Published in final edited form as:

DNA Repair (Amst). 2015 August ; 32: 172–179. doi:10.1016/j.dnarep.2015.04.029.

The role of DNA base excision repair in brain homeostasis and disease

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Abstract

Chemical modification and spontaneous loss of nucleotide bases from DNA are estimated to occur at the rate of thousands per human cell per day. DNA base excision repair (BER) is a critical mechanism for repairing such lesions in nuclear and mitochondrial DNA. Defective expression or function of proteins required for BER or proteins that regulate BER have been consistently associated with neurological dysfunction and disease in humans. Recent studies suggest that DNA lesions in the nuclear and mitochondrial compartments and the cellular response to those lesions have a profound effect on cellular energy homeostasis, mitochondrial function and cellular bioenergetics, with especially strong influence on neurological function. Further studies in this area could lead to novel approaches to prevent and treat human neurodegenerative disease.

Keywords

Base excision repair; oxidative damage; mitochondrial DNA; neurodegeneration; PARP-1

INTRODUCTION

DNA and other nucleic acids are susceptible to damage from endogenous and exogenous sources, including oxygen free radicals, UV-light, high energy cosmic particles and chemical compounds. Cells have mechanisms to prevent or limit the adverse consequences of such damage, when it occurs, including specialized DNA repair pathways.

The DNA base excision repair (BER) pathway repairs the majority of endogenous DNA damage. BER plays an important role in the brain homeostasis at least for three reasons. First, oxidative DNA damage is a frequent event in brain cells, because brain consumes more oxygen and has higher metabolic rate and lower antioxidant capacity than many other

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tissues [1]. Second, BER is critical for maintaining the integrity of the mitochondrial genome, which is essential for neurological function [2]. Third, BER repairs DNA damage caused by physiological neuronal activity [3, 4].

DNA base excision repair (BER)

BER is the primary mechanism for repair of DNA base damage, AP sites and variants of single-strand breaks. BER begins with the identification and removal of a damaged base by a DNA glycosylase leaving an AP-site. The AP-site is then incised on the 5'-side by AP endonuclease 1 (APE-1), followed by gap filling with a DNA polymerase and finally joining of the DNA ends by a DNA ligase (Fig. 1). In principle, BER can be reconstituted *in vitro* with four proteins; a DNA glycosylase, APE-1, DNA polymerase β (Pol β), and DNA ligase III (Lig III). In the cells, however, BER involves a number of other proteins; some are essential such as APE-1 and Pol β , while others play a more regulatory role and coordinate the BER response to damage such as X-ray repair cross-complementing protein 1 (XRCC1) and proliferative nuclear antigen (PCNA). BER is also regulated by the cell cycle, protein-protein interactions, and post-translational modifications [5, 6]. Some BER proteins also play roles in the adaptive immune response and in RNA quality control[7–10], indicating a multifunctional role in nucleic acid metabolism(Fig. 2).

BER enzymes act on both the nuclear and the mitochondrial genomes; however, all BER proteins are encoded by nuclear genes, and expression of mitochondrial BER (mtBER)protein variants involves alternative transcription initiation sites and alternative splice sites. Some mtBER proteins contain a canonical mitochondrial leader sequence [11, 12], while others localize to the mitochondria by other mechanisms [13].

The expression and enzymatic activity of BER proteins are regulated in a tissue-specific [14, 15], and cell cycle-specific manner[6, 16, 17]. Post-translation modifications [18], and protein-protein interactions [5, 19, 20] also modulate many BER enzyme functions. In the brain, the expression and the activity of BER proteins varies by brain region[21], but the significance of these differences is not well understood.

BER deficiency and neurodegenerative disease

In the mouse, null alleles of genes encoding several core BER proteins are lethal during embryonic development, indicating a critical early developmental role for BER in the mouse. In humans, rare cases of inherited defects in genes encoding BER proteins cause immune system dysfunction [22, 23], cancer[24], and some polymorphic variants seem to influence susceptibility to some human diseases (reviewed in [25, 26]). In addition, defects in BER proteins or in proteins that modulate BER are implicated in several neurodegenerative disorders [27, 28].

For the purpose of this review, we discuss different human disease syndromes linked to defects in BER and other DNA repair pathways. One group include syndromes caused by defects in gene products or genes encoding Polynucleotide kinase phosphatase(PNKP), Ataxia with oculomotor apraxia 1 (APTX) or Tyrosyl-DNA Phosphodiesterase 1 (TDP1) (Fig. 1). Other diseases are genetically and clinically complex, often further complicated

with potential environmental triggers or predisposing factors: examples include Parkinson's disease (PD), Huntington's Disease (HD) and Alzheimer's Disease (AD).

Polynucleotide kinase phosphatase (PNKP)—Oxidative damage to DNA by high energy reactive oxygen species (ROS) and γ -radiation can generate DNA single-strand breaks with damaged 5'- and 3'-termini including 5'-OH, and 3'-PO₄ that block DNA polymerase repair synthesis and DNA ligation. In BER, the bi-functional DNA glycosylases NEIL1 and NEIL2 possess an AP-lyase activity that produces a 3'-PO₄ group by a β , δ -elimination reaction which blocks ligation [29]. PNKP is a bi-functional enzyme with 5'-kinase and 3'-phosphatase activities and is the primary DNA repair protein for removing 5'-OH and 3'-PO₄ blocking groups.

In the nucleus, PNKP forms a complex with NEIL1, NEIL2, Pol β , and Lig III [30, 31]. PNKP has also been detected in mitochondria [32, 33], in close proximity to NEIL2 and Poly [33]. PNKP is also the major 3'-phosphatase in mitochondrial extracts, and PNKP depleted mitochondrial extract showed reduced mtBER activity [33]. These results indicate that PNKP actively participates in nuclear and mtBER.

Mutations in the phosphatase and kinase domains of PNKP have been identified in patients with microcephaly, early-onset seizures and developmental delay (denoted MCSZ Online Mendelian Inheritance in Man (OMIM) # 613402) [34]. A group of disorders of varying severity may be linked to defects in *PNKP*, as observed for other DNA repair deficiency diseases in which unique mutations give rise to different clinical presentations [35].

Ataxia with oculomotor apraxia 1 (AOA1)—During DNA ligation, a transient covalent bond is formed between AMP and a lysine in the ligase enzyme active site. The AMP moiety, derived from ATP, is then transferred to the 5'P of the DNA substrate, forming 5'-AMP-DNA. The transient 5'-AMP moiety then undergoes nucleophilic attack by the deoxyribosyl 3' OH, displacing AMP and facilitating ligation of the two DNA strands [36]. Premature termination of DNA ligation generates 5'-AMP termini. The enzyme that removes 5'-AMP from DNA is Aprataxin (APTX) [37]. APTX also removes AMP from 5'-AMP-dRP residues that arise in DNA after attempts to ligate ends with 5'-dRP groups [38].

Mutations in *APTX* cause the inherited disease ataxia with oculomotor apraxia 1 (AOA1, OMIM #208920) [39, 40]. AOA1 patients are not susceptible to cancer nor do they develop immunological deficiencies, which is consistent with the findings that APTX deficient cells are not distinctly more sensitive to genotoxins than APTX proficient cells [41–43]. APTX localizes to the nuclear and mitochondrial compartments of human cells [43]. Knocking down APTX in SH-SY5Y cells caused loss of mtDNA integrity, but had no detectable effects on the nuclear genome [43]. This suggests a mitochondrial component in the pathogenesis of AOA1. More recently, it has been reported that APTX may play a role in repair of adenylation adducts at RNA-DNA junctions that are likely to be abundant in normal DNA metabolism [44]. Further studies will clarify the role of APTX in the nuclear and mtBER and its relation to AOA1 pathology.

Tyrosyl-DNA phosphodiesterase 1 (TDP1)—Mutations in *TDP1* give rise to Spinocerebellar ataxia with axonal neuropathy (SCAN1, OMIM # 607250, [45]), characterized by cerebellar atrophy and peripheral neuropathy. TDP1 is important for the repair of 3′phosphoglycolate, 3′abasic sites, topoisomerase I (TOPO1)-linked DNA adducts and others [46]. During DNA replication or transcription, torsional stress is introduced into DNA and TOPO1 makes a transient SSB in the DNA to relieve this stress. During its catalytic cycle, TOPO1 makes a covalent bond between an active site tyrosine residue and the 3′ side of the SSB. If the enzyme is unable to re-ligate the SSB, TOPO1 becomes stuck and the DNA-protein adduct is then subjected to repair by TDP1[45, 47]. TDP1 is localized to both the nucleus and mitochondria [48]. *Tdp1*^{−/−} mice show age-dependent and progressive cerebellar atrophy[49]. A knockout of the TDP1 ortholog in *Drosophila* reduced lifespan of female flies, which was rescued by expression of TDP1 in neurons[50].

A high level of DNA damage is reported as a cellular phenotype of the disorders MCSZ, AOA1 and SCAN1. MCSZ and AOA1 patients are not susceptible to cancer or immune system dysfunction, MCSZ seems to be a developmental disorder, whereas AOA1 and SCAN1 are progressive neurodegenerative diseases. It is important to note that PNKP, APTX and TDP1 are expressed in mitochondria and features in these diseases may reflect mitochondrial dysfunction. Generation of exclusively nuclear or mitochondrial targeted enzymes should help to clarify this issue.

Poly(ADP)ribose polymerase (PARP1)—Poly(ADP)ribose polymerase 1 (PARP1) utilizes NAD⁺ to ADP-ribosylate itself and other protein substrates [51]. While it is not a core BER protein, PARP1 is activated by DNA damage and activated PARP1 plays a role in regulating the DNA damage response (DDR). PARP1 substrate proteins include Polβ, XRCC1 and Lig III[52]. There is much effort towards understanding the role of PARP1 in DNA damage and repair and mitochondrial bioenergetics(for recent reviews see [51, 53]). NAD⁺ is an important cofactor for many enzymes including PARP1 (and PARP2) in response to DNA damage. Under mild stress, PARP1 recruits proteins to damaged sites and facilitates repair. However, if the damage is too great, persistent PARP1 activation leads to overutilization of NAD⁺ that can substantially alter the cellular NAD⁺/NADH ratio and the size of the ATP pool, leading to cell death (reviewed in[54]). Conversely, preventing NAD⁺ depletion protects neurons against excitotoxicity, death by bioenergetics stress, and ischemia [55, 56]. Thus, one might expect that cells derived from DNA repair deficient patients would have a low level of NAD⁺, compromised cellular bioenergetics and higher cell death. Increased cell death and PARP1 activation has been seen in *Ogg1*^{−/−} cells exposed to oxidative stress [57], and in animal models lacking both *Ogg1* and *Mth1* (an 8-oxodGTPase) following treatment with the mitochondrial complex II inhibitor 3-nitropropionic acid [58]. In addition, in cells from individuals with DNA repair deficiency, chronic PARP1 activation promotes energetic and mitochondrial dysregulation and contributes to cellular dysfunction [59, 60].

Cockayne syndrome group B (CSB) protein—The CSB protein is a SWI/SNF-like DNA-dependent ATPase, a class of proteins that modify the structure of DNA surrounding sites of damage to facilitate repair. CSB is implicated in transcription coupled nucleotide

excision repair (TCR), a specialized sub-pathway of nucleotide excision repair (NER) and in BER [61, 62]. DNA damage can inhibit the movement of RNA polymerase II (RNA Pol-II) along DNA. CSB binds to stalled RNA Pol-II and recruits DNA repair proteins. CSB-deficient cells show a widespread transcription defect, indicating an important role for CSB in nuclear transcription [63], and likely also in mitochondrial transcription [64]. Mutations in CSB associate with Cockayne syndrome (CS), a rare inherited disease (OMIM #609413). CS patients are not cancer prone but exhibit growth and developmental defects, accelerating aging, and progressive neurodegeneration [65].

NER removes helix-distorting DNA damage, such as thymine dimers formed by UV-light, hence, the UV-light sensitivity of CSB deficient cells [66]. However, it is unlikely that UV-light penetrates the brain and generates the type of lesions that activate PARP1 in CSB patients [59, 60], suggesting other sources of DNA damage may be involved. CSB deficient cells are sensitive to oxidative stress and accumulate oxidative base lesions [67, 68]. CSB stimulates the activity of DNA glycosylases NEIL1 and NEIL2 [69, 70], APE-1 [71], and colocalizes with NEIL2 at sites of stalled transcription [69]. Furthermore, NEIL2 associates with RNA II, and NEIL2-depleted cells accumulate more damage in active genes [72]. All of this together suggests a potential role for CSB in BER, and that the observed persistent PARP1 activation in CSB brain may be, at least partly, related to BER deficiency. CSB directly interacts with PARP1 [73] and we have recently found that CSB can displace PARP1 from DNA and thus may inhibit excessive PARylation [59].

Ataxia telangiectasia mutated (ATM)—Ataxia telangiectasia mutated (ATM) is a serine/threonine protein kinase activated by DNA double-strand breaks (DSBs). ATM is a master regulator of the response to DNA damage. ATM deficient cells are sensitive to and ATM is activated by oxidative stress [74]. Defects in ATM cause ataxia telangiectasia (A-T), an autosomal recessive disease characterized by cancer predisposition, insulin resistance, and neurodegeneration (OMIM #208900).

ATM protein has been detected in mitochondria, where it appears to regulate both mtDNA copy number [75] and the process of mitophagy [75–77]. ATM deficiency downregulates Lig III and lowers BER capacity in the mitochondria [78]. Lig III is the only DNA ligase in mitochondria and is the rate-limiting enzyme in mtBER [79]. These observations suggest a mitochondrial defect in A-T cells and additional studies of mitochondrial function in A-T is warranted.

We have recently shown that A-T has a mitochondrial phenotype as supported by both bioinformatics and in vitro studies. Using a mitochondrial clinical data established by us (www.mitodb.com), analysis of A-T suggests a mitochondrial disease phenotype. We investigated mitochondrial parameters using in ATM cell lines and found significant mitochondrial defects as evidenced by increased intracellular ROS, mitochondrial ROS, and increased mitochondrial membrane potential. ATM also display accumulation of damaged mitochondrial probably due to defective mitophagy [59].

Alzheimer's disease, Parkinson's disease and Huntington's disease are among the most common neurodegenerative disorders worldwide. Although they each have their specific

genetic and physiological mechanisms of pathology, oxidative stress, oxidative damage to macromolecules, mitochondrial dysfunction and nuclear and mtDNA damage constitute the central features of these diseases.

Alzheimer's disease—Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive cognitive and memory decline (OMIM #104300). Sporadic AD with late-onset is more common, while the less prevalent form of AD is early-onset autosomal dominant, linked to mutations in genes encoding amyloid precursor protein (APP), PSEN1 (PS1), and PSEN2 (PS2) [80].

Multiple studies show that oxidative modifications of lipids, proteins, and nucleic acids are higher in brains of AD patients than in normal brain, often accompanied with impaired neuroprotective stress responses [81, 82]. Oxidative stress seems to be a systemic feature of AD and an oxidative stress phenotype has been seen in AD fibroblasts [83]. High levels of oxidative DNA base lesions have been reported in preclinical [84] and late stage AD brains [85]. Increased amounts of oxidative DNA damage are a manifestation of an imbalance between ROS production (e.g. from dysfunctional mitochondria), and antioxidant and BER capacity of the cell. Lower nuclear and mitochondrial BER activities have been observed in AD brain samples [86–88]. Mitochondrial dysfunction and increased mtDNA damage have been reported frequently in AD brains [89–91]. 5-hydroxyuracil (5OHU) incision and DNA ligation activities were significantly reduced in mitochondrial lysates from AD brains [87]. In the same samples, the concentration of NEIL1 DNA glycosylase was much lower than in the control samples [87]. Together, these results support the idea that increased mtDNA damage together with a reduction of mtBER play a role in AD pathology [82, 89].

Interestingly, the expression and activity of Pol β were considerably reduced in brains of mild cognitive impaired (MCI) and AD patients, and showed an inverse correlation with the severity of the disease [86]. A reduction of Pol β is also seen in Down syndrome (DS) [92]. DS brains exhibit high levels of ROS and have significant oxidative damage [93], and DS patients develop AD at very high rates. Thus, increased oxidative DNA damage concomitant with a reduction in BER capacity seem to be a common feature of DS and AD. For these reasons, a novel mouse model combining the 3xTg AD mouse with a Pol $\beta^{+/-}$ heterozygote was created to specifically test if loss of Pol β alters the timing or presentation of symptoms in this AD mouse [94]. Interestingly, the 3xTg AD/Pol $\beta^{+/-}$ mouse showed greater cell death, neuronal loss and impaired mitochondrial bioenergetics, thus demonstrating that reduced BER capacity can substantially exacerbate disease progression. Pol β deficient AD mice and human AD patients displayed mitochondrial dysfunction and altered gene expression, while similar patterns were not detected in AD mice. Pol β depletion also appeared to cause defects in memory and neurogenesis [94].

Parkinson's disease—Parkinson's disease (PD) is a progressive neurodegenerative disease characterized by motor and non-motor symptoms and the loss of dopaminergic neurons in substantia nigra in the midbrain (OMIM #168600). Oxidative damage to macromolecules is an intrinsic property of PD. ROS generated as a by-product of dopamine metabolism, is considered a significant contributor to dopaminergic neuronal loss in the PD brain [95].

A mitochondrial deficiency in PD pathogenesis, especially in the substantia nigra, is extensively documented [96–98]. Environmental toxins like rotenone that inhibit mitochondrial complex I, have long been known to cause pathological features of PD in humans and in animals. Exposure of mice to rotenone impaired mitochondrial complex I function and damaged mtDNA before the PD symptoms were manifested [99]. In a separate study, a significantly increased level of mtDNA mutations was identified in early PD cases [100]. These results suggest that loss of mtDNA integrity is among the early events in the onset of PD.

Huntington's disease—Huntington's disease (HD) is an autosomal dominant hereditary neurodegenerative disease characterized by progressive decline in motor and cognitive functions (OMIM #143100). HD is one of over 40 neurodegenerative disorders caused by the expansion of trinucleotide repeat (TNR) sequences in DNA. Huntingtin gene (*HTT*) codes for the huntingtin protein (Htt). The function of Htt is not completely understood, but it is essential for normal embryonic development and neurogenesis, and its complete knockout in mice is lethal [101]. The *HTT* gene has an unstable CAG repeat in its first exon and CAG expansion is especially significant in the striatum, the brain region that degenerates in HD. An expansion of 40 or more of the CAG repeats causes HD and the clinical severity of the disease directly correlates with the length of the expansion [102]. BER of oxidized DNA bases has been implicated in CAG expansion in HD. In support of this, loss of Ogg1 DNA glycosylase suppressed CAG expansion in HD mice [103].

A key role for mitochondrial dysfunction in HD neuropathology is well documented [104–107]. Moreover, HD brains show markers of enhanced oxidative stress including oxidative damage to nuclear and mitochondrial genomes [108–110], and targeting antioxidant to mitochondria reduced mtDNA damage and suppressed motor decline in a mouse model of HD [111]. Given the observed increased oxidative stress and the abnormalities in mitochondrial bioenergetics in HD, more studies on the state of mtBER in HD are warranted.

BER in ischemia and stroke—Ischemic-reperfusion (I/R) occurs when the blood supply to an organ is disrupted and then restored, as in stroke. Reperfusion can cause a sudden increase in free radicals causing tissue injury and cell death, for instance, following heart attack and stroke. Studies in mice suggest that BER is important for recovery from ischemic-reperfusion injury; however, some studies suggest that active BER may promote brain damage during ischemia [112].

Increased expression of mtBER and nuclear BER proteins in response to focal ischemia have been reported [113, 114], with the level of tissue and oxidative DNA base damage inversely correlating with BER capacity [114, 115]. In addition, the size of the brain infarct was reported to be larger in Ung, Ogg1, Neil1 and Neil3 null mice than in wild type mice after experimentally-induced stroke [116–119]. Conversely, depletion of alkyladenine DNA glycosylase (Aag1/Mpg), has a protective effect after induced stroke/ischemia [112]. Loss of Aag1 caused reduced PARP1 activation and less NAD⁺ depletion. Moreover, at least after liver ischemic injury, the detrimental effects of Aag1 could be offset by Parp1 knockout, further supporting the idea that PARP1 activation was the key. Clearly more research is

necessary to understand whether and how BER capacity and activity influences stroke outcome; and also whether PARP1 inhibitors and exogenous NAD⁺ have potential therapeutic applications for stroke patients.

Vascular dementia is a type of cognitive impairment thought to be caused by vascular damage from small strokes [120], that may contribute to pathology in AD patients [121]. Examination of BER null mice brains for small strokes and microvascular pathology may clarify the relationship between oxidative DNA damage and DNA repair in onset and progression of neurodegenerative disorders and AD.

PERSPECTIVES

Extensive experimental evidence suggests that oxidative stress, mitochondrial dysfunction, and persistent DNA damage play roles in onset and progression of human neurodegenerative disease. Although we do not yet understand in detail how tissue- and organelle-specific BER affects the risk of neurodegenerative disease, it is a subject of much research. Several promising but preliminary studies in this research area are mentioned briefly below; we also list significant roadblocks and bottlenecks inhibiting research in the field, and new research ideas relevant to BER related neurological disease.

Behavioral studies in Neil1 deficient mice revealed specific impairment of some memory functions, and defects in olfaction[119, 122]. As discussed earlier, the level of NEIL1 appears to be significantly lower in AD brain than in normal brain[122]. It is interesting to note that a poor sense of smell is considered an early sign of risk for cognitive decline and AD [123]. These results suggest a possible role for NEIL1 in brain homeostasis. It will be interesting to perform similar studies on mice lacking other DNA glycosylases as well as to examine other sensorineural functions in Neil-1 deficient mice. Notably, CSB deficient mice are defective in sensorineural hearing[60], which is considered to be a feature of normal aging in humans.

Post-mortem human brains are a very valuable resource for studying human brain neurodegeneration. However, many questions cannot be addressed using such tissue, nor can they be addressed by descriptive retrospective studies of diseased and normal brains. For example, it has been proposed that BER dynamics may modulate susceptibility to neurodegenerative disease. Such dynamics can only be addressed currently in animal- or cell-based model systems. If one proposes to study quantify or characterize specific BER enzyme functions in post-mortem brain, the amount of tissue available can be prohibitively small. For example, it is a big challenge to get enough and highly purified material to study mtBER activity in postmortem brain tissue [87]. Alternative approaches could include future use of induced pluripotent stem cells (iPSCs), where such cells could even carry putative AD susceptibility alleles. This technique has been successfully used to study sporadic and familial AD [124]. Future use of this technology could make it possible to test the hypothesis that BER capacity correlates with risk for neurological dysfunction.

Expression of BER proteins varies by brain region, brain cell type, and fluctuates with age[125]. BER imbalance can generate DNA repair intermediates that are mutagenic and

cytotoxic [126], and contribute to oxidative stress-induced neuronal loss [127]. *Caenorhabditiselegans* and *Drosophila melanogaster* might provide model systems to explore whether and how BER imbalance influences neurological function and animal behavior.

It has been proposed that somatic mutational load may correlate with susceptibility to neurodegenerative disease, possibly because somatic mutations can give rise to mutated proteins [128], activate the cellular DNA damage response and lead to apoptotic cell death. Because BER capacity appears to be lower in mitochondria than in the nucleus, lesions in mtDNA could persist longer and have more deleterious consequences than lesions in the nuclear DNA. Thus, quantitative analysis of steady state level of mtDNA damage is a critical area of future study. New technologies or established technology with improved sensitivity and specificity (i.e., liquid chromatography-tandem mass spectrometry) may help advance such studies [129].

Recent studies suggest that CSB modulates mitophagy (i.e., autophagic removal of damaged mitochondria) [130], and it has been suggested that persistent PARP1 activity, NAD⁺ depletion and mitochondrial dysfunction may contribute to pathology in XPA, ATM and CS [59]. We proposed that this reflects nuclear mitochondrial signaling mediated by PARYlation. This idea was tested by treating *C. elegans* and mice with exogenous NAD⁺ or PARP inhibitors, which seemed to restore mitochondrial function and mitigate other disease symptoms in these animal model systems[60]. As mentioned earlier in this review, additional study of exogenous NAD⁺ and PARP inhibitors as therapeutic agents for neurodegenerative diseases is warranted.

Alzheimer's disease is a major social and medical challenge. Our understanding of disease progression is limited and no effective treatments are yet available [131]. Studies discussed in this review[81–85, 91]support the notion that oxidative stress as well as deficient repair of oxidative damage contribute to the pathology of AD. Useful insight might emerge from experiments in which different DNA repair deficient genotypes were crossed into representative AD mouse models, followed by phenotyping of double heterozygotes or double heterozygous mice. Phenotyping should investigate physiological and behavioral characteristics of the novel mice strains as well as DNA repair capacity in brain and other tissues. Tau phosphorylation and pathology is associated with oxidative stress and possibly with mitochondrial function (reviewed in [132]). It would be of interest to explore whether there is a connection with DNA repair processes in mitochondria and Tau pathology. While a BER defect may not be the causative issue in AD, deficient BER may promote the progression of the disease [94], and thus be a significant risk factor in AD.

In our opinion, BER is a worthy target for interventions (Table I) but we also recognize that BER is a highly regulated and coordinated process. Thus, it is unlikely that overexpression of any one BER enzyme in an unregulated manner would be beneficial, even in BER deficient cells [133]. Furthermore, there is no general agreement as to which step of BER is rate-limiting; and the rate-limiting step of BER might be different in different cellular microenvironments, tissues or organelles. Another approach worthy of consideration might be to indirectly stimulate BER by modulating rates of protein ubiquitination [134, 135]or by

expressing regulatory microRNA species in a controlled manner[136]. Additionally, the identification and manipulation of microRNAs that regulate multiple proteins in the pathway could represent another means of upregulating the entire pathway.

Acknowledgments

We thank Dr. Mimi Sander, Page One Editorial Services for editing. We thank Thomas Wynn for assistance with graphics. We to thank Drs. Evandro Fang and Beverly Baptiste for critical comments on the article. This research was supported in part by the Intramural Research Program of the NIH, National Institute on Aging.

ABBREVIATIONS

AD	Alzheimer's Disease
AMP	Adenosine monophosphate
AOA1	Ataxia with oculomotor apraxia 1
APE-1	AP endonuclease 1
APP	Amyloid precursor protein
APTX	Aprataxin
ATM	Ataxia telangiectasia mutated
BER	DNA base excision repair
CS	Cockayne syndrome
CSB	Cockayne syndrome group B protein
DDR	DNA damage response
5'-dRP	5'-Deoxyribose phosphate
DSB	DNA double-strand breaks
HD	Huntington's Disease
Lig III	DNA ligase III
MCI	Mild cognitive impaired
MCSZ	Microcephaly, early-onset seizures and developmental delay
mtBER	Mitochondrial base excision repair
mtDNA	Mitochondrial DNA
NAD	Nicotinamide adenine dinucleotide
NEIL1	Endonuclease VIII-like
NER	Nucleotide excision repair

OGG1	8-oxoguanine DNA glycosylase
PARP1	Poly(ADP)ribose polymerase 1
PARylation	Poly(ADP-ribosyl)ation
PD	Parkinson's Disease
PNKP	Polynucleotide kinase phosphatase
Polβ	DNA polymerase β
PSEN	Presenilin
RNA Pol	RNA polymerase
ROS	Reactive oxygen species
SCAN1	Spinocerebellar ataxia with axonal neuropathy
SSB	DNA single-strand break
TDP1	Tyrosyl-DNA phosphodiesterase 1
TOPO1	Topoisomerase I
UNG	Uracil-DNA glycosylase
XRCC1	X-ray repair cross-complementing protein 1

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Figure 1.

DNA Base Excision Repair Pathways. Base excision repair (BER) can begin with the recognition of a damaged base by a DNA glycosylase, an AP site by APE1, or a single-strand break by end-processing proteins. BER can proceed via incorporation of a single nucleotide (short patch, SP), or by incorporation of two or several nucleotides (long patch, LP). Red rings around proteins denote that they are lethal if knocked out in mice. Black ring around multiple glycosylases denote that these proteins are non-lethal when knocked-out in mice. Mutations in TDP1, APTX and PNKP are associated with the following human diseases: Spinocerebellar ataxia with axonal neuropathy (SCAN1), Ataxia with oculomotor apraxia 1 (AOA1) and Microcephaly, seizures and developmental delay (MCSZ) and are noted on the figure.

Base Excision Repair is a Central Player

Figure 2.

Base Excision Repair is a Central Player. The proteins involved in base excision repair (BER) are denoted. Arrows indicate significant BER protein or pathway associations with other pathways, features or endpoints.

Table I

Points of Intervention

Up-regulation	Down-regulation
DNA glycosylases	PARP1
DNA polymerase β	
DNA ligase III	
NAD ⁺ levels	NAD ⁺ consumption