRCC1 (Campalans et al., 2005), and interacts with RAD23 / hHR23, that function in nucleotide excision repair and ubiquitination pathways (Miao et al., 1998; Miao et al., 2000).

Oxidized bases are generally removed by bifunctional DNA glycosylases. β–elimination is utilized by bifunctional DNA glycosylases OGG1 and NTH, and creates a 3'dRP and the phosphodiesterase domain of APE1 then cleaves the strand leaving a 1 nucleotide (nt) gap. Thymine glycol DNA-glycosylase (NTH) recognizes a wide range of oxidized pyrimidine residues including thymine glycol (Tg) and 5-formyluracil (Ikeda et al., 1998; Marenstein et al., 2003; Miyabe et al., 2002). However, Tg can also be excised by monofunctional MBD4 and TDG (Yoon et al., 2003). NEIL1, 2 and 3 are orthologs of the *E.coli Nei* DNA glycosylases

(Rosenquist et al., 2003; Takao et al., 2002a). While no glycoslyase activity has been found for NEIL3, NEIL1 and 2 recognize oxidized substrates (Hailer et al., 2005; Zhang et al., 2005), and are bifunctional enzymes. A β-δ base elimination and strand incision require polynucleotide kinase/phosphate (PNKP), not APE1, for processing the 3'phosphate ends generated through their lyase activities. These enzymes are also unique in their ability to remove oxidized bases from bubble structures in the DNA, suggesting a critical role for NEIL proteins in base repair during replication and/or transcription (Rosenquist et al., 2003; Takao et al., 2002a). Not surprisingly, NEIL proteins have multiple protein associations. NEIL1 interacts with the checkpoint protein Rad9/Rad1/Hus1 heterotrimer (the 9-1-1 complex) (Guan et al., 2007). Werner syndrome protein, WRN, is a DNA helicase which associates with and stimulates NEIL1 excision activity in bubble DNA (Das et al., 2007a). Y-box binding protein (YB-1) interacts with NEIL2 and improves base excision activity 7-fold (Das et al., 2007b). YB-1 is normally cytoplasmic but translocates to the nucleus under oxidative stress, providing a partner for NEIL2 excision of oxidized substrates.

Human 8-oxoguanine DNA glycosylase, hOGG1, is a bifunctional DNA glycosylase targeting the potentially mutagenic lesion 8-oxoguanine, 8-oxoG, and the formamidopyrimidine derivative of guanine, FapyG. Adenine pairs almost equally well as cytosine with 8-oxoG during replication, creating a scenario for a mutator phenotype in the absence of OGG1 (Nakabeppu, 2001). The human analog of the DNA glycosylase MuY, MYH, recognizes adenine mispaired to 8-oxoG or G and will repair these lesions formed post-replicatively (Gu et al., 2002; Ide and Kotera, 2004; Lee et al., 2004; Russo et al., 2007). The 8-oxoG lesion can itself be oxidized to more complex lesions such as spiroiminodihdantoin and cyanuric acid. These lesions are processed by NTH, NEIL 1/2, and MPG (Dherin et al., 2004; Hailer et al., 2005).

2.3. Strand incision, repair synthesis and ligation

From the initial damage recognition by one of a multitude of DNA glycosylases with overlapping specificities, the next steps in BER require very limited, specific proteins. Strand incision proceeds either from an innate AP-lyase activity in the original bifunctional DNA glycosylase or from one of 2 enzymes, APE1 or PNKP. APE1 performs the majority of strand incision steps in mammalian cells (Almeida and Sobol, 2007; Wilson and Barsky, 2001). XRCC1 acts as a scaffolding protein bringing APE1 into the lesion site as XRCC1 interacts with both DNA glycosylases and APE1 (Vidal et al., 2001). Subsequently POLβ will perform repair synthesis to replace the excised damaged base, and cleave the deoxyribosephosphate moiety with its lyase activity (Dianova et al., 2004; Tomkinson et al., 2001). Lastly an XRCC1/DNA ligase III complex seals the DNA. When a NEIL enzyme is the appropriate damage recognition protein, a 3' phosphate is produced that requires PNK/P that interacts in the complex with NEIL, POLβ, DNA ligase III and XRCC1 (Campalans et al., 2005; Das et al., 2006; Wiederhold et al., 2004)

2.4. Long-Patch BER

Lesions refractory to short-patch repair, such as a reduced AP site, a C1 oxidized AP site (Fortini and Dogliotti, 2007) or an adenine opposite 8-oxoG (Fortini et al., 2003b; Hashimoto et al., 2004), can undergo long-patch repair. A 5' blocking lesion appears to result in DNA POLβ release after which PCNA facilitates excision by FEN1 which stimulates strand displacement DNA synthesis (Gary et al., 1999; Liu et al., 2005; Prasad et al., 2000) by POLδ, ε (Dianov et al., 2003). Finally, DNA ligase 1 catalyzes strand ligation. The stoichiometry of BER enzymes may regulate BER. Excess APE1 relative to POLβ stimulates strand displacement by POLβ and allows POLβ to mediate long patch DNA repair (Sukhanova et al., 2004). Under conditions of low energy, poly(ADP-ribose) polymerase 1(PARP1) catalyzes the poly(ADP)ribosylation of proteins (Beneke and Burkle, 2004; Muiras, 2003;

Petermann et al., 2003) and stimulates long patch BER (Petermann et al., 2003). An apoptotic fragment of PARP1 can inhibit short-patch BER (Sukhanova et al., 2007). Whether short-patch or long-patch BER is chosen for hypoxanthine repair by MPG is dependent upon sequence context (Xia et al., 2005).

2.5. SSB repair

SSB repair ameliorates nicks in the DNA such as those caused by reactive oxygen species and ionizing radiation (Almeida and Sobol, 2007; Dianov and Parsons, 2007; Huber et al., 2004) or as repair intermediates created by the BER process itself. PARP-1 can bind to an AP-site, if present, at the SSB before any other BER proteins. DNA-PARP1 binding leads to recruitment of XRCC1 and then the typical BER short or long patch pathways prevail. Binding by PARP-1 stimulates automodification with PARP-1 poly(ADP-ribose) polymers and dissociation of PARP-1 from the DNA.

2.6. BER proteins in class switch recombination

In an overview of multifunctional BER and its biological importance, mention must be made of the role the BER machinery plays in class switch recombination in adaptive immunity. Uracil is a normal intermediate of somatic hypermutation and is generated by activation-induced cytosine deaminase (AID) on single stranded DNA. The uracil thus formed is then removed by UNG2 (Bransteitter et al., 2006; Sousa et al., 2007). AID and other members of the apoplipoprotein B editing catalytic polypeptide deamination family (APOBEC) can deaminate 5-methyl cytosine residues to thymine in the non-coding strand of single strand regions with implications in hypermutation, class switch recombination and loss of epigenetic information (Morgan et al., 2004). TDG and MBD4 are thought to initiate repair of the thymine mismatch (Hendrich et al., 1999; Wiebauer and Jiricny, 1989). Spontaneous 5-meCpG deamination can lead to a loss of epigenetic information and may require re-methlyation to complete repair (Walsh and Xu, 2006). A recent report of regarding association of DNA methyltransferase 3a, Dnmt3a, with TDG links BER, re-methylation and epigenetic regulation (Li et al., 2007c).

3. Subcellular localization of BER

BER is found where DNA is located, therefore BER is found in the nucleus and in mitochondria of animal cells (Bogenhagen et al., 2001; Croteau et al., 1999; Mandavilli et al., 2002; Weissman et al., 2007a; Wilson et al., 2003). Indeed, mitochondria are the major source of ROS and are thus in dire need of repair mechanisms such as BER. Differences do exist between nuclear and mitochondrial repair. UNG1 is the mitochondrial targeted variant of UNG. Similarly OGG1 has 4 isoforms produced from differential splicing and 3 isoforms are targeted to mitochondria (Nakabeppu, 2001; Nishioka et al., 1999; Shinmura et al., 2001; Takao et al., 1998). MYH and NTH are also found in mitochondria (Englander et al., 2002; Nakabeppu, 2001; Takao et al., 1998; Wang et al., 2000). APE1 is found in cytoplasm, mitochondria and nuclei (Tell, 2005; Tomkinson et al., 1988; Tsuchimoto et al., 2001) and can vary in location over the life of the animal. Repair synthesis is performed by DNA (POLγ) with ligation by mitochondrial targeted DNA ligase III (Bogenhagen et al., 2001; De and Campbell, 2007). Within mitochondria, the BER enzymes appear localized to the inner membrane, the site of mitochondrial DNA (Stuart et al., 2005).

4. Increased DNA damage and mutagenesis in aging

While a comprehensive review of DNA damage during aging is not the purpose of this review, it is important to ascertain if there is a change in DNA damage relative to age that is repaired through the BER pathway. There is abundant literature regarding DNA damage “accumulation” and age. We would argue that “accumulation” of damage is not the best term

to use. Rather, we suggest the terminology of greater steady-state levels of DNA damage. A brief overview of the literature is presented and base damage is considered first (Table 1).

Oxidative damage to DNA in the form of 8-oxoG, is the most commonly studied damage relative to age. These studies generally reveal increased levels of oxidative damage (i.e. 8oxodG). These data were questioned when it became commonly known that the method used to isolate the DNA itself caused oxidative damage. Methodology has now been identified for preparing the DNA without detectable induced oxidation (Hamilton et al., 2001a; Helbock et al., 1998). Using such procedures, greater steady-state levels of 8-oxoG were observed in DNA prepared from brain and liver of older rodents (Hamilton et al., 2001b). The vast majority of oxidized bases, including 8-oxoG, would be repaired via the BER pathway.

AP sites can be generated spontaneously via hydrolysis of the N-glycosidic bond, or as a repair intermediate through the action of a DNA glycosylase in the BER pathway. AP sites are repaired largely through the BER pathway. Using human diploid IMR90 cells, formation of AP sites occurs more slowly in young cells than in senescent cells (Atamna et al., 2000). AP sites are also repaired more slowly in senescent IMR90 cells after treatment with H2O2 or methylmethane sulfonate (MMS), a monofunctional alkylating agent. Human leukocytes obtained from old (58- to 75-year-old) individuals display more AP sites than cells from young (22- to 33-year-old) individuals. Analysis of AP sites in old and young rats, yields similar results; a greater prevalence of AP sites are observed in nuclear DNA obtained from old (24-month-old) compared to young (4-month-old) rats.

SSBs are another repair intermediate in the BER pathway and are formed via the action of AP endonuclease (APE1) or from the lyase activity of a bifunctional DNA glycosylase (Almeida and Sobol, 2007). SSBs can also be generated through the attack of reactive oxygen species. Many SSBs can be repaired with BER proteins. PARP1 and PNK are thought to be additionally involved in SSB repair (Dianov and Parsons, 2007; McKinnon and Caldecott, 2007; Wilson and Bohr, 2007). The prevalence of SSBs was examined in senescence-accelerated prone mice, SAMP1, and senescence-accelerated resistant, SAMR1 mice. The prevalence of DNA damage varied among the examined tissues, but was consistently great in SAMP1 tissues (Hosokawa et al., 2000; Zahn et al., 2000). Together, these examples demonstrate that DNA damage that is repaired through the BER pathway increases with age and leads to questions about a possible decline in BER activity with age.

Early mutagenesis studies gave results that supported in some cases and refuted in others, a greater mutant frequency at older ages. These studies were performed using selectable markers (e.g. *Hprt*) that necessitated maintaining cells in culture. Consequently, the studies were limited essentially to fibroblasts and immortalized cell lines. After the advent of transgenic mouse technology, transgenic lines carrying mutation reporter genes (e.g. *lacI*, *lacZ*) were established (Gossen et al., 1989; Kohler et al., 1990). The power of the transgenic models was that virtually any cell or tissue type could be studied for mutagenesis at any age. Analyses of spontaneous mutant frequencies relative to age consistently revealed an increase for liver, and no change in mutant frequency for brain (Dolle et al., 1997; Stuart and Glickman, 2000). The mutant frequency results for spermatogenic cells have varied with some showing no change (Martin et al., 2001) while others observed a significant increase in spermatogenic cells at old age (Walter et al., 1998). The reason for the different results in spermatogenic cells is not clear at present. Although there are tissue specific differences in mutagenesis, there are data generally indicating that mutagenesis increases with age in several tissues. The mutagenesis results combined with the DNA damage results lead to the question of whether BER activity changes with age.

5. BER activity changes with age

The first quantitative assays for the BER pathway, as initiated by uracil-DNA glycosylases (UDGs), revealed differences in activity among mouse tissues (Intano et al., 2001). Spermatogenic cells enriched from the testis displayed the greatest activity followed in order by mitotically active Sertoli cells, mitotically active thymocytes, small intestine, liver and brain. Using a similar assay, significant reductions, i.e. 50–75%, in BER activity were observed using tissues (brain, liver, spleen, testis or spermatogenic cells) collected from old (18- to 20-month-old or 28-months-old) mice compared to young (4- to 6-months-old or 3-months-old) mice (Cabelof et al., 2002; Intano et al., 2003). A reduction of POLβ with increased age was identified in all tested tissues in one study (Cabelof et al., 2002). The reduction of POLβ was observed by RNA abundance, protein abundance and enzyme activity assays. In contrast, POLβ was reduced only in brain in the second study (Intano et al., 2003). Individual BER proteins were added to nuclear extracts prepared from old animals in an effort to identify a protein activity that could restore BER activity to that of young mice. Addition of UNG, APE1, POLβ or DNA ligase 3 had essentially no effect with regard to stimulating BER activity for somatic tissues (Intano et al., 2003). Different genetic backgrounds were used by the groups and may have contributed to the different results. Experimental and/or environmental differences may have contributed to the lack of congruency in the results between the different laboratories.

In a subsequent study, calorie restriction was observed to completely reverse the age-related decline in BER activity and the decline in POLβ expression and activity (Cabelof et al., 2003). Calorie restriction was also found to enhance BER activity in extracts prepared from young mice. A second study examining the effects of calorie restriction on BER similarly found an increase in nuclear BER activity with calorie restriction, i.e. a 26% increase (not significantly different from *ad libitum* fed mice) in liver, and 42% increase (significantly different from *ad libitum* fed mice) in kidney (Stuart et al., 2004). The mechanism by which BER activity is modulated through calorie restriction has yet to be definitively determined.

The brain is a complex organ with different regions being involved in age-related neurodegenerative disorders. Some of these disorders are associated with increased oxidative damage, indicating the BER pathway may be important in protecting the brain from such disorders. Initial studies examining the activity of multiple DNA glycosylases in different mouse brain regions has recently been reported (Imam et al., 2006). The incision activities of OGG1, UNG and NTH1 were examined in cerebellum, brain stem, caudate nucleus, frontal cortex and hippocampus. Cerebellum and brain-stem displayed greater levels of OGG1 activity relative to the other studied regions, but also were the only regions showing a significant decline in activity with age. UNG incision activity declined in cerebellum with age. APE1 and DNA ligase III did not change with age in the tested brain regions.

These studies have provided the first insights into the levels of BER activity among mammalian tissues with age. It is clear that the activity varies among tissues and decreases with age. Because tissues consist of multiple cell types, it becomes important to assess BER in defined cell types. Along these lines, primary mouse skeletal muscle satellite cells were prepared, grown and differentiated into myotubes in culture to measure long-patch and short-patch BER activity. Myotubes displayed significantly less BER activity than proliferating cells (Narciso et al., 2007). This suggests that differentiated myotubes may be more likely to sustain greater levels of DNA damage. Indeed, when challenged with H2O2 myotubes displayed greater levels of oxidative base damage than proliferating cells. Sarcopenia is a common phenotype in the elderly and it will be interesting to determine if reduced BER activity contributes to the phenotype. Exercise training in old rats increased OGG and UNG activity but to different extents in red and white muscle fibers, again implying differential regulation of BER proteins

to maintain DNA fidelity in oxidatively stressed cells (Radak et al., 2005; Radak et al., 2007).

Primary rat neuronal cultures have been examined for the gap-filling and ligation steps of the BER pathway using adolescent (5-day-old), young adult (6-month-old) and old (≥ 24-month-old) Wistar rats (Krishna et al., 2005). Repair activity declined as age increased. Recombinant POLβ restored activity to the samples from old rats, but repair was more rapid when POLβ and T4 DNA ligase were added. These results suggest that POLβ and a necessary mammalian ligase restrict BER activity in neurons from old rats.

Human peripheral blood lymphocytes collected from individuals ranging in age from newborn to 91-years-old were assayed for OGG1 incision activity. Variation among individuals at each age was observed, but overall OGG1 activity declined significantly with age (Chen et al., 2002a). “Old” IMR90 cells, a human diploid fibroblast line, displayed an approximate 5-fold reduced repair by MPG compared to nonsenescent cells (Atamna et al., 2000). In other studies, late passage IMR90 cells showed reduced OGG1 activity and OGG1 transcription (Shen et al., 2003). The studies with primary human cells and human cell lines indicate that BER activity declines with age in human cells. It will be important to determine the mechanism(s) that mediate the decline in repair activity and to examine additional cell types and tissues.

Subcellular compartmentalization of DNA repair proteins has been a mechanism that potentially contributes to changes in BER activity. Using mouse liver cells, levels of APE1 protein and mRNA were found to be similar for young adult (4-months-old), middle-aged (10-months-old) and old (20-months-old) BALB/c mice. When APE1 distribution in subcellular compartments was examined relative to age, it was found that APE1 activity increased in nuclear and mitochondrial compartments by middle age (Szczesny and Mitra, 2005). APE1 activity was elevated approximately 2-fold by old age in the nuclear compartment. It was suggested that the changes in APE1 activity in subcellular compartments relative to age may reflect levels of oxidative challenge in the involved organelles. The 6-fold increase in APE1 activity seen in mitochondria occurred by 10 months, while the nuclear activity increased more slowly to a final 2-fold increase at 20 months (Szczesny and Mitra, 2005). Once within the nucleus itself, APE1 can be induced to relocate to nuclear speckles by UVA irradiation, co-localizing with OGG1 to facilitate BER (Campalans et al., 2007). In a recent paper (Chaudhry, 2007) whole cell extracts from synchronized HeLa cells were used to examine repair activities of hAPE1, hOGG1 and hNTH1 in different phases of the cell cycle. hAPE1 and hNTH1 were higher in G1 compared to G2 while OGG1 showed no such dependence.

BER activity has been measured by a variety of techniques including assessment of the full pathway and individual BER protein activities (Table 2). With very few exceptions, the results are in agreement that BER activity declines with age. The explanation for decreased BER activity has varied with different BER proteins implicated in different studies and different tissues (Table 3). Such differences may be explained by different techniques used, different strains or species of animals or to responses to different environmental conditions that are not presently understood. However, the overriding consistent feature is that BER activity declines with age.

7. Impact of altered BER on longevity

The field of aging research has been hampered by a paucity of biomarkers that can be used to establish physiological age, therefore longevity has long been used experimentally as a gold standard to functionally assess aging (Masoro, 2003). The natural (i.e. without known or intentional intervention) median and maximal lifespans can be characteristic for a species (e.g. human vs dog) and in some cases, between strains within a species (e.g. different mouse strains). In a classic comparison of lifespan and DNA repair activity Hart and Setlow (Hart and

Setlow, 1974) demonstrated a positive correlation between these quantitative traits. The publication of these data reawakened the scientific community to the possible relationship between aging and genetic integrity as first postulated in the 1950's. Data from multiple laboratories on multiple species was compared and normalized to the laboratory rat in a more recent publication (Cortopassi and Wang, 1996). Animals categorized with a short lifespan (i.e. 1.5–3.3 years; mouse, rat and shrew), medium lifespan (i.e. 3.5–20 years; hamster, rabbit and dog), long lifespan (i.e. 28–50 years; cat, horse, cow and elephant) or extra long lifespan (i.e. 50–120 years; gorilla and human) were positively correlated with DNA repair activity. Notably DNA repair activity measurements cannot be used to accurately predict maximal lifespan suggesting that while DNA repair is an important component to lifespan determination, it is probably not sufficient to determine lifespan.

Assuming that DNA repair is an important component to maximal lifespan, we can ask how alterations in BER activity affect lifespan. The first indication that BER might play an important role in lifespan was revealed in a comparison of longevity with poly(ADP-ribosyl)ation activity among several mammalian species using mononuclear blood cells (Grube and Burkle, 1992). Cells obtained from humans, the longest lived species in the comparison, displayed 5-fold greater activity than rat, the shortest lived species in the comparison. PARP1 protein abundances were similar among the tested species. The full explanation for differences in PARP activity among species is not understood. Two members of the PARP family, PARP1 and PARP2, participate in BER with complementary but not fully overlapping functions (Ame et al., 2004). Mouse models, deficient in PARP1 have been made (de Murcia et al., 1997; Wang et al., 1997). The homozygous null mice are viable, but have a smaller body size than normal littermates. The PARP1 null mice also show notable defects in BER. Surprisingly, no test of longevity for PARP1−/− mice is found in the literature. Therefore, it appears a direct test of PARP1 on longevity is lacking. A PARP2 null mouse was developed which was also sensitive to ionizing radiation and alkylating agents (Menissier de Murcia et al., 2003). The PARP1/PARP2 double mutant was an embryonic lethal (Menissier de Murcia et al., 2003).

UNG is a BER protein that recognizes uracil in DNA and catalyzes the hydrolysis of the N-glycosidic bond to leave an AP site where the uracil was previously located. UNG is the preferred glycosylase to remove uracil formed during somatic hypermutation. Mice deficient in UNG have been made and are viable when homozygous null (UNG−/−) (Nilsen et al., 2000). Longevity was assessed for UNG−/− mice in comparison to UNG+/+ mice. Median lifespan was significantly reduced to 101 weeks of age for UNG −/− mice compared to 116 weeks old for UNG+/+ mice (Nilsen et al., 2003). However, maximum lifespan was not altered in the UNG−/− mice. The old UNG−/− mice displayed more pathology, particularly lymphoproliferation and B-cell lymphoma. The increased prevalence of cancer may have impacted the median lifespan, but did not detectably alter maximal lifespan.

POLβ heterozygous (POLβ+/−) mice are the only other model of impaired BER for which longevity has been published. In contrast to the UNG−/− mice, neither median nor maximal lifespan was impacted (Cabelof et al., 2006). A very modest, but significant difference in mortality rates was detected between POLβ+/− and POLβ+/+ mice. Early and late life differences in mortality between the genotypes likely mediated the modest difference in mortality rates. It is noteworthy that the UNG deficient mice were homozygous null while POLβ deficient mice were heterozygous. It was necessary to use POLβ+/− rather than POLβ −/− because POLβ−/− mice die during the embryonic or early neonatal period (Sugo et al., 2000). POLβ+/− mice developed lymphoid hyperplasia (38% for POLβ+/−, 0% for POLβ+/+), adenocarcinoma (a 2.7-fold increase in POLβ+/− mice) and multiple tumors (20% in POLβ+/− mice and 5% for POLβ+/+ mice). Although POLβ+/− mice had a greater cancer prevalence as detected at old age (i.e. 24- to 26-months-old), median lifespan was unaffected.

In this model, unlike the UNG−/− model, increased cancer prevalence did not impact median lifespan.

The very limited information available on lifespan in the background of impaired BER activity has not revealed an effect on maximal longevity. Maximal longevity measurements are typically evaluated at 5–10% survival so that multiple animals can be compared statistically. Regardless, the number of mice remaining is few and may hamper the ability to detect differences. In contrast, at median lifespan sufficient animals are alive in a well planned lifespan study to have meaningful comparisons. UNG−/− mice displayed a reduced median lifespan, while POLβ+/− mice did not. The homozygous state of the UNG mice was likely influential in imparting a detectable difference. Both models clearly demonstrated that reduced BER activity results in a decreased health span, with a greater prevalence of cancer and other pathologies among the UNG−/− and POLβ+/− groups compared to control groups. Health span is unequivocally a critical factor in human longevity. It is possible that lifespan determinants, potentially including BER, exert their effects at different points in the lifespan and BER may impact survival early in the lifespan by improving health span in the first half of the lifespan.

8. Effects of aging and BER on male reproduction and development

8.1. Human studies

The production of mature male reproductive cells starts post-natally at puberty and continues throughout life into old age (Nielsen et al., 1986; Nieschlag et al., 1982; Snyder, 2001). Spermatogenesis, the process that culminates in the production of spermatozoa, is dynamic and complex involving germ cell proliferation and differentiation which is dependent upon extrinsic hormone support and local cellular interactions. The oldest proven paternity reported was for a 94-year-old man (Seymour et al., 1935), thereby indicating that spermatozoa can be biologically functional well into old age. Perhaps it is not surprising that aging effects on spermatogenesis and sperm production are known. Age-related alterations associated with male reproduction include histomorphological changes of the testis (e.g. atrophy, decreased numbers of Leydig cells) (Johnson et al., 1984; Neaves et al., 1984), an increasingly dysfunctional hypothalamic-pituitary-testis axis producing altered hormone concentrations (reviewed by Vermeulen and Kaufman, 1995), decreased semen parameters (e.g. semen volume, sperm count) (Nieschlag et al., 1982; Rolf et al., 1996; Spandorfer et al., 1998), and decreased sperm production (Kidd et al., 2001; Ng et al., 2004), all leading to lower fertility.

An important issue in the assessment of age related changes of male reproduction is the frequency of hereditary diseases in offspring. A positive relationship between paternal age and the incidence of a genetic disorder in offspring was first observed in 1912, when Wilhelm Weinberg noticed that children with achondroplasia, an autosomal dominant skeletal disorder, were more likely to be born later among their siblings (Weinberg, 1912). Since then, many autosomal dominant disorders have been reported to be associated with advanced paternal age (reviewed by Crow, 2000; Risch et al., 1987). Paternally derived base substitutions were found in some age-related disorders, such as achodronplasia (Wilkin et al., 1998), Apert syndrome (Moloney et al., 1996), multiple endocrine neoplasia (MEN) 2A (Mulligan et al., 1994; Zedenius et al., 1994), MEN 2B (Carlson et al., 1994; Kitamura et al., 1995; Mulligan et al., 1994; Zedenius et al., 1994) and progeria (Eriksson et al., 2003). The association between increased age and an increased risk of producing offspring with a genetic disease from a new germline mutation derived from the paternal lineage is known as the paternal age effect. The mechanisms that mediate the paternal age effect are poorly understood and a number of different possibilities have been suggested (Crow, 2000; Glaser et al., 2003; Goriely et al., 2003; Penrose, 1955; Tiemann-Boege et al., 2002). Regardless of the mechanisms by which these mutations are generated, the paternal age associated disorders are a reflection of the increasing mutant frequency in sperm as men age. A few studies have shown an increased

mutant frequency in sperm with age (Glaser et al., 2003; Goriely et al., 2003; Tiemann-Boege et al., 2002). However, the slight age-related increase in mutant frequency detected in sperm did not correspond to the exponentially increased incidence of age-related disorders in offspring (Glaser et al., 2003; Goriely et al., 2003; Tiemann-Boege et al., 2002), suggesting that multiple mechanisms exist and that they may work together to increase the number of affected offspring. Because sperm are the fully differentiated cell type generated during spermatogenesis, any adverse effects occurring in precursor cell types could affect sperm quality, including mutant frequency. Thus, monitoring mutation in different spermatogenic cell types during spermatogeneis with age should provide invaluable information on the paternal age effect. Monitoring differentiating cells in the spermatogenic lineage can be challenging for human studies because the procedure to obtain spermatogenic cells from the testis requires an invasive testis biopsy. As a result animal models are used frequently to study spermatogenesis and changes occurring during spermatogenesis.

8.2. Animal studies on germline mutant frequency

Taking advantage of transgenic mice carrying a mutation reporter transgene, i.e. *Lac I* transgenic mice, mutant frequencies were carefully examined in different spermatogenic cell types and from different aged mice. The spontaneous mutant frequency was elevated in mouse in pachytene spermatocytes, round spermatids and epididymal spermatozoa (Walter, 1998). Further characterization of the mutation spectra has shown that base substitutions accounted for more than 80% of the mutations in germ cells from young (3-to 6-months-old), middle-aged (14- to 16-months-old) and old mice (28-months-old) (Walter et al., 2004). Notably, the mutation spectrum in cells from old mice differed from those in the other two groups (Walter et al., 2004). Five mutation hotspots were identified in spectra for spermatogenic cells from young and middle-aged mice, but no hotspot was found in old mice (Walter et al., 2004). The data on mutation spectra in germ cells from old mice suggest that increased germline mutations in old mice occur as a consequence of different factors than those leading to mutations in young mice. Several mechanisms (e.g. selection, apoptosis, DNA repair) may play roles in regulating germline mutagenesis.

8.3. BER gene knockout animal models and reproductive phenotypes

Knockout mice carrying homozygous inactivation of POLβ APE1, XRCC1 DNA ligase I are embryonic or neonatal lethal (Friedberg and Meira, 2006), indicating that BER is indispensable for early development of mice. The only viable homozygous knockout mouse models in the BER pathway are deficient in one of the DNA glycosylases or PARP1. Table 4 contains a summary of the reproductive phenotypes described for available BER knockout mice including heterozygous and homozygous mouse models. Overall, BER deficiency has little effect on animal fertility, but increases susceptibility to mutagenesis and tumorigenesis. The majority of the BER knockout mice have not been studied with regard to aging so it is unclear whether and/or how the phenotypes change with age.

9. BER gene polymorphisms and diseases

9.1. Polymorphisms and cancer

There are currently about 150 known DNA repair genes, and most of them are known to have genetic variation in humans (Wood et al., 2005). Polymorphisms, defined as genetic variants that appear in at least 1% of a population, can be associated with increased risk for a disease or resistance to a specific disease. Over the last few years, a number of studies have probed the role of DNA repair gene polymorphisms with disease susceptibility, particularly with regard to cancer.

BER genes are known to have polymorphisms that are associated with increased risk for certain cancers (Table 5) (Berndt et al., 2007;Goode et al., 2002;Hung et al., 2005;Rybicki et al., 2004). There are several aspects comprising the association between BER gene polymorphisms and the likelihood of developing cancer. First, a multiple of polymorphisms may exist for a gene. For example, at least 20 validated sequence variants have been described to date for the OGG1 gene (Hung et al., 2005). More than 60 validated single nucleotide polymorphisms in XRCC1 are listed in the Ensembl database (Hung et al., 2005). Second, allele frequencies are different in different populations (reviewed by Hung et al., 2005). For example, the frequency of XRCC1 arg399gln polymorphism is 24.1% in the African-American population (Duell et al., 2001), but 36.7% in the Asian population (Chen et al., 2002b) and 46.1% is in the Caucasian population (Han et al., 2003). Third, the strength of the relationship between a polymorphism and predisposition to cancer depends on the position/type of the variant in the gene and the cancer type. For example, homozygous OGG1 cys326cys alleles confer a two-fold increased risk of lung cancer (Goode et al., 2002;Sugimura et al., 1999), and an elevated risk of prostate cancer and nasopharyngeal carcinoma (Chen et al., 2003b;Cho et al., 2003), but not of colon cancer (Hansen et al., 2005). The less frequent OGG1 polymorphism arg154his was found in human gastric cancers (Nohmi et al., 2005). Fourth, effects of polymorphisms may be apparent only in the presence of DNA-damaging agents. For instance, the XRCC1 homozygous gln399gln genotype was related to a significantly reduced risk of squamous cell carcinoma but, the relative risk of squamous cell carcinoma associated with painful sunburn history was significantly higher for homozygous variants (gln399gln and arg399arg) than wild type (Nelson et al., 2002). In addition, arsenic-induced skin lesions (Breton et al., 2007), levels of aflatoxin B1-DNA adducts (Lunn et al., 1999;Matullo et al., 2001) and bleomycin sensitivity (Wang et al., 2003) are associated with polymorphisms of the XRCC1 gene.

In addition to possible associations with cancer risk, BER gene polymorphisms are found associated with response to the cancer treatment (Stoehlmacher et al., 2001), with azoospermia (Gu et al., 2007) and with rheumatoid arthritis (Koyama et al., 2006). For example, polymorphism of the XRCC1 gene was investigated in patients with metastatic colorectal cancer treated with oxaliplatin and fluorouracil (5-FU). 73% of responders to treatment had an arg399arg genotype, but 66% of non-responders showed a gln399gln or gln399arg genotype (p=0.038). Patients carrying at least one Gln mutant allele were at a 5.2-fold increased risk to fail the 5-FU/oxaliplatin chemotherapy (Stoehlmacher et al., 2001).

BER gene polymorphisms have shown association trends in a variety of human cancers and other diseases, however, conflicting reports weaken any substantial conclusions in epidemiological studies. Therefore a functional study of these polymorphisms will be essential. So far the significance of these polymorphisms is still largely unknown. The most studied BER gene with regard to polymorphisms is perhaps XRCC1, which is required for efficient DNA SSB repair. Takanami *et al* (2005) has shown that the R280H variant when transfected into a CHO cell line null for the XRCC1 gene product impaired the function of XRCC1. Cell survival after treatment with methyl methanesulfonate (MMS) to induce DNA SSB was not affected. Cells with the R399Q genotype showed no difference in sensitivity to MMS compared to cells transfected with Q399R (Taylor et al., 2002). There was also no difference in the ability to repair MMS-induced SSB in the two isoforms as determined by the comet assay (Taylor et al., 2002). However, Pachkowski et al. (2006) found decreased DNA repair with the R280H variant in cells exposed to chemical stresses of peroxide, MMS or camptothecin in a measure of DNA repair by monitoring NAD(P)H levels. Other studies reported a significant increase in chromosomal deletions in cells with the R399Q genotype treated with UV light (Au et al., 2003) or bleomycin (Qu et al., 2005). Functional evidence of OGG1 gene polymorphism is also equivocal, with some *in vitro* studies showing the Cys326 variant has identical catalytic activity to wild-type Ser326, and others reporting significant differences (reviewed by (Weiss

et al., 2005). These contrasting results on functional studies raise some questions about whether the polymorphisms are completely neutral or harmless.

9.2. Polymorphisms and spermatogenesis

Xrcc1 is expressed in greater abundance in testis in rodents and primates and specifically most abundantly in pachytene spermatocytes and round spermatids of mice (Walter et al., 1994; Walter et al., 1996; Zhou and Walter, 1995). The expression profile of Xrcc1 during mouse spermatogenesis is accompanied with greater BER activity and lower mutant frequencies in these germ cell types (Intano, 2002; Walter et al., 1994). Because Xrcc1 knockout mice die early in embryogenesis (Tebbs et al., 1999), it is unknown how Xrcc1 depletion affects spermatogenesis. Studies of XRCC1 polymorphisms in human studies may provide some clues. The homozygous arg399arg genotype is found to be related to a decreased risk of idiopathic azoospermia in a Chinese population (Gu et al., 2007), indicating that the XRCC1 gene is important for normal spermatogenesis. Patients with an arg399arg genotype may have better BER activity compared to gln399gln and arg399arg genotypes, because the arg399arg genotype experienced more DNA damage after sunlight exposure (Nelson et al., 2002). Direct quantification of XRCC1 functions with different polymorphism genotypes has not been thoroughly examined.

9.3. BER and neurodegenerative disorders

Neurodegenerative disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and ataxia telangiectasia (AT), are characteristically associated with neurological deterioration. Although the etiologies of neurodegenerative diseases are largely unknown, aging is a major risk factor for most, and DNA damage and DNA repair are found to play an important role in these disorders (Table 6). ROS are considered major risk factors for aging and neurodegenerative disorders (Poon et al., 2004). ROS can mediate damage in mitochondrial and nuclear DNA which is largely repaired by BER (Seeberg et al., 1995). Brain uses more oxygen than other organs yet it has less nuclear and mitochondrial BER activity (Intano et al., 2001;Karahalil et al., 2002) than other somatic tissues, rendering the brain more vulnerable to ROS-induced damage. As noted above, BER declines in brain in general and in specific brain regions during aging thereby further increasing the vulnerability of this important tissue to DNA damage.

Age-associated decline of BER activity in the central nervous system has been linked to neurodegenerative disorders. Missense mutations in the APE1 gene (Olkowski, 1998), decreased APE1 protein levels and decreased APE1 activity (Kisby et al., 1997) were found in ALS patients. However, contradictory findings were also reported in ALS patients (Shaikh and Martin, 2002). In AD patients, expressions of the mitochondrial β-OGG1 (Iida et al., 2002) and DNA POLβ (Copani et al., 2006) was decreased; whereas expression of APE1 was increased in brain tissues (Davydov et al., 2003). A recent study has demonstrated that BER activity is decreased in both affected and non-affected brain regions in AD patients, resulting from reduced UDG, OGG1 and POLβ activities (Weissman et al., 2007b).

10. Future directions

Lifespan and health span can be extended by a simple procedure of reducing food consumption (Masoro, 2003). However, the molecular mechanisms that mediate the increases in lifespan and health span remain largely undefined. DNA repair, including BER, is clearly important for viability and health span. The extent to which DNA repair contributes to maximal lifespan is less clear. There are now animal models that can be used to directly ask questions about how BER contributes to health span throughout the lifespan of rodents and how BER contributes to lifespan. Although the Ape1, Polβ Xrcc1, Fen1 and Lig I knockouts are lethal, the

heterozygotes are viable and can be used to assess health span, repair over the lifespan, mutagenesis over the lifespan and lifespan itself in the background of heterozygosity for a BER gene. The DNA glycosylase knockout mice are viable as nulls and can be used to address the same questions. It is also important to understand the molecular mechanisms that mediate the decline in BER with increased age and the variability among tissues with regard to the apparently different proteins that mediate the decline in activity. Tissue specific knockdowns may also provide insight into the variability among tissues. The full impact of BER on aging and health span may be better displayed when models heterozygous or homozygous null for BER genes are combined with models deficient in apoptosis or cell cycle check point genes. Much remains to be elucidated concerning the role of BER in aging and health span.

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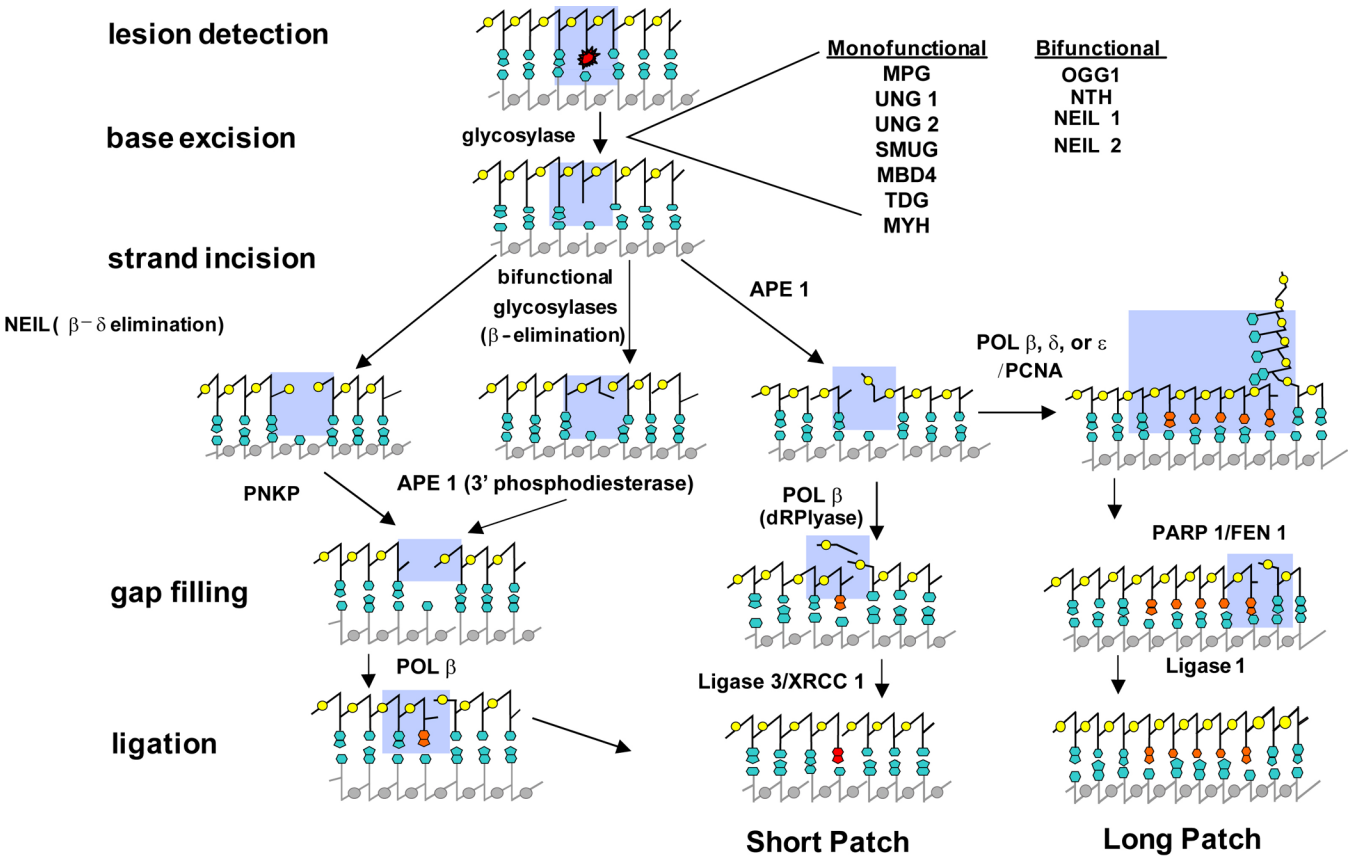

Fig 1. Diagram of base excision repair

Base damage recognition is performed by a monofunctional or bifunctional DNA glycosylase. The damaged base is removed by hydrolyzing the N-glycosidic bond thereby leaving an abasic site. Strand incision occurs at the abasic site primarily through the action of APE1, or alternatively via the lyase activity of a bifunctional DNA glycosylase. The ends of the phosphodiester backbone are processed to render them suitable for DNA repair synthesis. POLβ fills the gap for short-patch repair while a processive polymerase fills the gap in long-patch repair. XRCC1 and DNA ligase 3 seal the phosphodiester backbone in short-ptach BER while DNA ligase 1 completes the repair process in long-patch BER.

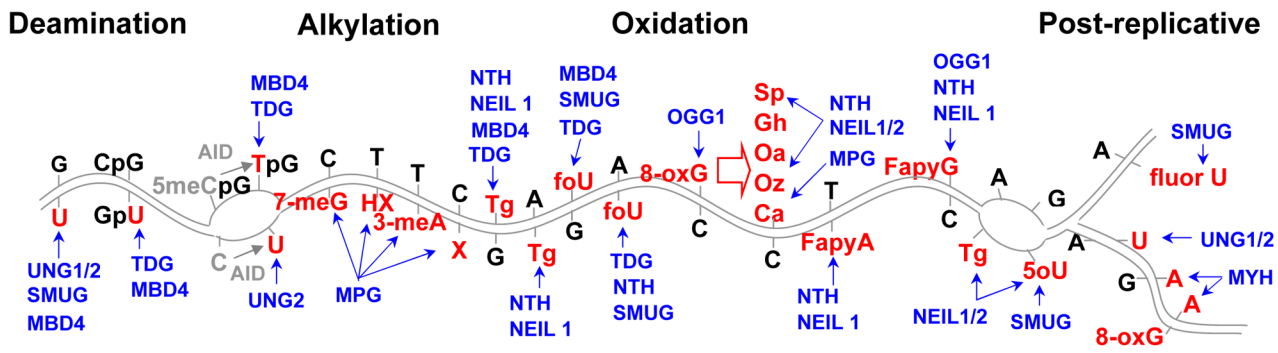

Fig 2. DNA glycosylases

Relationship between damaged bases, DNA structure and recognition by specific DNA glycosylases. While each DNA glycosylase has a limited substrate repertoire, there is redundancy in damage recognition among the DNA glycosylases. Damaged bases, deaminated, alkylated or oxidized, are shown in double-stranded DNA, bubble DNA or newly replicated DNA in conjunction with the DNA glycosylases that recognize the damaged base in the particular DNA structure. DNA glycosylases are shown in blue with arrows to the damaged base(s) recognized. Modified bases shown are in red and include U=uracil, X=xanthine, HX=hypoxanthine, 3-meA=3-methyladenine, 7-meG=7 methylguanine, Tg=thymine glycol, foU=5-formyl uracil, 8-oxG=8-oxoguanine; Sp=spiroiminodihydantoin, Gh=guanidinohydantoin, Oa=oxaluric acid, Oz=oxazolone, Ca=cyanuric acid, FapyG=formamidopyrimidine derivative of guanine; FapyA=formamidopyrimidine derivative of adenine, 5oU=5 hydroxy uracil, fluorU= 5 fluorouracil, 5-meCpG= 5-methyl cytosine in the CpG context. The cytosine to uracil and 5-methyl cytosine to thymine reactions catalyzed by activation induced cytosine deaminase, AID, are shown in grey (Bransteitter et al., 2006).

Selected references for the glycosylase repair of mispairs include: G/U, (Akbari et al., 2004; Barrett et al., 1998), CpG/GpU, (Krokan et al., 2002); X/C, HX/T, 3meA/T, 7meG/C, (Chakravarti et al., 1991; Engelward et al., 1997); G/Tg, (Bandaru et al., 2002; Ikeda et al., 1998; Marenstein et al., 2003; Yoon et al., 2003); Tg/A, (Dianov et al., 2001; Hazra et al., 2002b; Marenstein et al., 2003; Rosenquist et al., 2003); foU/G, (Liu et al., 2003); foU/A, (Ikeda et al., 1998; Matsubara et al., 2003; Miyabe et al., 2002); foU/A, (Liu et al., 2003; Miyabe et al., 2002); 8-oxG, (Asagoshi et al., 2000; Laval et al., 1998); oxidized 8-oxG bases Sp, Gh, Oa, Oz, Ca, (Dherin et al., 2004; Hailer et al., 2005); FapyA/T, (Hazra et al., 2002a; Rosenquist et al., 2003); FapyG/C; (Asagoshi et al., 2000; Hazra et al., 2002a; Ide, 2001); TpG/GpC, (Krokan et al., 2002; Sousa et al., 2007); TG in bubbles, (Englander and Ma, 2006; Hazra and Mitra, 2006); 5oU in bubble DNA, (Englander and Ma, 2006; Hazra and Mitra, 2006; Matsubara et al., 2004); fluorU/A, (An et al., 2007); U/A post-replicative, (Nilsen et al., 2000; Parlanti et al., 2007); 8-oxG/A and G/A post replicative, (Ide and Kotera, 2004; McGoldrick et al., 1995).

Table 1

DNA damage and mutagenesis relative to age

DNA Damage	Model	Ages	DNA Damage	Mutation	Selected References
8-oxoguanine	Rat (F344) male	6, 18, 24 mo*	↑ in nucl DNA in brain, heart, kidney, liver & muscle; ↑ in mitoDNA in liver	N.D.	Hamilton et al., 2001b
	Mouse (B62DF1) male	6, 25 mo	↑ in nucl DNA in brain, heart, kidney, liver & muscle; ↑ in mitoDNA in liver	N.D.	
	Mouse (C57BL/6) male	6, 26 mo	↑ in nucl DNA in brain, heart, kidney, & liver.	N.D.	
	Mouse (C57BL/6) female	6, 14, 26 mo	↑ in nucl DNA in brain, heart, kidney, liver & muscle; ↑ in mitoDNA in liver	N.D.	
AP sites	Rats (Sprague Dawley)	2–4 mo & 24 mo	↑ in liver N.C. in brain	N.D.	Atamna et al., 2000
	IMR90 cells	PDL*-25–30 (young) PDL 46–54 (senescent)	↑ in senescent cells		
	Human 1° leukocytes	21–33 yrs* & 58–75 yrs	↑ in cells from old donors.		
Single Strand Breaks	Mouse (SAMP1) female	1 d*, 1, 3, 6, 9, 11 mo	↑ in brain, heart, muscle, liver, lung and intestine; ↑ rate of accumulation in SAMP1, senescence prone mice.	N.D.	Hosokawa et al., 2000
	Mouse (SAMR1) (female)	1 d, 1, 3, 6, 9, 12, 18, 25 mo		N.D.	
	SAMP1 SAMR1	1, 6, 10 mo	↑ SSB after NQO in SAMP1, less so in SAMR1	N.D.	Zahn et al., 2000
Mutagenesis	Mouse (C57BL/6 LacI)	1–24 mo	N.D.	↑ mutation frequency	Lee et al., 1994
	Mouse (C57BL/6 LacZ)	1d, 4–6, 10–24, 25–34 mo.	N.D.	↑ mutation frequency in liver ↑ mutation frequency in brain between birth and 3–4 mo	Dolle et al., 1997
	Mouse (C57BL/6 LacZ)	3–4 & 30–33 mo	Genome rearrangements increased in liver at age >27 mo;.	↑ mutation frequency in small intestine, spleen, liver and heart N.C. in brain	Dolle et al., 2002
	Mouse (C57BL/6 LacI)	1.5, 6, 12, 18, 25 mo	N.D.	↑ mutation frequency in liver and bladder ↑ mutation frequency in brain at early ages	Stuart et al., 2000
	Mouse (C57Bl/6 LacZ)	1–33 mo	N.D.	N.C. in seminiferous tubules	Martin et al., 2001
	Mouse (LacZ MutaMice)	1 d, 2, 6, 12, 24 mo	N.D.	↑ mutation frequency in spleen, liver, heart, brain (modest), testis (modest) and skin (modest).	Ono et al., 2000
	Mouse (C6B3F1 LacI)	2, 15, 28 mo	N.D.	↑ mutant frequency in spermatogenic cells	Walter et al., 1998
	Mouse (C57Bl/6 LacI)	4–6, 22–26 mo	N.D.	↑ mutant frequency in liver ↑↑ mutant frequency after DMS	Cabelof et al., 2002

DNA Damage	Model	Ages	DNA Damage	Mutation	Selected References
	Mouse (C57Bl/6N)	2–22 mo	N.D.	↑ mutation frequency in mtDNA D-loop in liver	Khaidakov et al., 2003

*d=day; mo=month; wk=week; yrs=years; PDL=population doubling level; N.D. = not determined; N.C. = no change; ↑= increase; ↓ = decrease.

Table 2

BER activity with age

Activity Assayed*	Model	Age	Findings	Selected References
UDG-BER	Mouse (CD1)	5–8 d, 4–6 mo*	Spermatogenic cells > Sertoli cells > thymocytes > liver > brain nuclear extracts	Intano et al., 2001
	Mouse (C57Bl/6)	4–6 mo	Spermatogenic cells > liver > brain nuclear extracts	
	Mouse (B6D2F1)	4–6 mo	Spermatogenic cells > liver > brain nuclear extracts	
UDG-BER	Mouse (CD1)	6, 8 d, 3 mo	Liver activity > brain nuclear extracts. Activity greatest in neonatal liver and neonatal brain nuclear extracts.	Intano et al., 2003
	Mouse (B6D2F1)	6–8 d, 3, 16, 28 mo	Liver activity ↓ 50% by 16 mo. Brain activity ↓ 60% by 3 mo.	
UDG-BER OGG-BER POLβ	Mouse(C57Bl/6)	4–6, 22–26 mo	↓ activity with age in brain, spleen liver and testes nuclear extracts Testes have highest activity.	Cabelof et al., 2002
OGG1 UDG1 EndoG-activity	Rat (Wistar)	6, 12, 23 mo	Mitochondrial OGG/AP lyase activity ↑ with age in liver and heart; mitochondrial UDG-activity has slight increase in heart.	Souza-Pinto et al., 1999
OGG1 UDG	Mouse (C57Bl/6)	6, 14, 23 mo	↑ mitochondrial activity, ↓ nuclear activity with age in liver	de Souza-Pinto et al., 2001b
Gap repair	Rat (Wistar)	5 d, 6 mo, >2 yr	↓ activity with age in nueronal preparations	Krishna et al., 2005
OGG-BER OGG1 UDG1 APE1 Polγ ligase	Rat (Sprague Dawley)	17 d embryos, 1, 2, 3 wk 5, 30 mo	Overall BER and individual activities examined in brain mitochondria with sharp decline in OGG1, APE1, POLβ and ligation activities by 5 mo.	Chen et al., 2002a
APE1	Mouse (BALB/c)	4, 10, 20 mo	↑ nuclear and mitochondrial activity with age in liver; cytoplasmic activity ↓. N.C. whole cell activity	Szczesny and Mitra, 2005
OGG1 NTH APE1	IMR90	PDL11, 39*	↓ OGG-activity in nucleus with increased passage number. ↓ NTH and APE1 activity in mitochondrial and cytoplasmic fractions. N.C. in nuclear NTH or APE1 activities with passage number	Shen et al., 2003
OGG1	Human leukocytes	Newborn-91 yr	↓ with age	Chen et al., 2003c
OGG1 UDG NTH	Mouse (C57Bl/6)	6 & 18 mo	↓ in OGG, UDG, NTH activity in mitochondria in all brain regions. Variable patterns seen in nuclei. Cerebelleum with greatest activities and greatest ↓.	Imam et al., 2006
UDG-BER POLβ	Rat (Fisher 344)	6 wk, 60% calorie restricted; 4–6mo, 22–24 mo	↓ activity with age in brain, liver and testes nuclear extracts reversed by caloric restriction.	Cabelof et al., 2003

* BER-refers to complete base excision repair assay; UDG, OGG1, APE1 or NTH alone refers to strand incision activity assay; Pol- refers to gap filling activity; d=day; mo=month; wk=week; yr=years; PDL=population doubling level; ↑= increase; ↓= decreased; N.C.= no change

Table 3

BER protein abundance with age

Protein	Models	Ages	Findings	Selected Reference
POLβ	Mouse (C57BL/6)	4–6, 22–26 mo	↓ levels of POLβ protein in nuclear extracts from brain, kidney, liver, spleen and testes	Cabelof et al., 2002
POLβ	Rats (Fisher 344) rats	at age 6 wk, 60% calorie restricted; 4–6, 22–24 mo	CR completely reverses age related decline in POLβ abundance in nuclear extracts from brain, liver and testes	Cabelof et al., 2003
POLβ OGG1	Rats (Sprague Dawley)	17 d embryos, 1, 2, 3 wk 5, 30 mo	Age dependent decrease in protein levels in brain mitochondria.	Chen et al., 2002a
APE1	Mouse (BALB/c)	4, 10, 20 mo	N.C. with age in total liver extracts.	Szczesny and Mitra, 2005
DNA Lig1	Mouse (B6D2F1)	3, 16, 28 mo	N.C. liver or brain or spermatogenic cell nuclear extracts	Intano et al., 2002; Intano et al., 2003
DNA Lig3			N.C. liver or brain or spermatogenic cell nuclear extracts	
XRCC1			N.C. liver or brain or spermatogenic cell nuclear extracts	
POLβ			↓ in brain; N.C. in liver or spermatogenic nuclear extracts	
APE1			↓ in spermatogenic cells nuclear extracts; N.C. in liver or brain	
APE1	Mouse (BALB/c)	4, 10, 20 mo	No change total abundance; ↑ nuclear and mitochondrial localization with age in liver	Szczesny and Mitra, 2005
APE1 Ligase 3	Mouse (C57Bl/6)	6 & 18 mo	N.C. in levels with age in various brain regions	Imam et al., 2006

↑ = increase; ↓ = decrease; N.C. = no change.

Table 4

Selected BER knockout/knockdown mouse models with corresponding phenotypes.

Gene	BER Activity	Reproductive Phenotypes	Somatic Phenotypes	Reference
Mpg	glycosylase	Homozygous mice are fertile.	Mice appear normal. Cell lines derived are more sensitive to alkylating agents.	Engelward et al., 1997; Smith and Engelward, 2000
Ung1/2	glycosylase	Homozygous mice are fertile	Mice appear normal; accumulate 2000 uracils/cell; display a hyper IgM syndrome with B-cell lymphomas accumulating > 18 mo.; no change in lifespan but decreased median survival.	Hagen et al., 2006; Krokan et al., 2001; Nilsen et al., 2000; Nilsen et al., 2003
Smug	glycosylase	N/A	A mutator phenotype seen with siRNA to *Smug*.	An et al., 2005
Mbd4	glycosylase	Homozygous mice are fertile.	Increase in somatic C-->T mutations at CpG sites	Millar et al., 2002; Wong et al., 2002
Nth	glycosylase	Homozygous mice are fertile.	Mice normal to two years of age.	Ocampo et al., 2002; Takao et al., 2002b
Neil1	glycosylase	Homozygous mice are fertile.	Metabolic syndrome at 6- to 10-months-old	Vartanian et al., 2006
Neil3	glycosylase	Homozygous mice are fertile	No phenotype detected	Torisu et al., 2005
Ogg1	glycosylase	Homozygous mice are fertile. Mutation frequency was not significantly different in testis compared to wild type.	Increased levels of 8-oxoG seen. Increased prevalence of G to T transversions in the liver	Boiteux and Radicella, 2000; de Souza-Pinto et al., 2001a; Klungland et al., 1999; Le Page et al., 2000; Osterod et al., 2001
Myh	glycosylase	Homozygous mice are fertile.	A mutator phenotype seen in ES cells. No difference survival or tumor incidence to 17 mo.	Hirano et al., 2003; Xie et al., 2004
Myh, Ogg1	glycosylases	Double knockout mice fertile through at least 2 generations.	Median survival significantly decreased to 10.3 mo., tumor incidence increased; G to T mutation in *K-ras* in lung tumors	Xie et al., 2004
Ape1	AP-endonuclease	*Ape1*$^{+/-}$ animals were fertile, appear normal; but mutant frequency was elevated in spermatogenic cells.	Ape1 −/− is an embryonic lethal. Mutant frequency elevated in liver and spleen of *Ape1* +/− mice	Huamani et al., 2004; Meira et al., 2001
Polβ	DNA polymerase	*Pol*β+/− animals are fertile.	*Pol*β −/− is an embryonic/neonatal lethal.	Gu et al., 1994; Sugo et al., 2000
Fen1	Flap endonuclease	*Fen* +/− animals fertile, appear normal.	*Fen* −/− is an embryonic lethal. *Fen* +/− show rapid tumor progression in animals predisposed to cancer by mutation in adenomatous polyposis coli (Apc) gene..	Kucherlapati et al., 2002; Larsen et al., 2003
Parp 1	poly(ADP)-ribosylase	Homozygous mice are fertile.	Mice are viable although hypersensitive to mutagenic agents	de Murcia et al., 1997
Parp2	poly(ADP)-ribosylase	Null male mice are hypofertile, testis weight is reduced by 70% and the epididymal sperm counts were 0.1% of wild type.	Mice sensitive to ionizing radiation and have an increased post-replicative genomic instability.	Dantzer et al., 2006 Menissier de Murcia et al., 2003
Sir6	deacetylase	N/A	Progeroid mice with compromised BER, severe metabolic defects and death at 4-weeks-old.	Mostoslavsky et al., 2006

N/A = not applicable.

Table 5

BER polymorphisms and cancer associations

BER gene	Cancer association	Polymorphism	Selected references
MYH	Familial biallelic germline mutations implicated in 1–3% colorectal cancer	Tyr165Cys; Gly382Asp; Tyr90X/ 1103delC; Gln377X; 1314delA; Pro281Leu	Al-Tassan et al., 2002; Cheadle and Sampson, 2003; Croitoru et al., 2007; Halford et al., 2003; Jones et al., 2002
OGG1	Variants associated with increased prostate cancer risk.	Ser326Cys	Chen et al., 2003b
	Variants associated with increased gastric cancer risk.	Arg154His	Nohmi et al., 2005
	No association of variants with risk of adenomas; lowered risk of colorectal cancer.	Ser326Cys	Hansen et al., 2005
XRCC1	Polymorphisms implicated in lung cancer	Arg399Gln; Arg194Trp, Arg280His	Kiyohara et al., 2006; Zienolddiny et al., 2006
	Homozygous variants with increased risk of squamous cell carcinoma after sun overexposure.	Arg399Gln	Nelson et al., 2002
	Prostate cancer associated if XPD polymorphism also present	Arg399Gln	Rybicki et al., 2004
OGG1, *APE1*	Risk association between single SNP and lung cancer, is minimal		Kiyohara et al., 2006
OGG1, *POLβ*, *APE1*, *XRCC1*	Pancreatic cancer risk varies with BER protein polymorphisms.	*POLβ* A165G and T2133C; *OGG1* G2657A; *APE1* Asp148Glu; *XRCC1* Arg194Trp	Li et al., 2007a
OGG1 *XRCC1*	*OGG1* variant associated with increased risk; *XRCC1* variant associated with reduced risk in various cancers.	*OGG1* Ser326Cys; *XRCC1* Arg194Trp	Goode et al., 2002
OGG1 *XRCC1 APE1*	*OGG1* variant with increased lung cancer risk; *XRCC1* Arg194Trp variant with decreased risk; *XRCC1* Arg399Gln with increased risk light smokers, decreased risk heavy smokers; no association of *APE1* with lung cancer risk.	*OGG1* Ser326Cys; *XRCC1* Arg194Trp; *XRCC1* Arg399Gln; *APE1* Asp148Glu	Hung et al., 2005
OGG1 *XRCC1*	Variants with increased risk for nasopharyngeal carcinoma. Presence of both variants results in greater risk.	*OGG1* Ser326Cys; *XRCC1* Arg280His	Cho et al., 2003
APE1, *XRCC1*, *PARP1*	Polymorphisms in *APE1* and *PARP1* with decreased risk; polymorphism in *XRCC1*, and associated with increased risk in advanced colorectal adenoma.	*APE1* Gln51His; *PARP1* A284A and IVS13+118G>A) *XRCC1* Arg399Gln;	Berndt et al., 2007

Table 6

BER in neurodegeneration

Disease	Study	Results	Selected References
Alzheimer's Disease- age related dementia	AD patients and age-matched controls	Increased 8-oxoG in ventricular CSF DNA; decreased free 8-oxoG indicating accumulation of 8-oxoG lesions in patients.	Lovell et al., 1999
	Late stage AD patients and early stage with mild cognitive impairment	Elevated 8-oxoG, 8-OHA, and 5,6-diamino-5-formamidopyrimidine in nuclear and mtDNA isolated from vulnerable brain regions in amnestic mild cognitive impairment.	Lovell and Markesbery, 2007
	Brain tissue autopsies	Immunoreactivity to hOGG1-2a is associated with neurofibrillary tangles, dystrophic neurites and reactive astrocytes in AD.	Iida et al., 2002
	Post-mortem autopsies graded for disease progression.	POL-β is increased with increasing severity of disease; decreases with severe neuronal loss. Suggests POL-β involved early in AD pathology.	Copani et al., 2006
	Postmortem AD midfrontal cortex and age-matched controls.	APE1 expression significantly increased in AD subjects.	Davydov et al., 2003
	Post-mortem autopsies sporadic AD, mild cognitive impaired and age-matched controls.	Significant BER deficiencies; decreased OGG-BER, UDG-BER and POLβ activities. No decrease in APE1-BER. Decreases seen in both AD and mild cognitive impairment.	Weissman et al., 2007b
Parkinson's Disease	Autopsies PD and age-matched controls.	Up-regulation of MYH in the mitochondria of substantia nigra.	Arai et al., 2006
Amyotrophic Lateral Sclerosis	Mutant SOD mice	POLβ and mitochondrial OGG1 is decreased in symptomatic mice. POLγ is decreased in presymptomatic and symptomatic mice.	Murakami et al., 2007
	Patients with familial ALS	Identified missense mutations in the APE1 gene.	Olkowski, 1998
	Patients with sporadic ALS and age-matched controls.	APE1 levels and activity are significantly lower in ALS subjects than in controls.	Kisby et al., 1997
	Patients with sporadic ALS and age-matched controls.	Results suggest a possible involvement of the hOGG1 Ser326Cys polymorphism in sporadic ALS pathogenesis.	Coppede et al., 2007
Ischemia	Mouse and rat models	Ischemia causes transient decrease in BER proteins in the brain. Ischemic preconditioning increases BER capacity.	Chen et al., 2003a; Fujimura et al., 1999; Lan et al., 2003; Li et al., 2007b; Li et al., 2006; Luo et al., 2007
	UNG −/− mice	Increased post-ischemic brain injury compared to wild type mice.	Endres et al., 2004
	PARP1 −/− mice	PARP1 critical in ischemia-reperfusion injury.	Shall and de Murcia, 2000
	PARP2 −/− mice	Reduced stroke damage in PARP2 −/− mice.	Kofler et al., 2006
Huntington's Disease-trinucleotide instability	HD gene transgenic mice bred with MPG, OGG1 and NTH1 knockouts.	OGG1 excision of 8-oxo-G within CAG repeat DNA can initiate strand displacement and expansion in vitro during BER, creating a toxic oxidation cycle.	Kovtun et al., 2007

AD = Alzheimer's disease; 8-oxoG = 8-oxodeoxyguanine; 8-OHA=8-hydroxyadenine; mtDNA=mitochondrial DNA; hOgg1-2a=mitochondrial splice variant of hOgg1; OGG/UDG/APE-BER=complete base excision repair assay of OGG/UDG/APE substrate; PD=Parkinson's disease; SOD=superoxide dismutase; ALS= Amyotrophic Lateral Sclerosis; HD=Huntington's disease