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REPAIR MECHANISMS FOR OXIDATIVE DNA DAMAGE

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TABLE OF CONTENTS

1. ABSTRACT

Reactive oxygen species are formed as by-products of mitochondrial aerobic respiration, as induced products upon exposure to certain environmental/exogenous agents (e.g. ionizing radiation), or as intended products during the immune response against invading foreign microbes. Although serving as essential signaling molecules in certain biological processes (e.g. during gene activation responses), these chemicals, particularly during oxidative stress when at excessive concentrations, can react with cellular components, most notably DNA, and in this capacity, promote mutagenesis or cell death, and in turn, human disease. We review here several of the common oxidative DNA damages as well as the DNA repair mechanisms related to maintaining genome integrity, and thus, preventing cancer formation and age-related disease. We focus mainly on participants of the base excision repair (BER) pathway. In brief, the steps of BER include: (a) excision of the damaged base, (b) incision of the DNA backbone at the apurinic/apyrimidinic (AP) site product, (c) removal of the AP terminal fragment, (d) gap-filling synthesis, and (e) ligation of the final nick.

2. INTRODUCTION

The "oxygen paradox" is that while humans require oxygen for existence, it may very well be the by-products of oxygen that lead to our demise. More specifically, humans consume oxygen during mitochondrial aerobic respiration to generate essential energy (ATP) through a series of molecular reduction reactions. During this metabolic process, by-products, known collectively as reactive oxygen species (ROS; also referred to as free radicals), are produced. ROS are also formed following exposure to certain lifestyle/environmental agents, e.g. alcohol, cigarette smoke, a high fat diet, chlorinated drinking water, pesticides, ozone and nitric oxide from automobile emissions and diesel exhaust particles, heavy metals such as mercury, cadmium, and lead, and ultraviolet and ionizing radiation (1). In addition, as a component of the immune defense response, phagocytic cells, namely activated neutrophils and macrophages, release a transient burst of reactive oxygen and nitrogen chemicals that make up a cytotoxic arsenal against invading organisms (2). In total, these reactive byproducts, particularly when exceeding defendable concentrations, have the ability to attack most cellular constituents, including carbohydrates, lipids, proteins and DNA. If such cellular damage goes un-repaired, it can promote cancer, neurodegenerative disorders, atherosclerosis, rheumatoid arthritis, and ischemia/reperfusion injury, and likely contribute to the aging process (3-6).

The most prominent of the ROS are superoxide, hydrogen peroxide, and hydroxyl radical. Of specific interest here, reactions of these chemicals (or their metabolites) with DNA can lead to the formation of several oxidative damage intermediates, including modified bases, apurinic/apyrimidinic (AP) sites and atypical single strand breaks. If such damage persists, it can promote unwanted genetic change, which can in turn lead to cell death or cancer formation. Thus, to avert such deleterious outcomes, organisms have evolved multiple repair systems to restore DNA back to its unmodified state. The major pathway for correcting oxidative DNA damage is base excision repair (BER). This process involves the cooperative interaction of several proteins that work sequentially to excise the target damage and restore DNA back to its original form. In this review, we cover the main

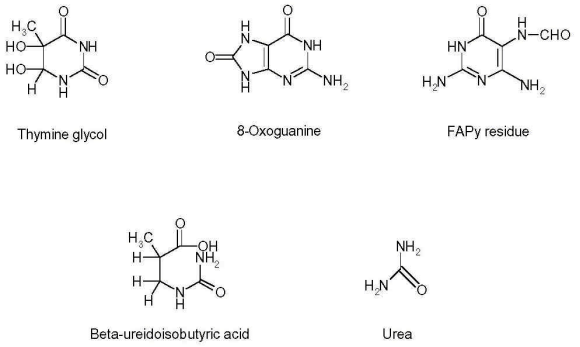

Figure 1. The Chemical Structure of Several Oxidized Base Damages. The names and corresponding chemical composition of five DNA base damages discussed in the text are shown. For a more comprehensive review of the gambit of oxidized base modifications see (38), (198) and (39).

types of oxidative DNA damage and the specific repair machinery for such damage. We focus mainly on the current understanding of the mammalian DNA repair systems, highlighting the lower eukaryotic and bacterial systems where beneficial.

3. OXIDATIVE DNA DAMAGE

3.1. Base modifications

There have been at least 24 base modifications related to free radical attack of DNA that have been identified to date. Of these, 8-hydroxyguanine (7,8-dihydro-8-oxoguanine; 8-oxoG) and thymine glycol (5,6-dihydro-5,6-dihydroxythymine; TG) have received the most attention (Figure 1), primarily due to their quantitative prominence and biological impact. We cover here the details of these two lesions, and mention a few other base damages that have potential mutagenic or cytotoxic consequences.

8-oxoG results from hydroxyl radical attack of the 8th position of the imidazoyl ring on guanine. Since 8-oxoG is one of the most abundant and highly mutagenic base lesions, it is often used as a molecular marker for oxidative stress (7). Experimental estimates have suggested that this base modification is present anywhere from 400 to 400,000 sites/cell under normal physiological conditions, with the lower end of this steady-state estimate likely being more accurate (reviewed in (8)). NMR (9,10) and X-ray crystallographic (11,12) studies reveal that 8-oxoG in the anti confirmation forms a "normal" Watson-Crick base pair with cytosine, causing little or no disruption to the overall B-form structure of duplex DNA. 8-oxoG can, however, assume a syn conformation and form a Hoogsteen base pair with adenine, providing the structural basis for the G:C to T:A transversions commonly associated with this base modification. Fourier transform-infrared spectroscopy and molecular dynamics simulations have revealed that 8-oxoG promotes unique local dynamics in duplex DNA, a feature that may be relevant to the biochemical and biological handling of this lesion (13-15). Mutational bypass studies using both bacterial and mammalian proteins indicate that, in general, replicative DNA polymerases (e.g. mammalian POLα and POLδ) tend to incorporate dATP opposite 8-oxoG, while repair polymerases (e.g. mammalian POLβ) favor dCTP insertion opposite this damage (16). More recent studies using error-prone human bypass polymerases (specifically, POLκ, POLμ, REV1, POLι, POLη and POLζ) have found that, depending on the polymerase employed, either an A or a C is preferentially inserted opposite the base lesion (17-21) although a deletion typically occurs with POLμ (22). However, it should be noted that for mutagenic lesions that can be readily bypassed during replication, such as 8-oxoG, error-prone DNA polymerases are not likely to be invoked. Instead, their services are thought to contribute primarily to the "successful" bypass of replication blocking lesions, such as TG (see below).

TG is the most common thymine lesion generated by exogenous oxidizing agents, such as hydrogen peroxide and ionizing radiation, and is formed at a spontaneous rate similar to or marginally higher than that of 8-oxoG (23). NMR studies (24), in agreement with subsequent molecular dynamics simulations (25), indicate that TG induces a significant, localized distortion in duplex DNA; the TG base is mainly accessible to the solvent (and thus other molecules) and appears to be largely extrahelical. It is this gross structural perturbation that presumably causes TG to serve as a replication block to DNA polymerases, resulting in a low mutagenic potential. Yet, in certain sequence contexts, TG is bypassed by particular DNA polymerases (26,27). Still, the TG lesion is generally thought to be cytotoxic, killing the cell by blocking DNA replication and creating DNA double strand breaks. Recent data indicate that the error-prone human bypass polymerase, POLκ, preferentially inserts adenine opposite TG; yet, upon extension of the "correct" A:TG base pair, misincorporation occurs more frequently beyond the site of the lesion (28). It is likely that the lesion-specific mutational pattern in human cells will be dictated by the "selected" bypass polymerase and thus the cellular environment at a given time (29).

Some other oxidative base lesions shown to be potentially mutagenic or to block the progress of DNA polymerases *in vitro* deserve mention as well (Figure 1). In particular, formamidopyrimidine (FAPy) residues formed from adenine and guanine are products of the direct action of ionizing radiation or from the indirect action of hydroxyl radical (23). *In vitro* bypass studies using a proofreading-deficient Klenow fragment found that the unsubstituted (i.e. non-methylated) FaPy-G lesion produces a significant amount of promutagenic FaPy-G:A base pairs, while FaPy-A increases the misinsertion frequency of A more modestly (30,31). The N-methylated analogues of FaPy-A and FaPy-G were found to be significant replication blocks *in vitro*, and thus are presumably cytotoxic (32). *In vivo* studies using the unsubstituted lesions have not yet been reported, and as a result, their biological effects are less well understood. Urea, another common base damage, is formed when an oxidized thymine residue undergoes fragmentation of the thymine ring structure. Like sites of base loss (discussed below), this product results in a lack of

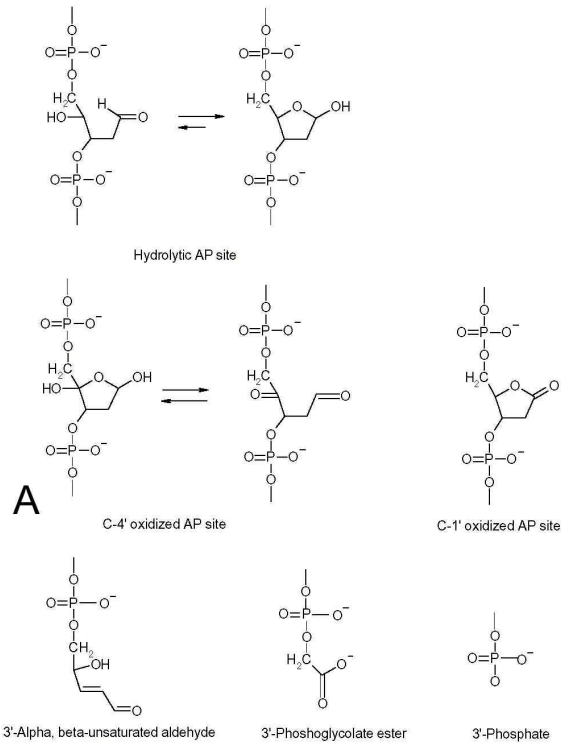

Figure 2. The Chemical Structure of Several AP Lesions and 3'-Blocking Termini. (A) Hydrolytic ("Natural") and Oxidized AP Sites. Where relevant, ring-opened and ring-closed versions are shown; the arrow indicates the relative amount. C-1' oxidized AP sites are also known as 2-deoxyribonolactone residues, and C-4' oxidized AP lesions are also called 2-deoxypentos-4-ulose residues. (B) Deoxyribose 3'-Strand Break Products. The α,β-unsaturated aldehyde is the β-elimination product of a bifunctional DNA glycosylase, while the phosphoglycolate and phosphate termini are typically generated by free radical attack of DNA. A 3'-phosphate end can be formed by some DNA glycosylases. See text for further details.

coding and stacking capacity (33). Thus, when encountered by a DNA polymerase, this lesion blocks DNA synthesis, and as such, is thought to be lethal (34). The final base lesion addressed here is *ß*-ureidoisobutyric acid. This oxidative lesion, a ring-opened product of dihydrothymine, is a potent blocker of DNA polymerases *in vitro* and *in vivo* (35). As seen with many replication-blocking lesions, *in vivo* studies have demonstrated that bypass of *ß*-ureidoisobutyric acid can occur in SOS-induced *E. coli* (i.e. where translesion, error-prone bypass synthesis is activated), with a base pairing preference of A>G>T. Consequently, under such stress-response conditions, this base modification can result in T to A transversions (27,36). To date, the bypass efficiency and mutational specificity of most of the 15 currently known mammalian DNA polymerases has yet to be determined for many of the identified base damages (37). This type of analyses will ultimately require both purified protein constituents and defined damage-containing DNA substrates. For more complete information on the greater than 24 oxidized base modifications, particularly the cytosine and adenine lesions, see two other review articles (38,39).

3.2. Deoxyribose products

AP sites (Figure 2A) form spontaneously at a rate of ~10,000 events per mammalian genome per day under normal physiological conditions, simply due to the intrinsic chemical instability of DNA (23). In addition, certain base modifications (from oxidation, deamination or alkylation) promote hydrolysis of the N-glycosylic linkage or are substrates for repair glycosylases, which excise target bases from DNA (see below). It is well documented that AP sites, which lack the instructional information of the base, impede RNA and DNA polymerases, and can therefore lead to abortive transcription/replication or to error-prone bypass synthesis (reviewed in (40,41)). Thus, such lesions represent both cytotoxic and mutagenic non-coding damages if unrepaired. In general, AP sites, as determined by NMR and molecular dynamics simulations, (a) induce little change in the basic cononical form of B-DNA, (b) promote some degree of sequence-specific conformational modification, including base extrusion and DNA collapsing, and (c) create a localized region of increased backbone flexibility (reviewed in (41,42)).

In addition to "natural" (i.e. hydrolytic) AP lesions, ROS, or more specifically hydroxyl radicals, can abstract a hydrogen atom from either the C-1' or C-4' position of the ribose ring to generate oxidized AP sites (Figure 2A). At present, limited information is available on the precise structural or biological impact of these chemical forms of AP sites, but they appear to serve as cytotoxic or mutagenic precursors *in vivo* (reviewed in (43,44)).

Another product resulting from hydroxyl radical attack of the sugar moiety is the "blocking" terminus. In particular, oxidation of C-4' results in the fragmentation of the deoxyribose, causing strand cleavage and the formation of a 3'-phosphate or a 3'-phosphoglycolate ester (Figure 2B). Such lesions, which block normal DNA polymerase or DNA ligase activity (as they lack the required 3'-hydroxyl group), are frequently formed following exposure to ionizing radiation (reviewed in (45,46)) or the anti-tumor drug bleomycin (reviewed in (47)). It has been reported that under normal physiological conditions roughly 25% of chromosomal strand break ends are refractory to polymerase extension or DNA ligation, seemingly due to the presence of 3'-blocking damages (48). Persistence of these termini would presumably lead to cell death or the promotion of gross chromosomal aberrations. For a more thorough description of the many oxidized sugar damages see the review of Dizdaroglu *et al.* (39).

4. REPAIR MECHANISMS FOR OXIDATIVE DNA DAMAGE

4.1. Repair of base damages

The cytotoxic or mutagenic potential of DNA damage depends on the repair capacity of the cell. That is, cells with inadequate repair will experience persistent DNA damage, which in turn can promote genetic mutation or cell

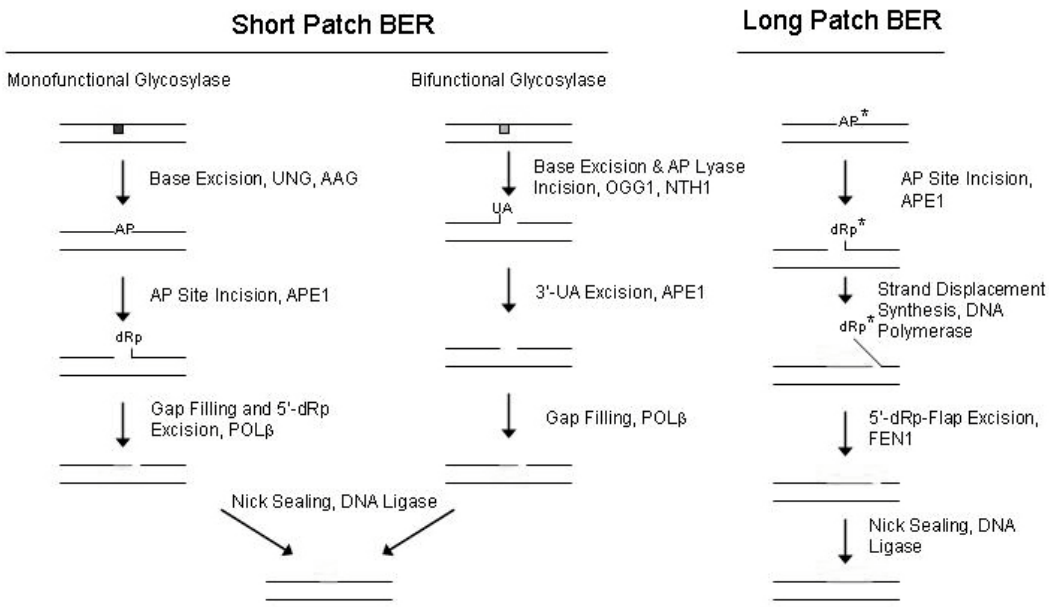

Figure 3. The Pathways of Mammalian Base Excision Repair. Short-patch (single nucleotide incorporation) and long-patch (repair synthesis that typically involves 2-7 nucleotides) BER pathways are shown. Short-patch can proceed by either a monofunctional or bifunctional DNA glycosylase-initiated event. Regardless, APE1, and presumably POLβ, function centrally to complete the process. In long-patch BER, either POLβ or a PCNA-dependent DNA polymerase (i.e. POLε or POLδ) executes strand displacement synthesis. FEN1 then excises the 5'-flap DNA intermediate. It appears that LIG3 (likely in a complex with XRCC1) operates more prominently in short-patch BER, while LIG1 functions more in long-patch BER. UNG and AAG stand for uracil DNA glycosylase and alkyl-adenine DNA glycosylase, respectively, enzymes that have not been reviewed here. For more complete overviews of mammalian BER and these DNA glycosylases see (199-204). The "*" indicates an AP site that is a poor substrate for the dRp lyase activity of DNA POLβ, e.g. one that is reduced, and is likely repaired by a strand displacement (long-patch) mechanism. UA = α,β-unsaturated aldehyde.

death. Damage-induced mutations at loci that regulate cell growth or differentiation can ultimately affect the organism's natural biology, and thus promote disease. To alleviate the potentially mutagenic or cytotoxic effects of base modifications, such as 8-oxoG and TG, cells possess DNA glycosylases that remove substrate bases. These enzymes initiate BER by hydrolyzing the N-glycosidic bond that links the target base to the deoxyribose sugar (Figure 3). In brief, the steps of BER include: (a) excision of the damaged base, (b) incision of the DNA backbone at the AP site product, (c) removal of the AP terminal fragment, (d) gap-filling synthesis, and (e) ligation of the final nick. We describe here the major, and in some cases alternative, repair mechanisms in mammals for the common oxidative DNA damages described above.

8-oxoG glycosylase (OGG1), which falls into the helix-hairpin-helix (HhH) superfamily of DNA binding proteins, is the major enzyme in humans responsible for the repair of 8-oxoG in nonreplicating DNA, i.e. when the lesion is positioned opposite a cytosine (49,50). OGG1 exists primarily in one of two isoforms (which arise from alternative splicing): a smaller α form (~39kDa; also known as type 1a) localized predominantly in the nucleus or a ß form (~47kDa) found primarily in the inner membrane of the mitochondria (51,52). Nuclear OGG1, which retains the same active site core found in the mitochondrial protein but a different C-terminal end, is a bifunctional DNA glycosylase, meaning it not only excises the substrate base, but incises the DNA backbone 3' to the resulting AP site via an AP lyase activity that involves a β-elimination reaction (49). This latter catalytic step generates a single strand break with a non-conventional 3'-α,ß unsaturated aldehyde (Figure 2b) and a normal 5'-phosphate residue (Figure 3; repair of atypical 3'-ends is discussed below). In addition to 8-oxoG, OGG1 has also been shown to remove FaPy-G residues from DNA, but not FaPy-A or 8-oxoA (50). The X-ray structure of the catalytic core of hOGG1 bound to 8-oxoG:C DNA reveals that this enzyme, like most, if not all DNA glycosylases, acts on single-base lesions by employing an extrahelical repair mechanism (also known as "base flipping") ((53) and references within). The bound DNA substrate is sharply bent about 70° away from the enzyme and the 8-oxoG base is fully extruded from the helix into the active-site specificity pocket of the enzyme. In humans, there is evidence suggesting that inactivation of OGG1 may be one step in the multistage process of carcinogenesis. Specifically, the OGG1 gene is located on chromosome 3p25, a region frequently lost in certain cancers, particularly lung and kidney tumors (reviewed in (54)). Moreover, the tumor suppressor gene p53, which is commonly inactivated during the process of carcinogenesis, frequently undergoes GC to TA transversions, a pattern consistent with 8-oxoG-directed mutagenesis. Nonetheless,

a conclusive link of mutations/genetic variation in OGG1 with cancer is lacking.

Animals deleted for OGG1 are viable, yet accumulate elevated levels of 8-oxoG in their mitochondrial and nuclear genomes, an amplification that amasses through age (55-57). However, despite this increase in 8-oxoG, OGG1-deficient mice exhibit only a moderately elevated spontaneous mutation rate in nonproliferative tissues. Moreover, these animals do not develop malignancies or show any marked pathological changes. While extracts prepared from OGG1 null mouse tissues were found not to exhibit excision activity for 8-oxoG, there was slow removal of this damage from proliferating cells *in vivo*. These findings suggested that in the absence of OGG1 (in apparent contrast to bacterial and yeast cells), an alternative mechanism exists to preserve a low endogenous mutation frequency and minimize the effects of an increased load of 8-oxoG.

While human OGG1 is homologous to the OGG1 protein in yeast and other members of the HhH superfamily, it is unrelated at the primary amino acid sequence level to Fpg (MutM), the major enzyme for the removal of oxidized purines in bacteria. Instead, three new human gene products have been identified based on their homology to members of the helix-two-turns-helix-containing Fpg/Nei class of proteins (58-61) – we note here that Nei (originally termed Ogg2) is a backup enzyme to Nth in bacteria (see below for more discussion), removing many of the same lesions, as well as displaying a low but detectable activity for 8-oxoG (62,63). These Fpg/Nei-like enzymes, termed NEIL1, NEIL2 and NEIL3, are primarily nuclear proteins (although some mitochondrial localization cannot be excluded), capable of excising oxidized base lesions from DNA. Specifically, NEIL1 efficiently removes 5-hydroxycytosine, 5-hydroxyuracil, FaPy and 8-oxoG base products, and like OGG1, exhibits preferential activity on 8-oxoG:C base pairs relative to 8-oxoG:A. NEIL2 is distinct from NEIL1 in that it exhibits negligible activity for 8-oxoG, but instead prefers ROS-generated cytosine derivative base damages, with highest activity for 5-hydroxyuracil, the deamination product of 5-hydroxycytosine. Both NEIL1 and NEIL2 are capable of incising at natural AP sites via a β,δ-elimination reaction (the first mammalian enzymes to be shown to do so), producing a single strand break with a nucleotide gap flanked by 3' and 5' phosphate residues. While the reported biochemical characterization of NEIL3 is limited to this point, the protein contains putative PCNA and RPA-binding motifs, implying a function intimately coordinated to DNA replication. Based on their gene expression patterns, NEIL1 appears to be a ubiquitous caretaker enzyme, likely providing the backup activity alluded to above for OGG1 (64), whereas NEIL2 (skeletal muscle and testis) and NEIL3 (thymus and testis) appear more tissue-restricted in their biological function. Studies to examine the *in vivo* contributions of these three mammalian enzymes are currently underway.

As noted earlier, upon replication past an unrepaired 8-oxoG residue, an A can readily be inserted opposite the base damage. This 8oxoG-A base pair, while not an effective substrate for OGG1, is capably recognized by the MYH DNA glycosylase (an *E. coli* MutY homolog) in humans (65-68). MYH excises A from the 8oxoG-A base pair, permitting the opportunity for insertion of C opposite 8-oxoG upon subsequent repair synthesis, and ultimately the preservation of genetic integrity (reviewed in (69)). MYH is also capable of removing premutagenic 2-hydroxyadenine residues from DNA (70) and may have a weak AP lyase activity (69). The N-terminal 225 amino acid residues of *E. coli* MutY (and presumably hMYH) show structural similarity to the catalytic core of human OGG1 and to the members of the HhH superfamily. Moreover, the C-terminal domain of the *E. coli* MutY protein determines the 8-oxoG specificity and has sequence and structural similarity to MutT, an enzyme that hydrolyzes 8-oxo-dGTP in the nucleotide pool to 8-oxo-dGMP via its nucleoside triphosphatase activity, preventing incorporation into the genome (71,72). As with several of the mammalian DNA glycosylases, alternative splicing appears to give rise to both nuclear and mitochondrial forms of MYH, however, the specifics of this issue are still under investigation (reviewed in (73)). Biochemical and co-localization studies suggest that MYH is intimately connected to the DNA replication machinery, primarily via interactions with PCNA, RPA and certain mismatch repair proteins (74-76). Recent variation studies have found a link of inherited mutations in the *MYH* gene to cancer predisposition, specifically adenomatous polyposis (77), the first definitive association found between a consensus BER gene and a human disease. Last, it is noteworthy that MYH, in combination with OGG1 and MTH (a *E. coli* MutT homolog), comprise what is referred to in *E. coli* as the "GO model" (78), a complex defense system that has presumably evolved to counteract the mutagenic potential of 8-oxoG.

In humans, oxidatively damaged pyrimidines such as TG are excised mainly by NTH1 (an *E. coli* EndoIII homolog). NTH1 also excises urea, 5-hydroxycytosine, 5-hydroxy-6-hydrothymine, 5,6-dihydroxycytosine, 5-hydroxyuracil and 5-formyluracil with varying efficiencies from DNA, and exhibits a β-elimination AP lyase activity (79-82). Like OGG1 and MYH, NTH1 belongs to the HhH superfamily of enzymes, and appears to be present in both nuclear and mitochondrial forms, perhaps localizing more so to the nucleus (51,83,84). Homozygous NTH1 mutant mice show no detectable phenotypical abnormalities, even out to 2 years, and embryonic cells with or without wild-type mNTH1 show no difference in sensitivity to the oxidizing agents menadione and hydrogen peroxide (64,85,86). Given these findings, it was not surprising that biochemical analysis of tissue extracts from mNTH1(-/-) mice revealed the existence of at least two additional enzymatic activities capable of cleaving DNA at sites of TG. More detailed analysis found that, in contrast to NTH1, which is most active against TG:A relative to TG:G, one of these activities was more efficient at removing TG when paired with G than A. Studies by Yasui and colleagues suggest that this major back-up activity belongs to the ubiquitously expressed NEIL1 enzyme (see above), which removes TG

and 5-hydroxyuracil in double- and single-stranded DNA more efficiently than 8-oxoG (64). In recent years, the overlap of DNA repair proteins/systems has become a reoccurring theme, and in part, may explain the lack of phenotypic response seen with some of the single DNA repair gene knockouts, particularly the glycosylases.

4.2. Repair of AP lesions

To combat the deleterious effects of AP damage, cells have evolved enzymes termed AP endonucleases that initiate repair of these lesions by incising the DNA backbone 5' to the AP site (reviewed in (41,87,88)). Such proteins have been divided into two families based on their homology to either *E. coli* exonuclease III or *E. coli* endonuclease IV. In mammals, only homologs to exonuclease III have been identified, with the major human AP endonuclease being APE1. This protein, which accounts for >95% of the total cellular AP site-specific incision activity in mammalian cell extracts (89), displays structural similarity to the non-specific endonuclease DNase I, ionositol polyphosphate 5-phosphatases, and sphinglomyelinases, proteins that comprise a superfamily of phosphohydrolases containing a four-layered α/β sandwich motif (90). "Natural" AP sites (Figure 2a), formed by spontaneous or chemical-induced hydrolysis of the N-glycosylic bond or as intermediates during glycosylase-initiated BER, are recognized and incised 5' to the lesion by APE1 in a Mg^{2+}-driven catalytic reaction, producing a nick with a 3'-hydroxyl group and a 5'-deoxyribose phosphate (a dRp group) (Figure 3). APE1 also incises efficiently at C-1' and C-4' oxidized AP sites (91,92) (Figure 2a). APE1 appears to be a structure-specific endonuclease (41). Following AP site incision, mammalian BER is then directed into one of two sub-pathways (short patch or long patch BER), but in general, involves gap filling, termini processing and ligation of the final nick (Figure 3). *In vitro* reconstitution studies indicate that APE1 is a primary coordinator of BER, communicating with several downstream protein factors, and in this capacity, regulating overall repair efficiency and sub-pathway selection (93-96). Another factor that influences sub-pathway choice is the initiating DNA glycosylase, and data also suggests that long-patch BER may be linked to DNA replication (97).

Mammalian cell biology studies indicate that reduction of APE1 by anti-sense RNA expression renders cells hypersensitive to both alkylating and oxidizing agents (98,99). Consistently, blastocysts from null APE1 embryos display increased sensitivity to ionizing radiation (100). APE1 heterozygous mutant cells/animals are also abnormally sensitive to increased oxidative stress, further supporting a role for this enzyme in protection against oxidative damage (101). Overexpression studies, while indicating that APE1 is not likely rate-limiting in the repair of oxidative DNA lesions, suggest – in support of prior biochemical results (102) – that APE1 may protect against the cytotoxic effects of chain-terminating nucleoside analogs frequently used in anti-cancer or anti-viral treatment schemes (103). Along these lines, *in vitro* studies have indicated a selective role for APE1 in the removal of 3'-mismatches (104,105). A more precise picture of the biological importance of the various *in vitro* biochemical activities of APE1 awaits the creation of a genetically-defined mutant cell line. As is the case for many DNA repair proteins, current efforts around APE1 involve defining the contribution of variation in the gene (and mild reductions in overall function) to disease susceptibility in the human population (reviewed in (106-108)). It is worth noting that, in addition to the many DNA metabolic activities described within, APE1 exhibits a function to modulate the DNA binding activity of several oncoproteins, namely p53, FOS and JUN. This activity, which resides in the N-terminal region of APE1 and is largely separable from its nuclease functions, may have an important role in regulating DNA damage response networks, not covered here. For a thorough review of the redox regulatory function of APE1, readers should refer to a recent review (109).

A second human protein was recently identified that shares amino acid sequence homology to *E. coli* exonuclease III and APE1. This protein, termed APE2, however, has been found to display poor AP endonuclease and 3'-repair diesterase (see below) activities, as assessed by *in vitro* biochemical assays and *in vivo* functional complementation experiments (110). This finding has raised the question of whether APE2 contributes to the repair of DNA damage *in vivo* or functions more prominently in a yet unidentified biological process (105). Perhaps consistent with this notion, computational studies have found that APE2 is a member of the α/β sandwich-containing superfamily, which as noted above, includes enzymes such as sphinglomyelinases and inositol 5'-phosphatases, phosphohydrolases that display a distinct substrate specificity from AP endonucleases. Nonetheless, yeast genetic studies targeting the human APE2 counterpart (termed Eth1 or Apn2 in *S. cerevisiae*) have indicated a significant, albeit largely redundant, role in repairing AP lesions and perhaps more so oxidative DNA strand breaks (111-113). The specific *in vivo* contributions of mammalian APE2 await the design and characterization of a genetically-defined mutant cell line. Human APE2 contains a functional proliferating cell nuclear antigen (PCNA)-binding motif in its C-terminal region, and laser scanning immunofluorescence microscopy of HeLa cells indicates that both APE2 and PCNA form foci in the nucleus, with some being co-localized (114). Last, while APE1 and APE2 appear to be predominantly nuclear, there is evidence suggesting a mitochondrial function for both (110,114-116).

4.3. Processing of non-conventional termini and repair of single-strand breaks

Biochemical studies indicate that, in addition to a powerful hydrolytic AP site incision activity, APE1 also possesses a 3'-phosphodiesterase activity for phosphate and phosphoglycolate damages (117-122). However, this 3'-repair activity has been estimated to be at best ~1/100th of its AP endonuclease function. To define more thoroughly the potential role of APE1 in the removal of 3'-blocking lesions, the ability of APE1 to excise phosphoglycolates was measured in a variety of structural contexts (121). APE1 was found to be most effective at removing 3'-

phosphoglycolates from single nucleotide gaps, less efficient at removing phosphoglycolates from nicks, blunt ends or 3'-recessed ends, and incapable of excising phosphoglycolates from single stranded DNA or 3'-overhangs; a similar pattern of specificity has been observed for its relatively weak, albeit significant, 3' to 5' exonuclease activity (DMWIII, unpublished results). Studies have found that APE1 can also excise the 3'-α,β unsaturated aldehyde products formed by bifunctional DNA glycosylases, e.g. OGG1 and NTH1 (see above) (55,123). Thus, as both the major AP endonuclease, and a contributor to atypical single strand break processing, APE1 appears to be central to BER, regardless of the pathway selected (Figure 3), perhaps explaining the inviability of the animal knockouts (100,124).

While APE1 may contribute to the repair of some 3'-damages (such as those at single strand breaks) – consistent with the fact that APE1-depleted cells exhibit hypersensitivity to oxidizing agents (see above) – there are presumably additional processing mechanisms for 3'-damages, particularly those at DNA double strand break ends. Karimi-Busheri *et al.* (125) and Jilani *et al*. (126) have identified a human gene that encodes a protein exhibiting 3'-phosphatase activity, as well as a 5'-OH DNA kinase activity; the protein does not excise 3'-phosphoglycolates (127). Known as PNK, this 57 kDa protein is a prominent contributor to the excision of 3'-phosphate damages in both single and double strand break contexts (128,129). Significantly, PNK has also been shown to interact with a number of proteins participating in BER, namely X-ray cross-complementing gene 1 (XRCC1), POLβ, and Ligase 3 (LIG3) (128); these proteins are described in more detail later. To date, mammalian cell biology studies indicating a specific role for PNK in oxidative DNA damage repair have not been reported. However, mutant studies in yeast point toward a prominent contribution for the gene equivalent in protecting against the cytotoxic effects of hydrogen peroxide, bleomycin, and ionizing radiation (130,131).

Mammalian cell extract fractionation experiments suggested as many as four unique 3'-damage excision activities (89,132). With this knowledge in mind, Povirk and colleagues searched for additional 3'-damage processing enzymes and discovered that human TDP1, a tyrosyl-DNA phosphodiesterase, makes up the major excision activity for 3'-phosphoglycolate residues from single-stranded oligomers and 3'-overhangs (127) – a pattern complementary to that of APE1's (see above). Notably, TDP1 was originally identified for its ability to release covalently linked Topoisomerase I-DNA intermediates, such as those formed during DNA relaxation (133). However, since, *S. cerevisiae* TDP1 has been shown genetically to function as a back-up enzyme to APN1 and APN2 (the two major yeast AP endonuclease/3'-repair diesterase proteins) in the repair of bleomycin-induced DNA damage, i.e. likely the removal of 3'-phosphoglycolates (134). Following excision of the 3'-DNA intermediate, TDP1 leaves behind a 3'-phosphate group, which appears to be a substrate for PNK (127,130). As with PNK, the contribution(s) of mammalian TDP1 to oxidative DNA damage repair awaits the creation of a defined mutant cell line. A presumed loss-of-function mutation in *TDP1* has been associated with spinocerebellar ataxia with axonal neuropathy (SCAN1; (135)).

Recent studies have begun to elucidate the potential roles of other 3' to 5' exonucleases (136) in 3'-damage repair. For instance, despite initial conflicting reports (137,138), a recent finding argues that TREX1 (also named DNase III) does not excise 3'-phosphate or phosphoglycolate residues from DNA (139). An independent study has found, however, that TREX1 can remove 3'-α,β unsaturated aldehyde products from BER-type DNA intermediates (140). The exonuclease activity of the WRN protein has been found to be unhindered by a 3'-phosphate group, suggesting that WRN can remove such 3'-blocking lesions (141). WRN mutant cells are also mildly hypersensitive to the oxidizing agents 4-nitroquinoline 1-oxide and ionizing radiation, suggesting a role in oxidative DNA damage repair (reviewed in (142)). For additional proteins reported to display 3' to 5' exonuclease activity (136), such as p53, MRE11, hRAD1, hRAD9 and the DNA polymerase editing subunits, 3'-damage excision has not been specifically assayed, and thus their precise contributions (if any) to this process remain unclear. To date, other than APE1, the relationship of PNK, TDP1 or the other enzymes described here to the 3'-repair activities identified in the fractionation experiments alluded to above remains unknown. It is worth noting that yeast mutant studies indicate a back-up role for the RAD1/RAD10 (in humans XPF/ERCC1) and MUS81/MMS4 3'-flap structure-specific endonuclease complexes in processing 3'-blocking lesions (134,143,144).

5'-abasic termini, such as those created by APE1 incision at hydrolytic AP sites (see above), are processed by dRp excision enzymes. The most prominent of these, particularly in the context of BER, is POLβ, the major mammalian gap-filling DNA repair polymerase (reviewed in (145)). POLβ exhibits a dRp lyase activity for 5'-natural AP sites, forming a transient Schiff base protein-DNA covalent intermediate during the catalytic excision process (146). Other polymerases, such as POLλ, POLι, and the mitochondrial protein POLγ, have also been shown to possess dRp removal activities, and therefore may operate as redundant or specialized factors in 5'-abasic residue repair (147-149). POLβ is also a major contributor to the removal of 5'-oxidixed AP termini (150), removing 5'-C-4'-oxidized AP lesions efficiently from DNA (91). However, following APE1 incision at a C-1' oxidized AP site (2-deoxyribonolactone), POLβ forms an undesirable stable covalent protein-DNA crosslink with the 5'-sugar product (92). While it seems reasonable to predict that FEN1, a 5'-flap structure-specific endonuclease (Figure 3), would be responsible for the repair of such lesions, Demple and colleagues reported that FEN1 was unable to remove this 5'-POLβ-DNA intermediate. Future studies aimed at defining the biochemical steps for removal and repair of these intermediates is a priority.

Other contributors to single strand break repair include XRCC1, poly ADP-ribose polymerase (PARP1),

and the DNA Ligases, LIG1 and LIG3. Thompson and colleagues identified XRCC1 (and several other repair-related genes) during a generalized hunt for Chinese hamster ovary (CHO) mutant cells that exhibit high sensitivity to ionizing radiation or the alkylating agent ethyl methanesulfonate (reviewed in (151)). It was subsequently shown that cells harboring XRCC1 mutations display enhanced sensitivity to several strand break-inducing DNA-damaging agents, abnormally high levels of single-strand breaks, increased spontaneous and induced chromosome aberrations, and a severely elevated sister chromatid exchange frequency. The encoded XRCC1 protein, while possessing no known catalytic activity, contains two BRCA1 carboxyl-terminal (BRCT) protein interaction domains critical to the biology of this factor. Most notably, mutations that lead to a reduced XRCC1 protein level, concomitantly lead to a reduced LIG3 level, apparently by disrupting an important *in vivo* stabilizing interaction mediated through their BRCT domains (152). Based on reported physical and/or functional interactions with APE1, PNK, POLβ, PARP1, and LIG3, known participants in the BER process (Figure 3), XRCC1 has been proposed to serve as a scaffolding factor to facilitate efficient single strand break repair (reviewed in (153)). Consistent with this model, NMR studies have identified structural features in the N-terminal domain of XRCC1 that permit gap- and nick-specific DNA binding (154). As with many of the central participants in BER (155), XRCC1-/- animals are inviable, suggesting an essential role in embryogenesis (156). Recent studies have begun to associate common polymorphic variants in the human XRCC1 gene with both reduced (i.e. a protective effect) and increased disease susceptibility (reviewed in (106-108)).

PARP1 is responsible for executing post-translational modification of proteins in response to endogenous and environmental genotoxic agents that generate DNA strand breaks (reviewed in (157,158)). Specifically, PARP1, a highly abundant 113 kDa nuclear protein (present at an estimated 10^6 molecules per cell), rapidly detects and binds single and double strand breaks through two zinc-finger motifs located in its N-terminus (reviewed in (159)). This binding event activates its poly ADP-ribose polymerase activity ~500-fold, and using NAD+ as a substrate, PARP1 reversibly poly(ADP)ribosylates (with chain lengths up to 200 units) target proteins, particularly itself (its so-called "automodification" function). The resulting negatively charged PARP1 molecule then dissociates from DNA, permitting completion of the DNA damage response. PARP1 is subsequently "reactivated" for DNA binding by poly(ADP-ribose) glycohydrolase, which catalyzes poly(ADP-ribose) catabolism. This rapid cycling of PARP1 is critical in regulating the repair or cell death responses to DNA strand breaks. With that said, a specific biochemical role for PARP1 in DNA repair remains controversial and undefined (notwithstanding the activities described above). For instance, while several studies indicate that exposure to PARP1 inhibitors (e.g. 3-amino-benzamide), *in vivo* expression of a dominant-negative PARP1 fragment, or mutations in the endogenous *mPARP1* gene render cells hypersensitive to both alkylating and oxidizing agents (160-164), an independent study found that PARP1-/- embryonic fibroblasts repaired BER-type methylation damage normally (165). This latter result appears consistent with biochemical studies demonstrating that repair of gamma irradiated or alkylated DNA proceeds efficiently independent of PARP1 status (166-168). However, again, not all results concur (169), and a recent crosslinking study has found PARP1 to be a major mammalian protein bound specifically to a BER-type DNA strand break intermediate (170). While the reason(s) for the apparent discrepancies remain unknown, it has been proposed that the genetic background of the organism studied, the assays employed, or the interpretation of the results, have contributed to the disparities (158,171). Regardless, it is generally accepted that PARP1 acts as a major "nick sensor" which functions to maintain genome integrity, a conclusion supported by the fact that PARP1-impaired cells display an increased frequency of DNA strand breaks, recombination, gene amplification, micronuclei formation and sister chromatid exchange. Based on recent PARP1 overexpression experiments, in conjunction with comparative work showing a link between high cellular poly(ADP-ribosyl)ation capacity and long life span, a picture is emerging where PARP1 behaves as a regulatory factor in tuning the rate of genomic instability events to a level appropriate for the longevity potential of a given organism or species (reviewed in (157)).

In the past few years, several other candidate poly(ADP-ribose) polymerases have been identified (172). Notably, only PARP1 maintains the DNA binding and automodification domains, suggesting that this protein is specific for the DNA strand break response. Nonetheless, as seen with PARP1, PARP2 has been shown to interact with XRCC1, POLβ, and LIG3, suggesting a function in BER (173). Furthermore, the phenotype of the *PARP2* null cells in terms of DNA damaging agent sensitivity is essentially the same as *PARP1* null cells, suggesting a role for the former in DNA repair, potentially as a heterodimer with PARP1 (173). Studies are ongoing to define the precise biochemical and cellular contributions of the members of this emerging family of "polymerases".

In any DNA repair process, the final step, nick sealing or DNA end joining, is executed by a DNA ligase. In base excision or single strand break repair, the major contributing ligases are LIG1 and LIG3 (reviewed in (174)). This conclusion stems in part from the findings that LIG3 interacts with XRCC1 (see above), and LIG1 associates with POLβ (175) and PCNA (176,177). Cappelli *et al* found that CHO cells deficient in both XRCC1 and LIG3 display a partial defect in single nucleotide replacement BER, linking these two proteins to the short-patch pathway (178). Work of Tomkinson and colleagues likewise argues that LIG3 operates primarily in short-patch BER, while LIG1 functions more prominently in long-patch repair. In these studies, extracts from 46BR.1G1 cells, derived from a patient displaying immunodeficiency, stunted growth and sun sensitivity, and later shown to be mutated in LIG1, are found to be defective in long-patch BER, but normal in the short-patch pathway (179). For a more thorough description of the mammalian DNA ligases, readers are referred to recent reviews (180,181).

Table 1. The Major Repair Proteins for Oxidative DNA Damage

Common Name	Gene Name[1]	Additional Names	Protein	Amino Acid Length of Predominant Isoform (predicted molecular weight in kDa)	General Summary
OGG1	OGG1	HMMH, MUTM, OGH1, HOGG1	8-oxoguanine DNA glycosylase	345 (38.7)	Member of the HhH superfamily. Major mammalian excision enzyme for 8-oxoG:C base pairs. Exhibits both glycosylase and AP lyase (β-elimination) activities. Alternative splicing of the C-terminal region of this gene classifies splice variants into two major groups, type 1 and type 2, depending on the last exon. Type 1 alternative splice variants end with exon 7 and type 2 end with exon 8. All variants share the N-terminal region. Many alternative splice variants for this gene have been described, but the full-length nature for every variant has not been determined. The N-terminus of this gene contains a mitochondrial targeting signal, essential for mitochondrial localization.
NEIL1	NEIL1	NEI1, HFPG1, HNEH1	nei endonuclease VIII-like 1	390 (43.7)	Member of the helix-two-turns-helix Fpg/Nei family. Likely the major backup activity for NTH1 and OGG1, with preferential excision of TG, and 8-oxoG opposite C. Possesses both glycosylase and β,δ-elimination AP site incision activities.
NEIL2	NEIL2	HNEH2	nei-like 2	332 (36.8)	Member of the helix-two-turns-helix Fpg/Nei family. Displays glycosylase activity mainly for cytosine derivative base damages, and exhibits β,δ-elimination AP site incision activity.
NEIL3	NEIL3	HFPG2	nei-like 3	605 (67.9)	Member of the helix-two-turns-helix Fpg/Nei family. Biochemistry poorly understood presently, but NEIL3 is potentially linked to the replication machinery.
MYH	MUTYH		mutY homolog	546 (60.1)	Member of the HhH superfamily. Major DNA glycosylase for excising adenosine from 8oxoG-A base pairs. Intimately connected to proteins functioning in DNA replication. MYH, OGG1 and MTH make up the participants of the "GO model", a defense system for the mutagenic effects of 8-oxoG.
NTH1	NTHL1		nth endonuclease III-like 1	312 (34.4)	A member of HhH superfamily. Major activity for the excision of oxidized pyrimidines, such as TG, and exhibits a β-elimination AP lyase activity.
APE1	APEX1	APE, APEN, APEX, HAP1, REF1	apurinic/ apyrimidinic endonuclease	318 (35.6)	The predominant class II AP endonuclease in mammals. Cleaves the phosphodiester backbone 5' to both hydrolytic and oxidized AP sites. Selective activity on 3'-damages, including phosphate and phosphoglycolate groups, as well as 3'-mismatches. Poor 3' to 5' exonuclease. Also functions to regulate the DNA binding activity of several oncoproteins, most notably p53, FOS and JUN, via redox-dependent and -independent mechanisms. In this context, may have a role-dependent cellular localization (117).
APE2	APEX2	XTH2, APEXL2	apurinic/ apyrimidinic endonuclease 2	518 (57.4)	A protein shown to have a weak class II AP endonuclease activity. Most of the encoded protein is located in the nucleus, in some instances co-localized with sites of PCNA, but is also present in the mitochondria. In vivo contributions of APE2 remain unclear.
PNK	PNKP		polynucleotide kinase 3'-phosphatase	521 (57.1)	PNK exhibits both 5'-DNA kinase and 3'-phosphatase activities. A prominent factor in the repair of 3'-phosphate damage in both single and double strand break contexts.
TDP1	TDP1	SCAN1	tyrosyl-DNA phosphodiesterase 1	608 (68.4)	The major activity for removing 3'-phosphoglycolate lesions from single stranded DNA. Yeast TDP1 was first identified as a protein that hydrolyzes the phosphodiester bond linking a tyrosine residue to a 3' DNA end (126). This type of linkage is formed as a covalent protein-DNA intermediate following strand cleavage by topoisomerase I, during the process of DNA relaxation. Upon removing 3'-protein or 3'-phosphoglycolate damages, TDP1 leaves behind a 3'-phosphate residue.
POLβ	POLβ		polymerase (DNA directed) beta	335 (38.2)	DNA polymerase β is the major gap-filling DNA polymerase. Also exhibits dRp lyase activity for hydrolytic and C-4' oxidized 5'-abasic residues. Can function in both short and long-patch BER synthesis.
FEN1	FEN1	MF1, RAD2	flap structure-specific endonuclease 1	380 (42.6)	A member of the XPG/RAD2 endonuclease family. FEN1 is the major activity for removing 5' overhanging flaps formed during DNA repair (e.g. long-patch BER) and recombination, as well as processing the 5' ends of Okazaki fragments in lagging strand DNA synthesis. One of ten proteins essential for cell-free DNA replication.
XRCC1	XRCC1		X-ray repair cross complementing protein 1	633 (69.5)	Contributes to the efficient repair of DNA single-strand breaks formed by ionizing radiation or alkylating agents, presumably by binding DNA nicks and gaps. Interacts with DNA ligase III, polymerase β, PNK and poly (ADP-ribose) polymerase to participate in BER, and likely serves as a scaffolding protein. No known enzymatic activity.
PARP1	ADPRT	PARP, ADPRT1	poly(ADP-ribosyl)transferase poly(ADP-ribose) synthetase	1014 (113.1)	Poly(ADP-ribosyl)transferase is a chromatin-associated enzyme, which modifies various nuclear proteins by poly(ADP-ribosyl)ation. This modification activity is dependent on DNA and regulates various important cellular processes such as differentiation, proliferation, tumor transformation and molecular events involved in the recovery of the cell from DNA damage. The precise biochemical role for PARP1 in BER is unclear.
LIG1	LIG1		DNA ligase I	919 (101.7)	Functions mainly in DNA replication, but can operate in BER, as an ATP-dependent DNA ligase. Mutations in LIG1 that lead to DNA ligase I deficiency result in immunodeficiency and increased sensitivity to DNA-damaging agents (46BR).
LIG3	LIG3		ligase III, DNA, ATP-dependent	922 (102.7)	Ligase III is more closely related to the DNA ligase encoded by pox viruses, than to replicative DNA ligases, such as mammalian DNA ligase 1. Appears to be more involved in DNA repair and recombination. Two biochemically distinct isoforms of ligase III, α and β, encoding polypeptides with different C-terminal amino acids have been identified, and result from alternative splicing of precursor mRNA. Only the longer α isoform stably interacts with XRCC1. The β form appears meiotic-specific.

Note: proteins such as RPA, PCNA, POLε and POLδ have been excluded from the list. [1] As defined by LocusLink.

5. CLOSING CONSIDERATIONS

It is important to keep in mind that oxidative DNA damage and oxidative effects are most likely manifested during periods of oxidative stress, that is, when ROS concentrations have exceeded the normal cellular tolerance and repair mechanisms. One important element of this equation not covered in this review is the preponderance of cellular enzymes or scavenger proteins involved in "neutralizing" ROS *in vivo*, known collectively as the antioxidant defense team (182). Representative members include superoxide dismutase, catalase, and glutathione peroxidase. In addition, it should be emphasized that, while oxidative stress is often undesirable due to the associated cellular damage generated, ROS are also important constituents of many vital biological processes. This fact is perhaps best exemplified by cellular events involving gene activation and cellular proliferation, where ROS act as critical signaling molecules (4). As noted earlier, ROS also serve as important cytotoxic agents in the immune response against invading microorganisms (2). Thus, in total, the maintenance and regulation of cellular ROS homeostasis within the host is central to the "good, bad and ugly" of these reactive chemicals. Since nearly all ROS are generated by oxidative phosphorylation at the site of mitochondria, and since mitochondrial defects occur in a wide variety of degenerative diseases, aging and cancer (183), it is presumed that this cellular compartment has evolved effective means to tolerate the comparatively high levels of lipid, protein and DNA damage that occur. We direct the reader to several recent reviews that have nicely covered in detail the topic of mitochondrial DNA repair (184-186).

We have detailed above the major mammalian repair responses for several common oxidative DNA damages (summarized in Table 1). In recent years, the concept of redundancy and of general tolerance (i.e. bypass synthesis) has gained significant appreciation. As described above, DNA glycosylases have overlapping substrate specificities. In addition, other DNA repair pathways, most notably nucleotide excision repair, have been found to exhibit corrective activity for simple oxidation products, such as TG, 8-oxoG and AP sites (187,188). Mismatch-deficient mouse cells exhibit higher than normal levels of steady state 8-oxoG damage, suggesting a role for this corrective system in the repair of 8-oxoG lesions (189). In fact, the human mismatch repair complex, MSH2 and MSH6 (also known as MutSα), has been shown to specifically bind 8-oxoG-containing DNAs (190). Last, yeast genetic analyses indicate that error-prone translesion synthesis and recombination pathways can also "process" spontaneous and oxidative DNA damages, namely AP lesions (191).

When discussing DNA repair, it is important to consider protein-protein and protein-DNA interactions involved in coordinating the players of the pathway. In BER, to mediate damage-specific recognition, many of the enzymes induce a conformational strain on their target DNA substrate. This structural alteration permits stable protein-substrate complex formation, and often facilitates the establishment of the transition state catalytic intermediate. Following catalysis, many of the BER proteins form stable enzyme-product complexes, which help coordinate the next step in the process by generating a more favorable binding target for the subsequent participant in the pathway. This phenomenon, known as "passing of the baton" (reviewed in (192,193)), describes the choreography observed between APE1 and POLβ, and may explain some of the proposed glycosylase-APE1 interactions. Additionally, auxiliary factors not typically thought of as part of BER, including but not limited to XPG, CSB and certain heat shock proteins (HSP), may have roles in affecting BER kinetic efficiency (194-196). Given these complex protein interaction networks, the future for *in vitro* biochemical analyses will be to integrate more complete reconstituted systems, which incorporate even higher-order chromatin structures. Recently reported nucleosome studies involving BER (197) represent an initial step towards understanding a broader spectrum of protein organization and may inevitably reveal other "non-intuitive" factors that influence the *in vivo* kinetics of BER and other DNA repair pathways.

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Abbreviations: Reactive oxygen species, ROS; apurinic/apyrimidinic, AP; base excision repair, BER; 8-hydroxyguanine or 7,8-dihydro-8-oxoguanine, 8-oxoG; thymine glycol or 5,6-dihydro-5,6-dihydroxythymine, TG; formamidopyrimidine, FAPy; helix-hairpin-helix, HhH; 5'-deoxyribose phosphate, dRp group; proliferating cell nuclear antigen, PCNA; Chinese hamster ovary, CHO

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