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Base Excision Repair and Cancer

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Abstract

Base excision repair is the system used from bacteria to man to remove the tens of thousands of endogenous DNA damages produced daily in each human cell. Base excision repair is required for normal mammalian development and defects have been associated with neurological disorders and cancer. In this paper we provide an overview of short patch base excision repair in humans and summarize current knowledge of defects in base excision repair in mouse models and functional studies on short patch base excision repair germ line polymorphisms and their relationship to cancer. The biallelic germ line mutations that result in MUTYH-associated colon cancer are also discussed.

1. Overview of the Base Excision Repair Pathway

Base excision repair (BER) repairs the majority of endogenous DNA damages including deaminations, depurinations, alkylations and a plethora of oxidative damages, a total of about 30,000 per human cell per day [1]. BER is a highly conserved system from bacteria to humans (for reviews see [2-8]) and is characterized by five distinct enzymatic reactions (for reviews see [3,9-11]) (Figure 1). The first step in BER is recognition and removal of an altered base by a DNA glycosylase that cleaves the N-glycosyl bond releasing the damaged base. If the enzyme is monofunctional, an abasic site results, which is subsequently recognized and cleaved by an apurinic endonuclease (APE1) which leaves 3' OH and 5' deoxyribose phosphate (5'dRP) termini (for a review see [12]). The 5'dRP at the nick is removed by the lyase activity of DNA polymerase β (Pol β) [13,14]. If the glycosylase is bifunctional, its associated lyase activity cleaves the DNA backbone and leaves either an α,β -unsaturated aldehyde (PUA) or a phosphate group attached to the 3' end of the break [15,16]. α,β unsaturated aldehydes are removed by the diesterase activity of APE1 to create a 3' hydroxyl substrate for Pol β [17]. If a phosphate group is left on the 3' end, it is removed by the phosphatase activity of polynucleotide kinase (PNKP) [18]. In short patch BER, also known as single nucleotide BER, DNA Pol β inserts the missing base [19,20]

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with the resulting nick sealed by DNA ligase III complexed to XRCC1 (for a review see [21]). XRCC1 is a non-enzymatic scaffold protein for BER [22] and has been shown to interact with a number of the BER proteins [23-25].

In long patch BER, a polymerase (β , δ , ϵ) fills in the one base gap and keeps synthesizing DNA while displacing the DNA downstream of the initial damage site, creating a flap of DNA. Pol β has been shown to be necessary for this step and possesses strand displacement synthesis activity [26]. FEN1 then removes this flap from the DNA, leaving behind a nick in the DNA [27] and 2-13 nucleotides are removed from the original site of damage. The choice of whether repair is accomplished via short or long patch BER mainly depends on whether the abasic sugar is oxidized or reduced, as Pol β cannot eliminate a modified sugar [28]. If the 5' sugar is modified, it is not removed by Pol β and long patch BER is initiated [28-31]. After initial strand displacement synthesis by Pol β , several additional nucleotides are added. It has also been shown that XRCC1 and LigIII α may play a role in switching between short and long patch BER [32,33]. Under conditions of low ATP concentration, strand displacement synthesis by Pol β can be stimulated by XRCC1/LigIII α . In addition, there is extensive evidence in mammalian cells that the BER enzymes interact with each other as well as other proteins that promote recruitment of downstream BER components and coordination of the BER process (for a review see [34]).

This review will focus on short patch BER with emphasis on mouse models and human germ line and tumor variants. The role of polymorphisms in DNA BER genes in disease susceptibility has recently been discussed in a number of excellent reviews (for example see [35-44]).

2. The uracil/thymine processing glycosylases: UNG, SMUG, TDG and MBD4

Uracil arises in DNA from misincorporation of dUMP from the nucleotide pools and by deamination of DNA cytosine; mispaired thymine is formed by deamination of methylcytosine. The deamination products are highly mutagenic since they would now pair with A instead of G. In fact, the first BER enzyme discovered by Tomas Lindahl some thirty-five years ago was *Escherichia coli* uracil glycosylase, the enzyme that removes deaminated cytosines and misincorporated uracils from DNA [2]. In humans (for reviews see [45,46]), the *UNG* gene encodes a nuclear version of uracil glycosylase, UNG2, whose primary role is to remove misincorporated uracils [47-49], and a mitochondrial version, UNG1. In addition, UNG2, as well as a second uracil glycosylase, SMUG1, excises uracils that arise from deamination of cytosine [49,50]. SMUG1 can also remove 5-hydroxymethyluracil from DNA [51]. UNG2 also plays a major role in somatic hypermutation and class switch recombination [52]. Both UNG1 and SMUG1 are members of the UDG superfamily which have similar structural motifs [53-55]. The structure of SMUG1 shows it to have a more invasive interaction with the DNA duplex disrupting more than one base pair [56].

Humans contain two mismatch DNA glycosylases, TDG and MBD4, that remove thymines from thymine:guanine mismatches arising from deamination of methyl cytosine. TDG has a strong preference for uracil over thymine and MBD4 removes uracil and thymine resulting from deamination of CpG and methylated CpG, respectively [57]. TDG is also a member of the UDG superfamily [55]. The crystal structure of human TDG has been recently solved [58-60]. Interestingly, unlike its bacterial homologs, human TDG contains an insertion loop that contributes to its CpG sequence specificity [60]. TDG has recently been implicated in the active demethylation process that takes place during development [61]. 5-methylcytosine (5-meC) can be converted to 5-hydroxymethylcytosine (5-OHmeC) by the ten eleven

translocation (Tet) family of dioxygenases. 5-meC and 5-OHmeC can be further oxidized to 5-carboxylcytosine by TET and recognized and removed by TDG [61,62]. MBD4, also called MED1, contains two domains, one that recognizes methylated and hemimethylated CpG and the other that contains glycosylase activity that removes G mispaired with T. The glycosylase domain of MBD4 is homologous to the helix-hairpin-helix superfamily of DNA glycosylases [57,63]. The methyl-CpG binding domain consists of a compact α/β fold with an extended loop between two anti-parallel β strands that inserts into the major groove containing methyl-CpG sequences conferring specificity [64,65]. MBD4 has also been suggested to play a role in active demethylation. In this case an AID deaminase converts 5-MeC to thymine which is then removed by MBD4 or TDG (for a review see [66]). All of the glycosylases in the UDG superfamily are monofunctional.

2.1 Mouse models for the uracil/thymine processing glycosylases

For the most part mice nullizygous for a single glycosylase exhibit very few phenotypes which is in contrast to the severe phenotypes associated with the enzymes downstream from the DNA glycosylases (for reviews see [67,68]). Many of the DNA glycosylases exhibit broad and/or overlapping substrate specificities and thus can compensate for one another. For example, Ung deficient mice exhibit a mild increase in spontaneous mutation frequency [48] which is in keeping with the presence of a second major uracil DNA glycosylase, Smug1. In *Ung*^{-/-} mice there was a 1000-fold increase in DNA uracil compared to wild type probably due to incorporation of dUMP which pairs correctly [48]. Ung deficient mice also display an increased incidence of spontaneous B cell lymphomas during old age consistent with the role of Ung in somatic hypermutation and class switch recombination [69]. In keeping with this, a deficiency of human UNG is associated with impaired class-switch recombination [52]. *Mbd4*^{-/-} mice generated by a targeted allele replacement were viable and fertile but exhibited an increase of C→T transitions at CpG sites [70]. When crossed with cancer-prone *Apc* heterozygotes, the *Mbd4*^{-/-} mice showed accelerated tumor production with CpG→TpC mutations in *Apc* [70].

A recent study has found that, unlike mice nullizygous for other DNA glycosylases, nullizygous *Tdg*^{-/-} mice are embryonic lethal which is apparently associated with an epigenetic defect that affects expression of developmental genes [71]. Tdg appears to initiate BER in response to aberrant *de novo* methylation [71].

2.2 Polymorphisms in the UNG superfamily and cancer

To date there have only been two *UNG* gene mutations that have been associated with cancer. The first, UNG Arg88Cys, is a polymorphism that was found in the germline of a family with colorectal cancer [72], and the second, an UNG Gly143Arg mutation, was found in a sporadic glioblastoma [73]. A number of sequence variants of UNG were studied in a variety of cell lines but none showed a significant decrease in uracil glycosylase activity [74]. Gastric cancers were of particular interest in this study since genetic instability has been observed in the region of *UNG* (12q24.1) [75], but again no defect was observed [74]. Recently germ line polymorphisms in SMUG1 were examined in over 1000 cases of breast cancer and 2000 cases of age and race matched controls. Two polymorphisms in the SMUG1 promoter region were found to moderately affect the risk of breast cancer in heterozygotes carrying them [76]. Interestingly, the DNA in individuals homozygous for these variants exhibit increased levels of uracil [77].

The human thymine DNA glycosylase, TDG, maps at chromosome 12q22-q24.1 which is also associated with a high loss of heterozygosity in gastric cancers [75]. However, none of the tumor samples analyzed showed a mutation in the coding sequence of the remaining TDG allele [75]. Two other polymorphic variants of TDG, G199S and V367M, were looked

at with respect to lung cancer risk and no statistically significant associations were found [78].

Frameshift mutations in *MBD4* have been identified in Japanese gastric cancers [79] and polymorphisms of the *MBD4* gene have also been linked to the risk for primary lung cancer and esophageal squamous carcinoma in a Chinese population [80,81]. A recent study showed that the Glu346Lys polymorphism was significantly associated with the risk of colorectal cancer [82]. However, the same study found no association between the frameshift mutations in the *MBD4* gene and gastric and colorectal cancers [82]. In an Australian study of hyperplastic polyposis syndrome four patients were found to be heterozygous for the *MBD4* Ala273Thr variant [83]. Interestingly, a study designed to predict survival from non-small cell lung carcinoma found that combining SNPs in six DNA repair genes including the *MBD4* Glu346Lys variant, provided significant prognostic markers for clinical outcome [84].

3. MPG: Methylpurine DNA glycosylase

3-Methylpurine DNA glycosylase (MPG), also known as AAG (alkyladenine DNA glycosylase), recognizes and removes a broad spectrum of alkylated bases including not only 3-methyladenine [85], but guanines methylated at the N3 or N7 position [86-89], etheno adenine and guanine [90,91], hypoxanthine [92] and 8-oxoguanine [93] as well as other alkylated and oxidized DNA substrates [94]. MPG/AAG is a monofunctional glycosylase. Although human MPG/AAG has a similar broad substrate specificity to bacterial and yeast AlkA, they are not structurally related [95] with AlkA being a member of the HhH superfamily that includes the glycosylases NTH1 and OGG1. The MPG/AAG DNA glycosylase consists of a single mixed α/β domain that is different from the other glycosylases [95], but like AlkA, the active site is lined with aromatic amino acids for binding to the electron-deficient alkylated bases that it recognizes [95].

3.1 Mouse models for MPG/AAG

Two groups generated Mpg/Aag defective mice. In both cases the mice were viable and developed normally with the cells being moderately sensitive to alkylating agents and showing a significant reduction in the repair of 3-MeA but not 7-MeG [96,97]. Also, the Mpg/Aag-null mice, when treated with azoxymethane to induce alkylation damage or dextran sulfate to induce inflammation exhibit a higher frequency of colon cancer than similarly treated wild type mice [98]. Mpg/Aag deficient mice also show more severe gastric lesions than wild type after infection with *Helicobacter pylori* [99]. Interestingly, although most *Mpg/Aag* null cells are sensitive to alkylating agents [97,100], myeloid cells from *Aag*^{-/-} mice are more resistant [101]. It has been suggested that an imbalance of BER enzymes can cause more damage once repair by MPG/AAG is initiated because the resulting AP sites would be lethal if there was not sufficient APE1 to continue the BER process [101,102].

3.2 MPG/AAG polymorphisms and cancer

Although most studies show no association between MPG/AAG polymorphisms and cancer risk [72,103,104], one patient with lung cancer had the MPG Arg55Cys polymorphism variant [105] and another patient with osteosarcoma was heterozygous for a SNP upstream of *MPG* [106].

4. Repair processing of 8-oxoguanine: OGG1 and MUTYH

Guanine has the lowest redox potential of any base in DNA and therefore it is readily oxidized to 8-oxoguanine. 8-Oxoguanine is recognized and removed by OGG1 when it is

paired with cytosine [107-112]. OGG1 also removes FapyG and 8-oxoA from DNA [113-116]. OGG1 is a member of the HhH family of DNA glycosylases which contains an HhH motif followed by a GlyPro-rich loop and a conserved aspartic acid which initiates a nucleophilic attack on the epsilon amino group of a conserved lysine. It then attacks the anomeric carbon and releases the free base. The Schiff base intermediate results in strand cleavage. Thus OGG1 is bifunctional. OGG1 has been crystallized, unliganded and bound to an 8-oxoG:C containing DNA [117,118]. In addition to the two alpha-helical domains common to all superfamily members, a third antiparallel beta sheet, which is found in *E. coli* AlkA is also found in OGG1. OGG1 is not cycle regulated and apparently scans the DNA for its oxidized purine substrates. If 8-oxoguanine (or FapyG) is encountered by a replication fork prior to repair, adenine is often inserted opposite the lesion by the replicative polymerase [119,120]. DNA glycosylase MUTYH can remove this adenine preventing mutation fixation [121-127]. The structure of the *E. coli* homolog of MUTYH, MutY, has been solved [128,129]. MUTYH is also a member of the HhH superfamily, but in addition to the HhH binding motif, it contains an iron sulfur cluster that is involved in DNA binding [130,131]. MUTYH is a monofunctional enzyme. OGG1 is the only human glycosylase that efficiently removes 8-oxoG from DNA and MUTYH is the only glycosylase that removes A incorporated opposite 8-oxoG, although the mismatch repair system is also able to remove this adenine [132-134].

4.1 Mouse models

Mice deficient in OGG are viable and fertile [135,136] although 8-oxoG lesions accumulate in the liver but not in other organs examined [137]. These increased levels are responsible for an elevated spontaneous mutation rate [135,136]. Also, when exposed to KBrO₃ [138] or UVB [139], the *Ogg*^{-/-} mice exhibited increased damage, mutations, and in the case of UVB, skin tumors.

MutY^{-/-} mice are also viable and healthy [140] but they have about a 2-fold increase in spontaneous mutation frequency in embryonic stem cells [141]. Again, there is an accumulation of 8-oxoG that seems to occur only in the liver [142]. In contrast to the single knockout *Ogg* and *MutY* mice, *Ogg*^{-/-}*Myh*^{-/-} double knockout mice exhibit a significantly increased tumor incidence with a higher frequency of lymphomas, lung and ovarian tumors compared to wild type and the single knockout mice [140].

4.2 OGG1 and MUTYH Polymorphisms and cancer

The most common polymorphic variant of OGG1, Ser326Cys, is observed at an average frequency in the population of approximately 32% and is the most well-studied variant of OGG1 (for recent reviews see [143,144]). There have been at least 100 published studies on this variant, most with marginally significant correlations with disease, and which will not be reviewed in detail here. Earlier reviews of the epidemiologic studies suggested that there was some evidence of risk for esophageal, lung, nasopharyngeal, oropharyngeal and prostate cancer related to the Ser326Cys polymorphism, but risk of breast cancer was not found [143,145-147]. There also appeared to be no risk of colon cancer associated with this variant [148]. A more recent meta-analysis [144] of OGG1 Ser326Cys and lung cancer risk concluded that individuals with the Cys/Cys genotype did not have a significantly increased risk of lung cancer compared to the Ser/Ser genotype. However, when the Asian population was separated out there did appear to be an increased risk for lung cancer among non-smokers with Cys/Cys and Ser/Cys genotypes compared to Ser/Ser [144], although others found an association with smokers [149]. The Cys/Cys genotype has also been shown to increase the risk of childhood leukemia [150] and renal cell carcinoma [151]. In addition, functional variations in the 5'UTR of OGG1 have been associated with an increased risk of breast cancer [152].

There have been a number of functional studies on the Ser326Cys variant. It does not have a major catalytic defect having a k_{cat} about 63% of wild type [153]. Other studies also showed the activity of the Ser325Cys variant to be less than that of the wild type protein [154,155]. In lymphocytes, the efficiency of removal of 8-oxoG by the variant was also similar to that of the wild type enzyme [156]. Several groups measured the ability of the OGG1 Ser326Cys variant to complement the high spontaneous mutation frequency observed in *E. coli fpg mutY* mutants. One group found no difference between the wild type and the variant in the ability to complement the phenotype [154] while another found the variant less able to suppress spontaneous mutagenesis in *E. coli* [157], and a third found the Ser326Cys variant less efficient in the repair of a plasmid containing 8-oxoG using a *SupF* forward mutation assay in human cells [158]. The Ser326Cys variant was shown to exhibit aberrant DNA binding probably involving dimerization [159] while oxidation of the Cys in the variant was shown to alter its repair competence [160,161]. It has also been suggested that the Cys substitution affects the nuclear localization of OGG1, possibly by altering its phosphorylation status [162].

The OGG1 Ile321Thr polymorphic variant was also found in the germline of one patient with colorectal adenomas and not in normal controls [163]. Two OGG1 polymorphic variants, Thr398Ser and Ser31Pro were observed in primary sclerosing cholangitis patients [164]. However, the Ser31Pro variant was found to have glycosylase and DNA binding activity similar to wild type [163,164].

In cancer cells, the OGG1 Arg154His mutation has been detected in one out of nine gastric cancer cell lines, Arg131Gln has been found in one out of forty human tumors, and Arg46Gln has been found in lung and renal tumors. All three of these have reduced glycosylase function [153,154,157,165,166].

In 2002 a British family was diagnosed with multiple colorectal adenomas and carcinomas but the family members lacked the inherited adenomatous polyposis coli (APC) gene defect ([167] and for reviews see [168-170]). When these investigators examined the tumors they found a high proportion of GC TA transversions in the *APC* gene [167], a signature of a defect in *MUTYH* (and OGG1), which removes adenine misincorporated opposite 8-oxoguanine or FapyG. It turns out that these patients have biallelic mutations in *MUTYH* and are predisposed to *MUTYH*-associated polyposis (MAP) [171]. MAP transmission occurs as an autosomal recessive trait with very high penetrance although the phenotype of MAP patients is closer to the attenuated form of the classic familial adenomatous polyposis, rather than the severe form [170]. Interestingly, most of the G T transversions observed in *APC* were at GAA sequences [167,172]. The *APC* gene contains 216 of these sequences where G→T transversions would lead to a truncated protein making it a particularly vulnerable target. In addition to mutations in the *APC* gene, individuals with serrated polyps had GC→TA transversions in *KRAS* in these polyps [173]. Although colorectal cancers predominate in MAP patients, a recent multicenter European study reported an excess of ovarian, bladder, and skin cancers with a trend towards an increased risk of breast cancers [174].

There are at least 30 mutations in the *MUTYH* gene that are predicted to truncate the protein including nonsense, small insertions and deletions and splice site variants. There are also well over 50 missense mutations of which over 30 have been observed in individuals with MAP. The most common missense variants found in MAP patients (about 70%) are Tyr165Cys and Gly382Asp (for locations of these variants see [168,169]). Interestingly, the *Bacillus stearothermophilus* Tyr88 corresponding to Tyr165 in *MUTYH*, is a wedge residue that intercalates 5' to the 8-oxoG in the DNA molecule and participates in the extrusion of the adenine into the active site pocket [129]. This residue corresponds to the phenylalanine

wedge amino acid in bacterial formamidopyrimidine DNA glycosylases (Fpg) that crystallographic studies have suggested intercalates adjacent to cytosine opposite the 8-oxoG and senses the differences in sugar pucker between 8-oxoG and G [175]. The same phenylalanine residue in Fpg has been shown in single molecule experiments to probe DNA for the lesion [176].

A number of assays have been used to assess the activity of the MUTYH variants (Table 1) including substrate binding and glycosylase assays [164,177-185] as well as the ability of the variants to complement the spontaneous mutation frequency of *E. coli mutY* mutants [177,180,182]. Using these assays, the human MUTYH variant, Tyr165Cys, was found to have little or no substrate binding [177,181,183] or glycosylase activity [182-185] and a greatly reduced ability to complement the increased spontaneous mutation frequency exhibited in *E. coli mutY* mutants [177,182]. Recently, the effect of expression of MUTYH variants in *Muty*^{-/-} mouse embryo fibroblasts on hypersensitivity to various stressors has been used to assess function and both the Tyr165Cys and Gly382Asp variants had severe defects [185].

The Gly382Asp variant is present in the C-terminal domain of MUTYH which shares homology with MutT. MutT hydrolyzes 8-oxodGTP into 8-oxodGMP thereby preventing its incorporation into DNA [186-188]. In MUTYH this domain has been shown to be important for 8-oxoG recognition [129,189,190]. When the corresponding *E. coli MutY* Gly253Asp variant was examined, it showed a loss of affinity to duplexes that had 8-oxoG rather than G which was similar to results observed with *E. coli MutY* that was truncated for the C-terminal domain [177]. The Gly253Asp variant of *E. coli MutY* also showed an 85% reduction in glycosylase activity and failed to complement the *mutY* mutator phenotype of *E. coli* [141]. In single turnover experiments the MUTYH Gly382Asp variant exhibited about 30-40% the activity of wild type and was able to partially suppress the spontaneous mutation frequency observed in *E. coli* mutants [182]. Other studies showed glycosylase levels to range from 15% to 50% [182-185] of wild type levels. In keeping with the *in vitro* studies, it was reported that MAP patients with homozygous Gly382Asp mutations and heterozygous Tyr165Cys/Gly382Asp mutations had a milder phenotype than homozygous Tyr165Cys patients [191].

A number of other MUTYH variants have been recently characterized (Table 1) and many were shown to have reduced 8-oxoG:A binding and glycosylase activity as well as a substantially reduced ability to suppress the spontaneous mutation frequency of *E. coli mutY* mutants. Thus there has been substantial progress in understanding which variants are nonpathogenic polymorphisms that are only coincidentally found in patients with MAP and which polymorphisms are functional. Also, several recent studies found a clear increase in colon cancer incidence in individuals with only a single germline MUTYH mutation [192-195].

5. Recognition of oxidized pyrimidines: NTH1, NEIL1, NEIL2 and NEIL3

There are four human DNA glycosylases that recognize oxidized pyrimidines and formamidopyrimidines and all are bifunctional. Human NTH1 appears to be a housekeeping DNA glycosylase that scans the DNA for these damages [115,196-200]. NTH1, like OGG1 and MUTYH, is also a member of the HhH superfamily [201], and like MUTYH, also contains an iron sulfur cluster [201]. NTH1 recognizes a fairly broad spectrum of oxidized pyrimidines.

In contrast to NTH1, the NEIL proteins appear to have specialized functions. NEIL1 is cell cycle regulated [202] and because NEIL1 binds to a number of replication proteins, it may be associated with the replication fork [18,203-205]. NEIL1 recognizes oxidized

pyrimidines, formamidopyrimidines (FapyG and FapyA) [202,206-216], spiroiminodihydantoin (SP) and guanidinohydantoin (Gh) [217,218]. The crystal structure of NEIL1 has been solved and is structurally related to its bacterial homologs although it contains a “zincless” finger used for binding rather than the prototypic family zinc finger [219]. NEIL2 recognizes the same lesions as NEIL1 but prefers them in single-stranded DNA [220,221]. Recent evidence showing that NEIL2 binds to RNA polymerase II and other transcription-associated proteins, suggests that NEIL2 may be associated with transcription [222]. NEIL3 has the same substrate specificity as NEIL2 [223] and in humans is found in the thymus and testis [224]. NEIL1 and 2 have a $\beta/6$ AP lyase activity which leaves a phosphate attached to the 3' side of the nick while NEIL3 has poor AP lyase activity that primarily cleaves the DNA backbone by β -elimination [223,225].

5.1 Mouse models for NTH and the NEIL glycosylases

Nullizygous mice have been generated for *Nth1* [226,227], *Neil1* [228] and *Neil3* [209,224]. Mice are viable, fertile and resemble wild type mice during the early stages of life [67] but most showed an increase in base lesions in the genomic DNA of targeted organs [226,229]. A number of the NEIL1 knockout mice, primarily males, developed symptoms of fatty liver disease and obesity similar to that of human metabolic syndrome [228]. These symptoms were attributed to accumulation of unrepaired damages in mitochondrial DNA. More recent studies have demonstrated that the *Neil1* mice are more susceptible to obesity because of lower tolerance for oxidative stress [230]. Although, with the exception of *Neil1*, there are no obvious phenotypes in nullizygous mice lacking a single oxidative DNA glycosylase, double knockout mice are tumor prone. *Nth*^{-/-}*Neil1*^{-/-} mice exhibit lung and liver tumors with a higher frequency compared to the single knockout mice [231].

5.2 Polymorphisms in NEIL1, NEIL2 and NEIL3 and cancer

There are a number of polymorphic variants of NEIL1, NEIL2 and NEIL3 in the SNP databases (see for example [44]). The Gly83Asp NEIL1 polymorphic variant has been found in two patients with cholangiocarcinoma [164]. The Gly83Asp variant shows reduced base excision activity on double stranded DNA with altered AP lyase activity [164,232]. However, this variant was able to remove bases from single stranded DNA with wild type efficiency [164]. A NEIL1 Glu181Lys variant was also observed in a patient with primary sclerosing cholangitis but the protein was insoluble upon expression in bacteria [164]. Two rare NEIL1 variants, Pro208Ser and Arg339Gln, were found in patients with colorectal adenomas but the Arg339Gln variant was also found in a normal control [163]. Neither of these variants was characterized functionally. Three other variants of NEIL1 found in the SNP databases have been characterized with Ser82Cys and Asp252Asn exhibiting wild type activity, while Cys136Arg showed both reduced glycosylase and AP lyase activity [232].

Two NEIL1 variants, Lys242Arg and Gly245Arg, were identified in gastric tumors in Chinese patients and another NEIL1 variant, Arg334Gly, was identified in a Japanese patient [233]. These variants all behaved like wild type NEIL1 in an activity assay [233]. A NEIL1 deletion mutant, Gly28Del, that results in a truncated protein and a NEIL1 splicing mutation have also been found in gastric cancers. The Gly23del variant had little to no activity while the truncated protein from the splicing variant lost its nuclear localization signal [233]. Three novel NEIL1 promoter polymorphisms were also found in patients with gastric cancer [234].

Three polymorphic variants of NEIL2, Arg103Gln, Pro123Thr and Arg257Leu, were identified in patients with family histories of colorectal cancer and were not observed in controls [72]. The NEIL2 Arg103Gln and Arg257Leu variants were also found in patients with multiple colorectal carcinomas but were also found in controls [163]. An additional

NEIL2 variant, Arg164Thr, was found in a single patient and not in the control population [163]. Ten variants of NEIL3 were found in patients with multiple colorectal adenomas, but only one of these, Glu132Val, was present in a patient but not in a control population [163]. The NEIL2 and NEIL3 variants have not been evaluated for function. Finally, although there are a number of NTH1 polymorphic variants identified in the databases (and see [44]), as of yet none have been associated with disease.

6. AP Endonuclease, APE1 (also called APEX1, REF1)

There are two genes encoding AP endonucleases in humans. *APEX1* encodes the principal enzyme, APE1, that has both AP endonuclease and 3' phosphodiesterase activity (for a review see [235]). APE1 also contains redox-enhancing factor I (REF1) which reductively activates a number of transcription factors [236,237]. APE1 cleaves an AP site generated by a monofunctional DNA glycosylase and leaves a 3' hydroxyl and a 5' deoxyribose [238-240]. APE1 is the major enzyme in humans responsible for this activity. The diesterase activity of APE1 also removes the α,β -unsaturated aldehyde left on the 3' side of the nick produced by the lyase activity of NTH1 and OGG1 [17]. The structure of APE1 shows it to have a four-layered α,β -sandwich fold characteristic of this family of proteins and contacts the DNA in the minor groove [241]. There is a second *APE1* gene that encodes human APE2. APE2 has 3' phosphodiesterase activity and in addition has a 3-5' exonuclease activity that supports removal of mismatched nucleotides from the 3' end of the nick [242-244]. APE2 has a very weak AP endonuclease activity but efficient 3' phosphodiesterase activity [244,245]. Recent data suggest that APE2 is involved in maintaining and regenerating B cell precursor pools [246].

6.1 Mouse models for APE1 and APE2

Mice nullizygous for APE1 suffer early embryonic lethality [247-249]. Nullizygous *Ape1*^{-/-} mouse embryonic fibroblasts (MEFs) [250] containing a human *APE1* gene under CRE control were used to distinguish between the AP endonuclease activity of APE1 from the redox regulatory function of APE1. When hAPE1 was removed from these cells, apoptosis ensued and could only be restored by complementing with both functions showing that both are essential for cell viability. In contrast, in RNA knockdown experiments with human cells, apoptosis was prevented by expression of an unrelated AP endonuclease suggesting that it was only AP endonuclease that was required for viability [251]. APE1 heterozygous mice are viable with no abnormal phenotype compared to wild type mice [252]; however, APE1 heterozygotes exhibit a higher spontaneous mutation frequency in spleen and liver [252], sensitivity to oxidative stress [249] and lower BER activity in liver and brain [253]. Mice nullizygous for *APE2* appear to develop normally but exhibit defects in lymphopoiesis supporting the idea that APE2 repairs DNA damage during lymphoid development [246].

6.2 APE1 Polymorphisms and cancer

The *APEX1* gene that encodes APE1 maps to chromosome 14q11.2-q12. A number of polymorphisms have been identified in the *APEX1* gene, but the most common polymorphic variant is Asp148Glu, present at about 46% of the population. Like the Ser326Cys variant in OGG1, this common variant has also been extensively studied resulting in over 50 publications which will not be completely reviewed here. A number of studies have suggested associations between the Asp148Glu variant and various types of cancer. For example, one study showed it to predict cancer risk for bladder cancer [254], but another showed it to be associated with a decreased risk for bladder cancer [255]. Similarly, one study showed individuals with the Asp148Glu polymorphism to have an increased risk of lung cancer [256] while other studies showed carriers of the Asp148Glu polymorphism to have no increased risk [36,257]. Asp148Glu was also shown to predict risk for prostate

cancer [258] and gastric cancer [259]. There has also been a study suggesting that Asp148Glu conferred a risk for breast cancer [260] while genome-wide association studies discounted this [36,261-264]. One meta-analysis showed a moderately increased risk for all cancer types for individuals with the Asp148Glu polymorphism [265], while others found no increase [36].

The Asp148Glu variant protein, as well as other variants such as Gly241Arg and Gly306Ala, have been biochemically characterized and display essentially normal AP endonuclease and DNA binding activities [266,267]. The Leu104Arg, Glu126Asp and Arg237Ala exhibit 40-60% reduction in AP endonuclease activity while the Asp283Gly variant exhibits only 10% of the repair capacity of the wild type APE1 [266]. Two of the APE1 polymorphic variants, Gln51His and Ile64Val are in the N-terminal region of the protein not in the catalytic domain.

Mutations in APE1, Pro12Leu and Arg237Cys and one with a premature stop codon, have also been found in three out of 20 endometrial tumors [268]. Arg237Cys behaves similarly to the Arg237Ala having a substantially reduced AP endonuclease activity [266].

7. DNA polymerase beta (Pol β)

Pol β is the main polymerase involved in BER, and is responsible for two key activities in the BER pathway: DNA polymerase and dRP lyase activities. Pol β is a small (39kD) polymerase, which unlike replicative polymerases delta and epsilon, does not possess any proofreading exonuclease activity. This leads to Pol β being a relatively error prone polymerase, misincorporating the wrong nucleotide in about one of every 10,000 nucleotide insertion events [269].

Pol β consists of two main domains, 8kD and 31kD, each responsible for one of the activities of the polymerase [270,271]. The 31kD domain possesses three subdomains named for their structural correlation to a hand: thumb, palm, and fingers. The thumb subdomain connects to the 8kD domain and is the main center for DNA binding by the polymerase as it contains two HhH motifs. The palm domain contains the polymerase active site residues: Asps 190, 192, and 256 [272]. The palm domain is connected to the fingers domain through a flexible hydrophobic hinge region. The fingers domain of the polymerase is responsible for nucleotide binding and selection. The 8kD domain houses the deoxyribose phosphate (dRP) lyase activity.

The polymerization mechanism of Pol β consists of four basic steps. First, Pol β binds to one base gapped DNA to form a polymerase-DNA binary complex. This binary complex next binds nucleotide, forming an enzyme-DNA-dNTP ternary complex. Once dNTP is bound in the active site, there is a rapid conformational change wherein the fingers domain rotates through the hydrophobic hinge region to close around the nucleotide. This movement initiates the nucleotidyl transferase activity in the active site, adding the nucleotide to the DNA strand. Lastly, in a likely rate-limiting step, the DNA product extended by one nucleotide is released from the polymerase generating an *apo*-enzyme that can complete the cycle again [273].

One putative source of mutagenesis is the lack of removal of 8-oxoG, which is a major product of oxidative base damage that is usually repaired by BER. DNA polymerases, including Pol β , insert A opposite this base if it is present in DNA. Unmodified G assumes an *anti* conformation, but crystal structures show that this lesion assumes a *syn* conformation that is consistent with efficient DNA synthesis. This conformation is stabilized through Hoogsteen bonding with the incoming adenine and a hydrogen bond with Asn279 [274]. Another underlying mechanism of mutagenesis is the insertion of ribonucleotides into DNA.

Pol β , like many other DNA polymerases, inserts ribonucleotides with an efficiency that is four orders of magnitude less than that for dNTPs. Once incorporated, Pol β can efficiently extend from the ribonucleotide. Pol β can insert arabinofuranosylsytosine triphosphate (araC), but this is poorly extended. For araC it is predicted that the O2' of araC would clash with Asp276, but this does not seem to occur, suggesting that this side chain can adjust to accommodate a hydroxyl at C2' [275]. Exclusion of the ribonucleotide does not occur via an amino acid side chain as in other DNA polymerases, known as the steric gate, but instead involves the backbone which in the case of Pol β is Tyr271. This residue plays two significant roles. Its backbone carbonyl is unfavorably close to the 2'-OH of the ribose with little room for adjustment. Tyr271 also binds to the minor groove edge of the terminal primer base and the presence of a ribonucleotide obstructs this interaction, which modulates active site geometry [276].

The Wilson laboratory has produced elegant high resolution crystal structures of Pol β ternary complexes with mispairs in the active site, using nonhydrolyzable analogs that were soaked into the crystals. With a G-A mispair, the closed conformation is observed and the mispaired bases are staggered. One hydrogen bond is observed between the template and nascent bases. Staggered bases, but no hydrogen bonds were observed for the C-A mispair. To accommodate the staggered bases, the template strand shifts, generating an abasic templating pocket. Interestingly R283 occupies the space vacated by the templating nucleotide. The primer terminus rotates as the complementary base is repositioned, which moves the O3' of the primer terminus away from the alpha phosphate, decreasing polymerase catalytic efficiency [277]. A nonhydrolyzable A analog was soaked into crystals with a tetrahydrofuran (THF) "template" and a closed conformation was observed. However, the THF shifts upstream as in the structure with the mispair and the primer terminus position is tenuous, and likely not stable. Results suggest that R283 facilitates insertion of A opposite the abasic site (THF) [278].

Additional evidence has recently shown that both the hydrophobic hinge and LoopII of Pol β are important for fidelity [279,280]. Yamtich showed that alteration of Ile174 to Ser resulted in an active polymerase that exhibited decreased fidelity for insertion opposite template G. In the Ile174Ser variant the ground state binding was altered, suggesting that the hinge is critical for the position and/or structure of the dNTP binding pocket [279]. Loop II is a highly flexible loop that sits beneath the palm domain and alteration of this loop leads to a decrease in the rate of DNA synthesis by Pol β and in fidelity [280]. Interestingly, the Pro242Arg germline variant of Pol β is present within Loop II [281].

7.1 Pol β mouse models

Like mice nullizygous for the other downstream BER enzymes, Pol β null mice generated by the Cre-lox P system were not viable [282] while another pol β knockout survived embryonic development but died from lung failure immediately after birth [283]. Pol β heterozygous mice exhibit higher levels of single strand breaks (SSBs) and chromosomal aberrations than wild type [284], as well as hypersensitivity to alkylating agents [284].

7.2 Germline and tumor-associated variants of Pol β

Variants in Pol β have been the topic of numerous reviews by our group (see Nemec and references therein [43]). Genotyping of the Pol β gene at 14 different sites along the gene has confirmed the presence of two exonic germline variants, Arg137Gln and Pro242Arg, in a few different global populations with minor allele frequencies of nine and three percent, respectively [281]. This study also revealed that there was a marked difference between haplotypes in African versus non-African populations. The Arg137Gln Pol β germline variant was shown to have lower DNA polymerase activity than WT Pol β , was unable to

complement Pol β MEFs for cellular sensitivity to alkylating agents, and was deficient in BER reconstitution assays [285]. Little is known about the activity of the Pro242Arg Pol β variant protein, but patients with lung cancer who carry this variant have decreased survival [286].

Approximately 30% of human tumors studied to date appear to carry mutations in the Pol β gene that are not found in the germline (for a review see [287]). Many of these mutations have functional phenotypes that are associated with cancer, including deficient polymerase or dRP lyase activity or they exhibit mutator activity [288-291]. Pol β tumor-associated variants identified in lung, gastric, colorectal, and prostate cancer induce cellular transformation in immortalized epithelial cells [290,292] by inducing genomic instability.

Pol β has also been shown to be overexpressed in a variety of human tumors [293]. Overexpression in Chinese hamster ovary cells has been shown to induce cellular transformation and genomic instability [294,295]. Using a transgenic mouse model, Sobol and colleagues demonstrated that overexpression of Pol β in certain organs, such as the stomach, resulted in hyperplasia [296]. Overexpression of Pol β can lead to imbalances in BER, which has been shown in *Saccharomyces cerevisiae* to result in a mutator phenotype [297]. In human cells imbalances in BER proteins can result in the accumulation of BER intermediates including single strand breaks (SSBs) and double strand breaks (DSBs) that lead to genomic instability.

8. Ligase III α

Ligase III α (LigIII α) seals the nick in the DNA backbone left after Pol β fills in the gap and eliminates the dRP group. The *LIGIII* gene is distinct from the other ligase genes (*LIG1* and *LIG4*) in that there are no homologs of *LIGIII* in lower eukaryotes [298]. There are three forms of LigIII: α , β , and mitochondrial; all of which are encoded by the same gene, another feature unique to *LIGIII*. LigIII α interacts tightly with XRCC1 via a BRCT domain at its C-terminus, and the LigIII α -XRCC1 complex is the major source of nick joining activity in BER. LigIII β lacks the C-terminal BRCT domain and is found only in male germ cells where it is thought to function in meiotic recombination. Mitochondrial LigIII (mtLigIII) possesses an N-terminal mitochondrial localization signal in addition to the C-terminal BRCT domain and functions in mitochondrial DNA maintenance in the absence of XRCC1. It has been shown that LigIII is phosphorylated at Ser123 in replicating cells by Cdk2, a cell cycle kinase; however, in response to oxidative DNA damage is dephosphorylated, and this is dependent upon ATM [298].

The nick-sealing ligase reaction is a three-step reaction that utilizes the consumption of ATP. The consumption of ATP is required to force the equilibrium of the ligase reaction to the right to avoid the potentially disastrous reverse reaction where single SSBs are induced in the DNA. LigIII α attacks the ATP molecule through a catalytic lysine residue (Lys421) [33], releasing pyrophosphate and covalently linking AMP to the enzyme. Next, the AMP is transferred to the 5'-end of the DNA at the nick. Finally, the hydroxyl group at the 3'-end of the nick attacks the 5'-phosphate on the 5'-end, expelling the once ligase-bound AMP and joining the two sides of the nick together.

LigIII α binds to the nicked DNA via its DNA binding domain. This DNA binding is enhanced by the presence of the ZnF domain; although, exactly how this stimulation is accomplished remains unknown. Once bound to the DNA, LigIII α curls in upon itself, encircling the DNA. This allows for the DNA binding domain to bend the DNA and unwind it, which exposes the nick on the opposite side of the DNA to the catalytic domain. A consequence of the need for LigIII α to encircle the DNA substrate is that the complex of LigIII α -XRCC1 disrupts nucleosomes containing single nucleotide gaps. As a result, the

gap is more externally exposed for action by Pol β , and thus, the activity of Pol β is stimulated on nucleosomes by the LigIII α -XRCC1 complex [299].

8.1 LigIII nullizygous mice and human polymorphism variants

Like the rest of the downstream BER knockout mice, mice containing a targeted knockout of LigIII are embryonic lethal [300]. In mouse embryonic stem cells with a conditional allele of LigIII, mitochondrial but not nuclear LigIII appears to be required for viability [301]. Also, unlike XRCC1-deficient cells, LigIII⁻ null cells are not sensitive to a number of DNA damaging agents [301]. In addition, although there are a number of LIGIII polymorphic variants identified in the data bases (and see [44]) none have yet been associated with a disease outcome.

9. X-ray cross complementing 1 (XRCC1)

XRCC1 acts as a scaffold during BER and single-strand break repair (SSBR) and has no enzymatic activity of its own. XRCC1 interacts with several proteins that function in BER and SSB repair including Pol β , PARP1, LigIII α , APE1. For a recent comprehensive review see [302]. It has recently been found that XRCC1 also functions in an alternative nonhomologous end-joining pathway (alt-NHEJ), which is microhomology-mediated [303]. XRCC1/ligIII α interacts constitutively with MRN/RAD50 in WT cells, but in cells deficient in LigIV, the protein that acts in the major NHEJ pathway, significantly less ligIII α interacts with MRN. Rather, these proteins interact specifically in the presence of DNA damage [304]. The NBS1 and RAD50 proteins interact directly with both ligIII α and β . The MRE11-RAD50-NBS1 complex (MRN) stimulates intermolecular ligation of compatible ends by LigIII α and XRCC1 and also stimulates ligation of incompatible ends using microhomology that is revealed by the nuclease activity of MRE11 but in complex with RAD50 and NBS1.

New studies regarding functional interaction of XRCC1 with several proteins are providing important insights into the critical scaffolding role of XRCC1. For example, lack of interaction between XRCC1 and polynucleotide kinase (PNKP) results in a remarkably slow rate of SSBR. The 3' DNA phosphatase activity of PNKP is critical for rapid SSBR, which is facilitated by interaction with XRCC1. The authors suggest that the interaction of PNKP with XRCC1 ensures that PNKP is not rate limiting during SSBR [305].

Recent studies have also suggested that XRCC1 functions at replication forks. XRCC1 is in complex in the cell with uracil DNA glycosylase 2 (UNG2) and these proteins are colocalized with PCNA, suggesting that they are at replication forks. This complex, isolated from replicating cells, is able to function in the repair of DNA with uracil residues. Interestingly, there is a reduced rate of repair of uracils in XRCC1 deficient cells. UNG2 and XRCC1 colocalize specifically in S-phase cells and therefore might catalyze a specialized repair process in these cells [306]. The BRCT domain of XRCC1 interacts with the p58 subunit of DNA polymerase alpha-primase (Pol β -primase) and XRCC1 and p58 colocalize in damaged cells. P58 also interacts with polyADP ribose polymerase, which inhibits its activity. Overexpression of the BRCT domain of XRCC1 in HeLa cells increased PAR synthesis, which interferes with ongoing DNA synthesis. The authors propose that inhibition of primase activity by PAR is facilitated by interactions with XRCC1 and PARP-1 and that this leads to fork slowing to allow for SSBR to be completed. Thus, XRCC1 could play an important role in coordinating break repair with replication [307].

Radicella previously demonstrated that XRCC1 interacts with APE1 [308]. Recently it has been shown that APE1 interacts with SIRTUIN1 (SIRT1), a protein deacetylase, and this interaction is increased in response to genotoxic stress. SIRT1 deacetylates APE1. Stress

increases acetylation of SIRT1. Activation of SIRT 1 with resveratrol stimulates binding of APE1 to XRCC1 and genotoxic stress stimulates the binding of XRCC1 to APE1 which is suppressed by knockdown or inhibition of SIRT1. Resveratrol stimulates AP endonuclease activity of the APE1-XRCC1 complex. Thus, SIRT1 may have a role in the regulation of BER by promoting association of APE1 with XRCC1 [309].

9.1 XRCC1^{-/-} mice

Mice nullizygous for XRCC1 die as early embryos [310]. XRCC1 heterozygous mice appear to develop normally but when treated with an alkylating agent exhibit liver toxicity and an increase in precancerous colon lesions [311]. XRCC1^{-/-} mouse embryo fibroblasts and Chinese hamster ovary cells devoid of XRCC1 are hypersensitive to a variety of damaging agents including ionizing radiation and alkylating agents and exhibit a defect in SSB rejoining [310,312,313].

9.2 XRCC1 cancer-associated variants

For reviews on XRCC1 germline and tumor-associated variants see [43,314,315]. The XRCC1 Arg399Gln germline variant has a minor allele frequency of around 10% and has been associated with cancer risk and responses to various cancer therapies [314]. One study in Polish women suggests that the presence of the Arg399Gln variant is associated with increased risk of cervical cancer [316]. The other study suggests that subjects who carry at least one XRCC1 Arg399Gln variant allele have decreased risk for cervical cancer regardless of papilloma virus infection [317]. These differing results may be due to a difference in populations characterized or from low numbers of women studied. A meta-analysis of several studies demonstrated that the XRCC1 Arg399Gln variant is significantly associated with prostate cancer in Asian, but not Caucasian men [318]. However a different meta-analysis of the association of XRCC1 Arg399Gln variant suggested that it was associated with significant increase in prostate cancer risk regardless of the population studied [319]. Finally postmenopausal women carrying the Arg399Gln allele appear to be at increased risk for breast cancer [320].

The XRCC1 Arg194Trp variant was shown to be associated with a decreased risk of papillary thyroid cancer [321] but with an increased risk for differentiated thyroid cancer [322]. In a meta-analysis of Arg194Trp, Arg280 and Arg339Gln, no association was found with gastric cancer [323].

The presence of XRCC1 germline polymorphisms is also associated with responses to exposures of various types. For example, a significant difference in the ability to repair ionizing radiation damage was detected in lymphocytes of individuals who are homozygous for Arg399Gln, using a modified comet assay [324]. In another study, chromosomal aberrations were measured in welders exposed to chromium and in a control population. Significantly increased numbers of aberrations in lymphocytes were detected in individuals homozygous for the Arg399Gln variant [325] and correlated with levels of chromium in blood. In a third study, smokers carrying both alleles of the XRCC1 Arg399Gln variant had significantly increased frequencies of micronuclei and chromosomal aberrations [326]. Finally, individuals with non-small cell lung cancer treated with 45 Gy of ionizing radiation plus platin-based chemotherapy and carrying the XRCC1 Arg399Gln allele responded significantly better than those carrying the wild type Arg399 [327].

10. BER and cancer therapy

For reviews on BER as a cancer therapy target see [328-330]. The intermediates in the BER pathway are usually more toxic than the initial base lesion. Overexpression of the MPG/AAG DNA glycosylase results in the accumulation of abasic sites that are processed by

APE1, Pol β , and XRCC1/LigIII α . Overexpression of MPG/AAG along with down-regulation of Pol β would be expected to lead to the accumulation of SSBs and DSBs and in fact, sensitizes cells, including glioma cells, to temozolomide (TMZ). TMZ is currently being used in the clinic to treat glioblastomas and other tumors and methylates predominantly the N7 rather than the O6 of guanine [331], thus eliciting BER. Taken together, these results suggest that a major mechanism of repair of TMZ is BER. In cells that are down-regulated for Pol β , the dRP group remains attached to the 5' end of the DNA break and is suggested to mediate cell death via a non-apoptotic pathway [332]. Interestingly, cell death in response to the lack of removal of the 5' dRP group has been shown to result from energy depletion [333]. A combination of inhibition of BER and NAD⁺ biosynthesis sensitizes glioma cells to TMZ-induced cell death [334]. Therefore, modulation of the levels of BER proteins could be a possible gene therapy approach for killing cancer cells.

APE1 is also being explored as a cancer therapy target. A structure-based screening approach using a fluorescence assay to monitor AP site cleavage identified several APE1 inhibitor compounds [335]. The APE1 Asp148Glu variant appears to be more sensitive to one of the compounds than wild type APE1. Potentiation of MMS was demonstrated in glioma and melanoma lines with some of the inhibitor compounds. Using an adapted fluorescence-based *in vitro* assay in a high throughput screening format, several novel APE1 inhibitors were identified. Three compounds emerged from this screen were found to inactivate AP site cleavage in whole cell extracts from mammalian cells and enhanced MMS sensitivity in cells [336]. The compounds exhibit structural diversity, suggesting that they act by different mechanisms. For excellent reviews on the status of APE1 inhibitors see [337,338].

Pol β is also a potential cancer therapy drug target. Lithocholic acid (LCA) is a known inhibitor of the binding of Pol β to DNA and a dRP lyase inhibitor. We have shown that LCA enhances the cytotoxicity of TMZ significantly in BRCA2 deficient EUFA 423 cells and also somewhat in the BRCA2⁺ complemented cells. Thus, BER and homology-directed repair (HDR) exhibit a synthetic lethal phenotype [339], which is not surprising given the important finding that synthetic lethality is observed in BRCA-deficient cells treated with PARP inhibitors (for an excellent review on this topic see [340]). Inhibition of PARP likely leads to an increase in SSBs and DSBs during DNA replication that results in cell death. Another possibility is that PARP inhibitors may cause PARP to be trapped on DNA, leading to obstruction of the replication fork [340]. Pol β cells are very sensitive to PARP inhibitors (for review see [341]). When PARP1 is deleted in Pol β MEFS, the cells are no longer hypersensitive to MMS [342].

McKenna and Goodman have introduced a series of dNTP analogs modified at the α - β or β - γ bridging atom. These nonhydrolyzable analogs prevent turnover of Pol β and act as a transition state probe [343]. Based on these data and the emergence of novel strategies for the delivery of dNTP analogs into cells, the authors suggest that these analogs might be part of a new platform for drug design [344].

DNA ligases are also important cancer drug targets. Tomkinson and colleagues have developed a ligase inhibitor screen [345,346] and have employed *in silico* drug design based upon the structure of human Ligase I to identify inhibitor compounds. This group chose compounds that were predicted to bind to the DNA binding domain from the *in silico* work to test using a fluorescent ligation assay and identified several inhibitors of LigI. Two of the compounds that inhibited LigI also inhibited LigIII but not the polymerase gap-filling step. These compounds are competitive inhibitors and bind to DNA binding domain. They

potentiate the killing of cancer cells with MMS and ionizing radiation, and may be useful in treating cancer.

11. What have we learned?

To state the obvious we know that BER removes the preponderance of endogenous DNA lesions as well as damages produced during episodes of inflammation and exposures to ionizing radiation and a variety of chemical carcinogens. This conclusion comes from decades of research where the *in vitro* biochemical studies showed that these damages could be removed by the BER enzymes as well as studies in prokaryotes and numerous mammalian cell types which demonstrated that in the absence of BER enzymes cells accumulate mutations and are hypersensitive to a variety of damaging agents. We also know from the knockout mouse models that as the glycosylase-deficient mice age they accumulate damage and develop mutations in various organs and when fibroblasts are cultured from embryos of mice that do not survive the embryonic stage, these MEFs also accumulate mutations and are sensitive to DNA damaging agents. What is also clear is that the BER process itself is required for development since mice deficient for APE1, Pol β , ligase III α , and XRCC1 are embryonic lethals. From the mouse models, we also learned that the glycosylases that recognize the damages in DNA have redundant functions since mice deficient in any single DNA glycosylase have less than profound phenotypes. This should not have been a surprise since early studies with prokaryotes already showed that this was the case when spontaneous mutagenesis or sensitivity to damaging agents was assessed. Moreover, all of the biochemical assays told us that these enzymes had redundant substrate specificities. We also know that the damages repaired by the BER pathway can initiate carcinogenesis since when more than one glycosylase is knocked out, the mice develop tumors at an early age. So, taken together, these data strongly suggest that individuals who have compromised BER are at risk for developing cancer.

This obvious conclusion has led to a large number of studies asking whether having a particular polymorphic variant in a BER enzyme can predispose an individual to the risk of cancer. In the case of OGG1 and APE1, the most common variants, OGG1 Cys326Ser and APE1 Asp148Glu were examined primarily because better statistical correlations could be obtained if a larger population harbored the polymorphisms. For the most part these data have been unsatisfactory with often conflicting studies showing predisposition or not to a particular type of cancer. Again, this should not be particularly surprising, since both these variants have wild type or close to wild type enzymatic activity when examined biochemically. It is more likely that polymorphic variants that have substantially reduced function would predispose an individual to the risk of cancer. However, these defective variants are present at a much lower frequency in the population, thus statistical power in an epidemiological study is more difficult to attain. What is most probable is that it will take a combination of polymorphisms to predispose each of us to a particular type of cancer, and moreover, this is unlikely to be a unique combination. This question may be answered sometime in the future when the DNA from an entire population has been sequenced using massively parallel sequencing technologies. At this point the bioinformaticists should be able to tell us what combinations of mutant alleles will predispose us to which particular cancer.

Having said this, the MUTYH case is a clear exception. Here, low frequency variants clearly predispose the individuals who possess them to colon cancer. Several reasons might account for this. For example, with highly proliferating cells such as in the colon, the backup to MUTYH, DNA mismatch repair, may not be enough to protect the cells from accumulating mutations. An additional factor is that the target *APC* gene contains sequences that are particularly vulnerable to the G T transversions that MUTYH protects against. As expected,

in the case of MUTYH-associated colon cancers, the biochemical, function of the particular MUTYH variant protein usually correlates with the patient's genotype.

Analysis of mutations in BER genes in tumors should provide insight into tumor development in a particular organ and even more importantly, the potential role of BER in metastases. Also, as described in Section 10 the BER enzymes are important cancer drug targets since, in their absence, cells are sensitized to a variety of chemical agents as well as ionizing radiation. Taken together, it is clear that we need the basic biochemistry and cell biology not only to guide the epidemiology, but help interpret any epidemiological results. Furthermore, the basic science, including structural biology, will be central for rational drug design and for developing strategies to identify small molecule inhibitors for individual enzymes.

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Figure 1. Short Patch Base Excision Repair

Table 1

Characterized MUTYH Variants Found in MAP Patients *

Variant	Glycosylase Activity	Substrate Binding	Complementation of <i>E. coli mutY</i> spontaneous mutation frequency
V22M	WT [11]	WT [11]	
V61E	WT [12]		
R83X	No activity [12]		
Y90X	No activity [11]	No binding [11]	
I103delC	No activity [11]	No binding [11]	
I37insIW	35% [13], 40% [14]	Slight decrease [14]	
Y165C	No activity [13,14], severe defect [11], 4.5% [12] 30-40% [15]	Greatly reduced [11,14,16]	No [15,16]
R168H	No activity [12]		
R171W	No activity [13,14]	Greatly reduced [14]	
I209V	66.9% [12]		
D222N	No activity [12]		
R227W	Severe defect [17]	Greatly reduced [17]	
R231H	Severe defect [11]	Severe defect [11]	
R231L	Severe defect [18]	Severe defect [18]	No [18]
V232F	Partial activity [17]	Partial binding [17]	
R260Q	Reduced [11], severe defect [19]	Reduced [11]	
M269V	10.7% [12]		
P281L	Severe defect [11]	Greatly reduced [11]	
R295C	WT [12]		
Q324H	Reduced [11]		
Q324R	No activity [12] 30-40% [15]	WT [15]	
A359V	WT [12]		
L374P	No activity [12]		
Q377X	No activity [11]	No binding [11]	
G382D	15.2% [12], 30-40% [15], 50% [14], Reduced [11], WT [13]	Greatly reduced [16] Reduced [11,14]	Partial [15]
P391L	No activity [12] 30-40% [15]		No [15]
H434D	WT [19]		
A459D	Severe defect [110]		
E466del	No activity [11-14]	No binding [11] greatly reduced	

Variant	Glycosylase Activity	Substrate Binding	Complementation of <i>E. coli mutY</i> spontaneous mutation frequency
		[⁴]	
S501F	WT [²]		

* The MUTYH variant amino acid numbers used in this Table follow the original notation (see [¹¹],[¹²]). However, the MUTYH variants used in (1) are the mitochondrial form which is -14aa from that used here. Also, the most up-to-date annotation uses the full length protein +14aa from the notation used here [¹³].

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