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Review

Bacterial DNA repair genes and their eukaryotic homologues: 1. Mutations in genes involved in base excision repair (BER) and DNA-end processors and their implication in mutagenesis and human disease★

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Base excision repair (BER) pathway executed by a complex network of proteins is the major system responsible for the removal of damaged DNA bases and repair of DNA single strand breaks (SSBs) generated by environmental agents, such as certain cancer therapies, or arising spontaneously during cellular metabolism. Both modified DNA bases and SSBs with ends other than 3′-OH and 5′-P are repaired either by replacement of a single or of more nucleotides in the processes called short-patch BER (SP-BER) or long-patch BER (LP-BER), respectively. In contrast to *Escherichia coli* cells, in human ones, the two BER sub-pathways are operated by different sets of proteins. In this review the selection between SP- and LP-BER and mutations in BER and end-processors genes and their contribution to bacterial mutagenesis and human diseases are considered.

Keywords: AP endonuclease, BER, DNA damage, DNA repair; glycosylase, mutagenesis, protein interaction, SSB, SSBR

INTRODUCTION

Living organisms are continuously exposed to damaging agents both from the environment and from endogenous metabolic processes, whose action results in modification of proteins, lipids, carbohydrates and nucleic acids. Events that lead to DNA modification include radiation, hydrolysis, exposure to reactive oxygen or nitrogen species and other reactive agents, like alkylating agents and lipid peroxidation products (Lindahl, 1993; Tudek *et al.*, 2006; Olinski *et al.*, 2007; Tudek, 2007). To counteract these threats organisms are equipped with multiple damage prevention and repair systems to ensure the stability of DNA and to protect the genome from potential mutagenic modification and allow accurate transmission of genetic information.

The knowledge of DNA repair processes is critical to our understanding of how and why the genome is affected during the lifespan of the organism, and how the DNA, RNA and nucleotide repair systems efficiently work *via* several different pathways, such as: (1) sanitization of the nucleotide pool (for more details see accompanying review by

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Abbreviations: AP, apurinic/apyrimidinic; AP-site, apurinic/apyrimidinic site; AP endonuclease, apurinic/apyrimidinic endonuclease; BER, base excision repair; SSB, single strand break; SSBR, SSB repair.

Arczewska & Kusmierek, this issue), (2) direct reversion of base modifications by (*i*) demethylation processes (for more details see accompanying review by Nieminuszczy & Grzesiuk, this issue) and (*ii*) by 6–4 photolyase or CPD photolyase (Kim *et al.*, 1994; Sancar, 1994), or (3) excision of (*i*) misincorporated bases in the newly replicated DNA strand by mismatch repair (MMR) (for more details see accompanying review by Arczewska & Kusmierek, this issue), (*ii*) excision of bulky damage from both DNA strands or from the transcribed strand by nucleotide excision repair (NER) (for more details see accompanying review by Maddukuri *et al*., this issue), and (*iii*) excision of oxidized, methylated or misincorporated bases from DNA by base excision repair (BER) which is described in more details in this review. Damaged bases are also a source of the single strand breaks (SSBs) and double strands breaks (DSBs). SSBs repair (SSBR) is also discussed in this review. The strand breaks are subject to recombinational repair (for more details see accompanying review by Nowosielska, this issue). Despite the protection provided by these mechanisms some of the damage escapes repair. Unrepaired DNA damage may block replication and engage alternative DNA polymerases in the process of so-called translesion synthesis (TLS) to by-pass the lesion in an error-free or error-prone fashion (reviewed by: Bebenek & Kunkel, 2004; Shcherbakova & Fijalkowska, 2006). To sum up, the unrepaired DNA damage leads to replication and transcription errors and in consequence to mutagenesis, ageing and various diseases, including carcinogenesis and neurodegeneration (reviewed by: Krokan *et al*., 2004; Bartsch & Nair, 2006).

PROCESSES LEADING TO DNA BASE MODIFICATIONS

DNA base modifications are formed by both exogenous (i.e. environmental) and endogenous factors. Endogenous DNA damage occurs at a high frequency compared with exogenous damage and the types of damage produced by normal cellular processes are identical or very similar to those caused by some environmental agents (Jackson & Loeb, 2001). It has been proposed that the DNA damage from endogenous sources gives rise to 20000 lesions per mammalian cell per day, most of the lesions being deaminations, spontaneous hydrolysis of the N-glycosidic bond, alkylations, and damage by reactive oxygen or nitrogen species and lipid peroxidation products (Lindahl, 1993; Drablos *et al*., 2004; Tudek *et al.*, 2006; Olinski *et al*., 2007). Lesions are also caused by errors in DNA metabolism, including the formation of SSBs and DSBs from the collapse of replication forks and the introduction of modified nucleic acid bases during DNA replication. Examples of base modifications discussed below and repaired by BER are shown in Fig. 1.

Deamination of DNA bases

DNA bases containing an exocyclic amino group, namely adenine (A), guanine (G), cytosine (C), and 5-methylcytosine (5-meC) are susceptible to spontaneous hydrolytic deamination to hypoxanthine (Hyx), xanthine (X), uracil (U), and thymine (T), respectively. Deamination occurs more frequently in single-stranded than in double-stranded DNA, where the amino groups are protected by participating in hydrogen bonds (Lindahl, 1993). Spontaneous deamination is rather slow, but it can be significantly accelerated *in vivo* by nitrogen dioxide (NO_2) and dinitrogen trioxide (N_2O_3) formed during inflammation or by UV- as well as by γ-irradiation (reviewed by: Kavli *et al*., 2007).

Loss of DNA bases *via* N-glycosidic bond hydrolysis

The N-glycosidic bond between base and deoxyribose in DNA can be hydrolyzed spontaneously or by DNA *N*-glycosylases during removal of damaged or incorrect bases from DNA by BER. This process leads to formation of an apurinic/apyrimidinic (AP) site (AP-site). Additionally, reactive oxygen species (ROS) and alkylating agents promote the release of bases, often by introducing lesions that destabilize the N-glycosidic bond (Lindahl, 1993; Guillet & Boiteux, 2003). AP-sites are among the most frequent endogenous lesions found in DNA and about 10000 lesions are formed per human cell per day (Lindahl, 1993). Purines are lost at a rate 500 times higher than pyrimidines, and the depurination rates of A and G are comparable (Loeb & Preston, 1986). AP-sites are highly damaging lesions, can block replication and are both cytotoxic and mutagenic (Loeb & Preston, 1986; Guillet & Boiteux, 2003). Additionally, unrepaired AP-sites may rearrange to generate SSBs (Lindahl, 1993).

Alkylation of DNA bases

Alkylating agents can react with 12 different positions of DNA bases, including all exocyclic oxygens and most of ring nitrogens, and can also modify oxygen atoms in the phosphates groups of the sugar-phosphate backbone. Depending on the mode of action, alkylating agents are divided into two types: S_N1-type agents (e.g. *N*-methyl-*N*-nitrosourea, MNU) alkylate both oxygens and nitrogens in nucleic acids, and S_N2-type agents (e.g. methyl methanesulfonate, MMS) alkylate mainly nitrogens.

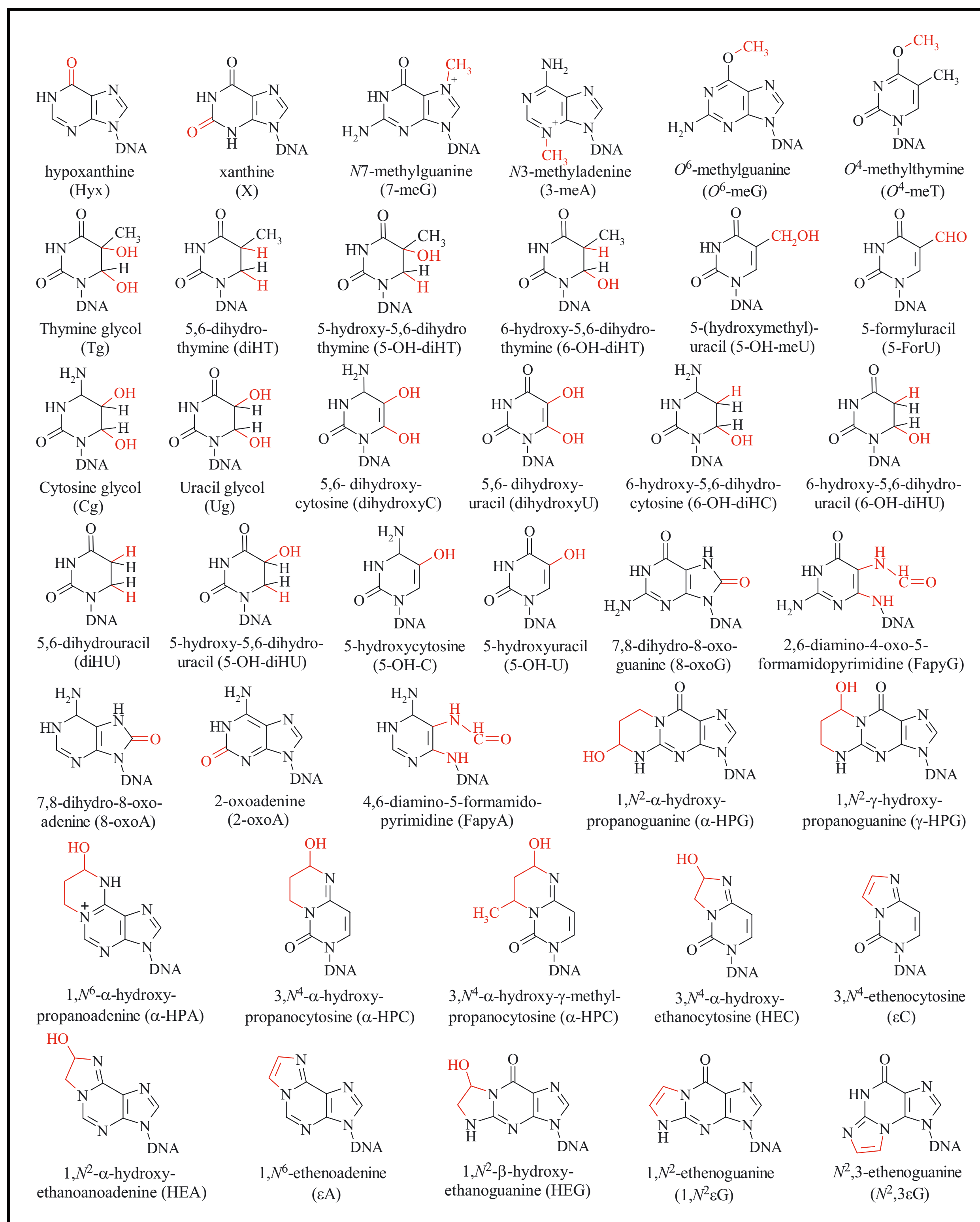

Figure 1. Major endogenous DNA base modifications.
Modified positions are shown in red.

In general, ring nitrogen atoms engaged in hydrogen bonding are almost non-reactive in double-stranded DNA (dsDNA), but can be more readily alkylated in single stranded DNA (ssDNA) or RNA (e.g. *N*3 of cytosine and *N*1 of adenine) (reviewed by: Drablos *et al.*, 2004; Sedgwick, 2004; Nieminuszczy & Grzesiuk, this issue). The major product of DNA base methylation is *N*7-methylguanine, a rather non-muta-

genic and non replication-blocking lesion. However, destabilization of the N-glycosidic bond due to the *N*7-substitution of guanine results in the formation of AP-sites or imidazole ring opening to yield very mutagenic lesion 7me-FapyG (Tudek *et al.*, 1992). The second most common DNA base methylation is *N*3-methyladenine (3-meA), which is a potent replication-blocking lesion and is perhaps the most toxic adduct produced by alkylating agents, resulting in TP53 induction, S-phase arrest, chromosomal aberrations and apoptosis (Engelward *et al.*, 1998). In contrast to the limited miscoding potential of N-purines, O^6-methylguanine (O^6-meG) and, to a lesser extent, O^4-methylthymine (O^4-meT) are major contributors to mutagenicity induced by alkylating agents. Endogenous agents may alkylate DNA bases, and among them the best known is *S*-adenosyl-L-methionine (SAM) (Rydberg & Lindahl, 1982). Physiologically, SAM is a methyl donor in many biochemical reactions, and among others it participates in enzymatic methylation of DNA cytosines at C5 position, which, in Eukaryotes, regulates gene expression. Furthermore, adenine methylation in the GATC sequences is used by the MMR system to distinguish between the newly synthesized and template DNA strands in *E. coli* cells (reviewed by Arczewska & Kusmierek, this issue).

Oxidation-induced DNA damage

Reactive oxygen species (ROS), together with reactive nitrogen species (RNS) are known to induce both deleterious and beneficial effects. They can be induced by exogenous or environmental factors such as UV light, X-rays or γ-rays (which produce hydroxyl radical ($^{\bullet}OH$) by radiolysis of water), xenobiotics, cigarette smoke are present as pollutants in the atmosphere. Endogenously, they are formed as by-products of the respiratory electron transport chain, cytochrome P450 and xanthine oxidase metabolism, by micorsomes and peroxisomes, and are also produced by neutrophils, eosinophils and macrophages during inflammation and in various metal-catalyzed reactions (reviewed by: Valko *et al.*, 2006). Aerobically growing cells depend on energy formed by reduction of atmospheric oxygen (O_2) to H_2O by the respiratory electron transport chain (Babcock & Wikstrom, 1992). The main product of mitochondrial respiration is superoxide anion radical ($O_2^{\bullet-}$), which shows limited reactivity, but upon escape from the respiratory electron transport chain induces side effects by further conversion to H_2O_2 by superoxide dismutase (SOD), and then to hydroxyl radical ($^{\bullet}OH$). $O_2^{\bullet-}$ induces $^{\bullet}OH$ formation in the Haber-Weiss reaction ($O_2^{\bullet-} + H_2O_2 \rightarrow O_2 + {}^{\bullet}OH + OH^-$) and also liberates Fe^{3+} from ferritin and reduces it to a Fenton reaction constituent, Fe^{2+}, or liberates Fe^{2+} from iron-sulfur cluster-containing enzymes (Kruszewski & Iwanenko, 2003). H_2O_2 can be reduced to water by catalase and glutathione peroxidase. However, in the presence of transition metal ions, such as iron or copper, H_2O_2 is reduced to $^{\bullet}OH$ by the Fenton-type reaction ($H_2O_2 + Fe^{2+} \rightarrow {}^{\bullet}OH + OH^- + Fe^{3+}$). The reactivity of $^{\bullet}OH$ is so high that it can diffuse no further than one or two molecular diameters before reacting with a cellular component, so it must be generated close to the DNA molecule to be able to oxidize it (Michiels *et al.*, 1994).

In terms of the potential to generate modified bases, oxidation represents the major contributor to baseline DNA damage, with estimates of the total number of oxidized bases formed approximating 10000 adducts per cell per day. Nearly one hundred different free radical DNA modifications have been identified, classified as base- or deoxyribose lesions, strand breaks and cross-links, and among them base alterations comprise about 50 lesions (Halliwell & Aruoma, 1991; Dizdaroglu, 1992). Free radicals attack thymine at two principal sites, i.e. the 5,6-double bond and 5-methyl group. The following oxidized thymines have been detected in DNA: thymine glycol (Tg), 5,6-dihydrothymine (diHT), 5-hydroxy-5,6-dihydrothymine (5-OH-diHT) and 6-hydroxy-5,6-dihydrothymine (6-OH-diHT), 5-hydroxy-5-methylhydantoin (hmh), and many others. Cytosine is oxidized only at the 5,6-double bond, which results in changing the planar aromatic ring structure into a non-planar non-aromatic structure, similarly as in the case of thymine. The main oxidative cytosine modifications found in DNA are 5,6-dihydroxy-5,6-dihydrocytosine (cytosine glycol, Cg), its deamination and dehydration products 5,6-dihydroxy-5,6-dihydrouracil (uracil glycol, Ug) and 5-hydroxycytosine (5-OH-C), respectively; 5-hydroxyuracil (5-OH-U) (formed from Ug by dehydratation or from 5-OH-C by deamination), and many others (Kreutzer & Essigmann, 1998; Purmal *et al.*, 1998).

Hydroxyl radicals react with C8 of guanine, yielding C8-OH adduct radical. The C8-OH adduct radical is oxidized to 7,8-dihydro-8-oxodeoxyguanine (8-oxoG) or is reduced to 2,6-diamino-4-hydroxy-5-formamidopirymidine (FapyG). Both 8-oxoG and FapyG are the major oxidative damages of guanine, and 8-oxoG is regarded as the most abundant oxidative DNA damage being often used as the marker of cellular oxidative stress. Two or three residues of 8-oxoG are present per 10^6 G sites in human leukocytes and roughly 80 8-oxoG residues are continuously generated per human cell per day (Lindahl, 1993; Halliwell, 1999).

Hydroxyl radicals and peroxynitrite can cause damage to DNA both by direct attack on the bases or sugar moieties or indirect, *via* cell membranes lipids peroxidation (LPO). LPO products interact with

DNA resulting in generation of adducts to bases, abasic sites, single or double strand breaks and subsequently chromosomal alterations. Polyunsaturated fatty acids (PUFAs) are constituents of phospholipid membranes, with the most abundant linoleic and arachidonic acids. Attack of ROS and RNS on polyunsaturated fatty acids causes formation of radicals and breaking of double bonds, which leads to lipid molecules fragmentation with generation of aldehydes, epoxides and other reactive keto-compounds, such as malondialdehyde, acrolein, crotonaldehyde, *trans*-4-hydroxy-2-nonenal, and 2,3-epoxy-4-hydoxynonenal. These lipid peroxidation compounds react with exocyclic nitrogen atoms of DNA bases and form exocyclic DNA adducts, in this indirect pathway contributing to oxidative DNA damage (Burcham, 1998).

DNA damage induced by other exogenous and endogenous factors

Apart from the above-described agents also numerous other endogenous and exogenous factors contribute to DNA damage and human diseases. These endogenous factors which can induce DNA modification include: (*i*) base propenols, formed by oxidative DNA damage; (*ii*) estrogens, which can induce DNA damage directly and indirectly, through redox-cycling processes that generate reactive radical species; (*iii*) reactive carbonyl species (RCS) (e.g. glyoxal and methylglyoxal), originating from lipid peroxidation and glycation; (*iv*) chlorinating agents; (*v*) heme precursors; (*vi*) and also amino acids (reviewed by: Burcham, 1999). Another important environmental source of DNA damage is UV light, which induces formation mainly of cyclobutane pyrimidine dimers (CPDs) and 6–4 photoproducts ([6–4]PPs), which have proved to be involved in skin carcinogenesis (reviewed by: Pfeifer *et al.*, 2005).

DNA damage induced by anti-cancer treatments

Agents that induce DNA damage in cells and inhibit DNA repair have successfully been used for decades to treat patients with tumors (Bentle *et al.*, 2006). The DNA affected by anti-cancer treatments is detected by DNA damage sensors, which leads to the activation of TP53. Activation of TP53 can lead to the death of cancer cells (Roos & Kaina, 2006). The efficacy of genotoxins used in humans as anticancer agents is, however, limited by their toxicity to normal tissues. Specific sensitization of tumor cells to the action of anti-cancer treatments would reduce the efficacious doses of genotoxins to be used in patients, diminishing the detrimental side-effects of the drugs on normal tissues. Some drugs, namely bleomycin and neocarzinostatin act by induction of DNA strand breaks (Dedon & Goldberg, 1992; Dedon *et al.*, 1992). DNA cleavage by bleomycin depends on oxygen and metal ions. It is believed that bleomycin chelates metal ions (primarily iron) producing a pseudoenzyme that reacts with oxygen to produce superoxide and hydroxide free radicals that cleave DNA. In addition, these complexes also mediate lipid peroxidation and oxidation of other cellular molecules. The drug is used in the treatment of Hodgkin lymphoma, squamous cell carcinomas, and testicular cancer, pleurodesis as well as plantar warts (Katsara *et al.*, 2006; Kopp *et al.*, 2006; Proctor & Wilkinson, 2006). Temozolomide is an alkylating agent which forms O^6-meG, 7-meG, 3-meA base lesions in DNA. The drug is used for the treatment of refractory anaplastic astrocytoma, a type of cancerous brain tumor (Rabbani *et al.*, 2007).

BER AS THE MOST FREQUENTLY USED DNA REPAIR

The base excision repair pathway is responsible for removal of more than 10 000 DNA lesions daily in each human cell. In addition, lesions targeted by the BER pathway are relatively small, causing little helix distortion. Many of these lesions have been shown not to inhibit elongation by some DNA and RNA polymerases both *in vivo* and *in vitro* (Doetsch, 2002). However, BER is the major repair pathway involved in the removal of DNA damage involving structurally non-distorting and non-bulky lesions, e.g. oxidized or ring-saturated bases, alkylated and deaminated bases, as well as apurinic/apyrimidinic sites, and also some type of mismatches (Lindahl *et al.*, 1997). Proteins engaged in BER are conserved from bacteria to eukaryotes. BER is initiated (*i*) by a damage-specific DNA *N*-glycosylase that recognizes and removes the modified or mismatched base by hydrolysis of the N-glycosidic bond between a 2′-deoxyribose and the base, or (*ii*) by non-enzymatic hydrolytic depurination leading to base loss (described above), as well as (*iii*) by SSBs with ends other than 3′-OH and 5′-P.

DNA damage recognition by DNA *N*-glycosylases

At least 12 genes (plus their splicing variants) and eight ones encoding various glycosylases have been found in mammalian and *Escherichia coli* cells, respectively, with different substrate specificities and modes of action (summarized in Table 1). Glycosylases effectively ensure repair of the majority of endo- and exogenous DNA base lesions. They often contain a conserved motif of helix-harpin-helix (HhH) in the active site, which enables them to bind DNA. These HhH motifs bind a metal ion but only

Table 1. Human and bacterial DNA *N*-glycosylases

Superfamily	**Name** (alternative name)	Size (aa)	Additional activity	Known substrates	Cellular localization	Gene	Chromosomal localization	Biological effect of deficiency	Gene ID at NCBI Entrez
				human *N*-glycosylases					
UDG	**UNG1**	304	no	ssU > U:G> U:A, 5-fluoroU	mitochondria	*UNG*	12q23	ND	7374
UDG	**UNG2**	313	no		nucleus			human have skewed SHM and defective CSR, resulting in elevated IgM and strongly reduced IgG, IgA and IgE; knockout mice show small increase of GC→AT transitions	
UDG	**TDG**	410	no	U:G > εC:G > T:G > T:C > T:T T:O^6-meG, ds5-OH-meU, 5-fluoroU	nucleus	*TDG*	12q24.1	ND	6996
UDG	**SMUG1**	270	no	ssU > U:G > ss5-OH-meU > 5-OH-meU:G > U:A > 5-OH-meU:A > εC:G > 5-fluoroU:A; 5-ForU; 5-OH-U	nucleus	*SMUG*	12q	ND	23583
UDG	**UDG2** (cyclin-like uracil-DNA glycosylase)	327	no	U:A	nucleus	*UDG*	5	ND	10309
AAG	**ANPG** (AAG, MPG, MDG)	298 293 281	no	3-meA, 7-meA, 3-meG, 7-meG, 1,N^2εG, εA, EA, β-Hme-εA, HX, 8-oxoG:C	nucleus	*MPG*	16pter-p13.3	knockout mice are susceptible to 3meA-induced S phase arrest and have chromosome aberrations and show apoptosis	4350
Fpg/MutM	**α-OGG1** (hMMH)	345	AP-lyase *via* β-elimination	me-FapyG:C > FapyG:C > 8-oxoG:C > 8-oxoG:T >> 8-oxoG:G > 8-oxoG:A; 8-oxoA:C	nucleus	*OGG1*	3p26	lung adenoma/carcinoma in human; knockout mice show higher mutation rates in proliferating tissues	4968
Fpg/MutM	**β-OGG1**	424		8-oxoG:C, 8-oxoG:A	mitochondria			ND	
Fpg/MutM	**NEIL1** (NEH1, NEI1, FGP1, hFpg1)	390	AP-lyase *via* β/δ-elimination	8-oxoG:C > 8-oxoG:G > 8-oxoG:T, Tg:G, 5-OH-C, 5-OH-U, diHU, FapyA, FapyG, Me-FapyG; diHT	nuclei in nucleus	*NEIL1*	15q22.33	knockout mice severe obesity, dyslipidemia, fatty liver disease, tendency to develop hyperinsulinemia	79661
Fpg/MutM	**NEIL2** (NEI2)	332	AP-lyase *via* β/δ-elimination	5-OH-U, diHU, 5-OH-C, diHT, Tg, diHU, 8-oxoG:C, 8-oxoG:A	nuclei, and low level in mitochondria	*NEIL2*	8p23.1	ND	252969
Fpg/MutM	**NEIL3** (NEI3, FGP2, hFpg2)	605	AP-lyase *via* β-elimination	FapyG	nuclei but not nucleus	*NEIL3*	4q34.2	ND	55247

HhH-GPD	**MUTYH** (MYH)	521	no	A from A:G, A:8-oxoG, >> 2-oxoA:G, A:C mismatches	mitochondria	*MUTYH*	1p34.3	colorectal adenomatous polyposis in human; knockout mice increased mutation rates, intestinal adenoma/adenocarcinoma	4595
	MUTYH	535			nucleus				
	MBD4 (MED1)	580	no	U or T from U/TpG:5-meCpG or U/T:G, ss5-OH-meU, 5-OH-meU:G, 5-ForU:G, 5-meC, ds5-fluoroU:G	nucleus	*MBD4*	3q21	knockout mice increase of C→T transitions, promotes tumor formation	8930
	NTH1	312	AP-lyase *via* β-elimination	5-OH-C, Tg:A > Tg:G, 5-OH-U, diHU, FapyG:A/G/T, 5-ForU Cg, diHT, 5-OH-diHT	nucleus	*NTHL1*	16p13.3	knockout mice lack of abnormalities	4913
				***E. coli N*-glycosylases**					
UDG	**Ung** (Ugd)	229	no	ssU, dsU:G, 5-OH-U, dihydroxyU	–	*ung*	58.52 min	GC→AT and AT→GC transitions	947067
	Mug (dsUGD, MUG)	166	no	dsU, U:G, T:G, εC, β-Hme-εC, EC, HEC, HPC, meHPC, 1,N^2εG, 5-OH-C, 5-OH-U, 5-OH-meU, 5-ForU	–	*mug*	69.25 min	AT→CG transversions	947560
AAG	**AlkA** (3-meA glycosylase II)	282	no	N^2,3εG, εA, EA, ds3-meA, ss3-meA, 3-meG, O^2-meC, O^2-meT, 7-meA, 7-meG, 8-meG, 5-OH-meU, 5-ForU, HX, X	–	*alkA*	46.23 min	ND	947371
Fpg/MutM	**Fpg** (MutM)	269	AP-lyase *via* β/δ-elimination, dRP-lyase	8-oxoG, FapyG, Me-FapyG, oxz, FapyA, 5-OH-C, 5-OH-U, Tg, diHT, hmh, 5-OH-meU, 5-ForU, Ug, εA, ring opened εA	–	*fgp*	82.08 min	GC→TA transversions	94676
	Nei (endo VIII)	263	AP-lyase *via* β/δ-elimination, dRP-lyase	8-oxoG, FapyA, Tg, 5-OH-diHT, 5-OH-diHU, hmh, 5-OH-meU, 5-ForU, Ug, 5-OH-U, 5-OH-C, diHT, diHU, 5-OH-diHU, dihydroxyU, dihydroxyC	–	*nei*	16.06 min	weak mutator *nth nei* double mutant GC→AT and GC→CG substitutions	945320
HhH-GPD	**Nth** (endo III)	211	AP-lyase *via* β-elimination	Ug, 5-OH-C, 5-OH-U, diHU, Tg, diHT, hmh, 5-OH-diHT, 6-OH-diHT, 5-OH-meU, 5-ForU, 6-OH-diHC, 6-OH-diHU, 5-OH-diHU, dihydroxyC, dihydroxyU, FapyA, ring opened εA	–	*nth*	36.85 min	weak mutator GC→AT and GC→CG substitutions	947122
	MutY	350	no	A from A:8-oxoG, A:G and A:C pairs; 2-oxoA:G	–	*mutY*	66.84 min	GC→TA transversions	947447
	Tag (3-meA glycosylase I)	187	no	3-meA>>3-meG, 7-meG	–	*tag*	79.99 min	low survival rates	947137

during contact with DNA. Four structural superfamilies of DNA glycosylases have been identified. UDG superfamily-1 is based on structural similarity to uracil DNA glycosylase UDG. Enzymes belonging to this family are active against uracil in ssDNA and dsDNA, and recognize uracil explicitly in an extrahelical conformation *via* a combination of protein and bound-water interactions. Some of these enzymes are mismatch specific and explicitly recognize the widowed guanine on the complementary strand rather than the extrahelical scissile pyrimidine. AAG superfamily-2 is based on structural similarity to human alkyladenine DNA glycosylase AAG. Members of the UDG and AAG superfamilies are compact single-domain enzymes with relatively small DNA-interaction surface. MutM/Fpg superfamily-3 is based on structural similarity to bacterial 8-oxoguanine DNA glycosylase Fpg. All known members have the unique feature of using their N-terminal proline residue as the key catalytic nucleophile. HhH-GPG superfamily-4 is named for the characteristic active site borne by family members comprising a helix-harpin-helix followed by a Gly/Pro-rich loop and catalytic aspartate residue (reviewed by: Pearl, 2000; Fromme *et al.*, 2004).

Glycosylases are generally divided into two types: (*i*) *E. coli* Tag, AlkA, UDG, Mug, and MutY and human ANPG, hUNG1 and hUNG2, hSMUG1, hTDG, hUDG2, MUTYH, and hMBD4 monofunctional DNA *N*-glycosylases that remove a deaminated, alkylated or mismatched base leaving an AP-site, and (*ii*) *E. coli* Fpg, Nth, and Nei and human hOGG1, hOOG2, hNTH1, hNEIL1, hNEIL2, and hNEIL3 bifunctional DNA *N*-glycosylases/AP-lyases that remove oxidized or ring-saturated bases and additionally to the glycosylase activity have a 3′-AP-lyase activity which incises the phosphodiester bond at the 3′ side of the deoxyribose *via* β-elimination leaving a single strand break (SSB) with 3'-phospho-α,β-unsaturated aldehyde (3'-PUA) and 5'-phosphate (5'-P) ends. Moreover, *E. coli* Fpg and Nei or mammalian NEIL1 and NEIL2 bifunctional glycosylases additionally carry out δ-elimination reaction with removal of the deoxyribose residue and generation of 3'-phosphate termini (3'-P).

Role of end-processors in DNA repair

The AP-sites or DNA ends generated after lesion excision or excision and incision by mono- or bifunctional glycosylases, respectively, are not suitable for the next repair steps, and as the repair intermediates are very mutagenic when unrepaired by BER (Simonelli *et al.*, 2005). DNA ends containing modified 3′ and/or 5′ ends may also arise as a result of direct chemical modification during SSB formation through the action of ROS (Demple & DeMott, 2002). However, ionizing radiation is a major contributor to the formation of damaged 3′ ends, and anti-tumor drugs, such as bleomycin and neocarzinostatin, can also generate SSBs containing 3′ PUA and 3′-P, respectively (Dedon & Goldberg, 1992). Moreover, blocked 3′ ends in human cells may arise as a result of abortive DNA topoisomerase I (TOP1) activity (reviewed in (Leppard & Champoux, 2005).

At least a few enzymes occur in *E. coli* and human cells that can restore conventional 3′-OH and 5′-P moieties to allow gap filling and DNA ligation (summarized in Table 2). DNA-end processing is probably the most diverse enzymatic step due to the variety of termini that can arise.

AP-endonuclease (APE) is the main enzyme responsible for processing of the BER-intermediates. APE generates 3′-OH termini either by cleaving the phosphodiester bond at the 5′ side of the intact AP-site (after action of a monofunctional *N*-glycosylase or hydrolytic depurination) by its 5′-AP-lyase activity, leaving 5′-deoxyribose phosphate (5′-dRp), or by removal of 3′-PUA or 3′-P (after double action of a bifunctional *N*-glycosylase) by its 3′-phosphoesterase and 3′-phosphatase activities, respectively. *E. coli* APEs, Xth (exonuclease III) and Nfo (endonuclease IV) efficiently incise AP sites and remove both β- and β/δ-elimination products, but mammalian APE1 (termed also APEX, HAP1 or Ref-1) and APE2 have strong AP-lyase and 3'-phosphoesterase activities (Burkovics *et al.*, 2006), respectively, but their 3′-phosphatase activities appear to be very weak. Additionally, Xth, APE1 and APE2 also possess a 3′→5′ exonuclease activity that allows them to remove more than one nucleotide. Xth, APE1 and APE2 can act as a proofreading activity in BER (Hadi *et al.*, 2002; Burkovics *et al.*, 2006).

Additionally, 3′-P can be removed by mammalian polynucleotide kinase (PNK), which, together with NEIL1/NEIL2 glycosylases, forms the APE-independent BER subpathway (Wiederhold *et al.*, 2004). Human PNK is the major DNA 5′-kinase and 3′-phosphatase that is able to phosphorylate the 5′ end of SSBs and removes blocking phosphate lesions from the 3′ end (reviewed by: Dianov & Parsons, 2007). Moreover, also *E. coli* nucleoside diphosphate kinase (NDK) has been shown to have AP-lyase, 3′-phosphodiesterase, 3′-phosphatase and 3′→5′ exonuclease activities (Postel & Abramczyk, 2003; Goswami *et al.*, 2006) but its role in BER is still unclear. An *E. coli* strain lacking NDK shows elevated levels of MMR-dependent base substitutions and frameshifts, induced probably by an altered dNTP pool. All these NDK activities provide a good explanation of the mutator phenotypes induced by NDK depletion (Postel & Abramczyk, 2003; Goswami *et al.*, 2006). Furthermore, human NM23/NDP kinase has been identified as tumor suppressor, and is associated

Table 2. Human and bacterial nucleases engaged in DNA-ends processing during SSBR

Family	**Name** (alternative name)	Size (aa)	Activity	Known substrates	Gene	Chromosomal localization	Biological effect of deficiency	Gene ID at NCBI Entrez
				human nucleases				
Xth/Exo III	**APE1** (APEX, HAP1, Ref-1)	318	AP endonuclease, 3′→5′ exonuclease, 3′ diesterase, 3′ phosphatase	AP-site, 3′-PUA, 3′-P, 3′-OH	*APEX1*	14q12	homozygous deficient mice died during embryonic development following blastocyst formation	328
	APE2	518	AP endonuclease, 3′→5′ exonuclease, 3′ diesterase, 3′ phosphatase	AP-site, 3′-PUA, 3′-P, 3′-OH	*APEX2*	Xp11.21	unknown	27301
RecJ	**FEN1** (MF1)	380	5′dRP-lyase, 5′→3′ exonuclease	5′-flap DNA, 5′-dRP	*FEN1*	11q12	knockout mice are not viable	2237
NM23/ NDK	**PNK** (PNKP)	521	5′-kinase, 3′-phosphatase	3′-P	*PNKP*	19q13.3	unknown	11284
PLD (phospholi- pase D)	**TDP1**	608	tyrosyl-DNA phosphodiesterase 1	3′-TOP1-SSB-peptide	*TDP1*	14q32.11	spinocerebellar ataxia with axonal neuropathy-1 (SCAN1)	55775
p53	**TP53** (LFS1, TRP53, p53)	393	3′→5′ exonuclease	3′-OH	TP53	17p13.1	colon tumors and breast cancer predisposition	7157
HIT (histidine triad)	**APTX** (AOA, AOA1, AXA1, EAOH, EOAHA, FHA-HIT, FLJ20157, MGC1072)	342	5′ exonuclease, 3′ exonuclease	5′-P-adenylate group, 3′-PUA, 3′-P	*APTX*	9p13.3	ataxia oculomotor apraxia (AOA1)	54840
HMG-box proteins	**HMGB1** (DKFZp686A04236, HMG1, HMG3, SBP-1)	215	5′dRP-lyase	5′-dRP	*HMGB1*	13q12	unknown	3146
DnaQ	**TREX1** (AGS1, AGS5, CHBL, CREN, DKFZp434J0310, DRN3)	369 314	3′→5′ exonuclease	3′-OH, 3′-mismatch	*TREX1*	3p21.31	mutant mice do not exhibit a phenotype	11277
	TREX2	236	3′→5′ exonuclease	3′-OH, 3′-mismatch	*TREX1*	Xq28	unknown	11219
				***E. coli* nucleases**				
Xth/Exo III	**Xth** (exo III)	268	AP-endonuclease, 3′→5′ exonuclease, 3′ diesterase, 3′-phosphatase	AP-site, 3′-PUA, 3′-P, 3′-OH	*xth*	39.46 min	increased level of base substitutions	3897515
Endo IV	**Nfo** (endo IV)	285	AP-endonuclease, 3′→5′ exonuclease, 3′ diesterase, 3′-phosphatase	AP-site, 3′-PUA, 3′-P, 3′-OH	*nfo*	48.48 min	increased level of base substitutions	946669
RecJ	**RecJ**	577	5′dRP-lyase, 5′→3′ exonuclease	5′-dRP, 5′-ssDNA	*recJ*	65.41 min	ND	947367
Endo V	**Nfi** (endo V)	223	3′ exonuclease	AP-site, 3′-mismatch	nfi	90.45 min	increased level of AT→GC and GC→AT transitions	948502
NM23/ NDK	**NDK**	143	AP-endonuclease, 3′-phosphatase, 3′→5′ exonuclease	AP-site, 3′-P, 3′→5′ exonuclease	*ndk*	54.2 min	increased level of base substitutions and frameshifts	945611

with tumor metastasis. Its reduced expression seems to be related to an increased metastatic potential in most cancer cell types. Moreover, NM23/NDK kinase was also shown to activate transcription and to have a nuclease activity (Postel *et al.*, 2000; 2002).

Although, tyrosyl-DNA phosphodiesterase 1 (TDP1) is not involved in the major BER pathway, it may be a DNA-end processor during SSBs repair. The primary substrates for TDP1 are the TOP1-linked 3′ ends (TOP1-SSBs) that arise through abortive topoisomerase I (TOP1) activity, which can be induced by the drug camptothecin or by nearby unusual DNA secondary structures or other types of DNA lesions (Plo *et al.*, 2003; Caldecott, 2007; El-Khamisy *et al.*, 2007). TDP1 converts the 3′-TOP1-SSB peptide complex into a 3′-P end further processed by PNK (Connelly & Leach, 2004). TDP1 is mutated in the neurodegenerative disease spinocerebellar ataxia with axonal neuropathy-1 (SCAN1). In addition to being defective in the removal of stalled 3′-TOP1–SSB intermediates, SCAN1 cells also exhibit a reduced capacity to excise the 3′-phosphoglycolate end, a common oxidative damage (Straussberg *et al.*, 2005; Zhou *et al.*, 2005).

Aprataxin (APTX), the protein defective in the neurological disorder ataxia oculomotor apraxia (AOA1), is a member of the HIT domain superfamily of nucleotide hydrolases/transferases. Cells deficient in APTX are defective in SSBR. APTX has been found to be involved in resolution of abortive DNA ligation intermediates by catalysing the nucleophilic release of adenylate groups covalently linked to 5′P-ends at single-strand nicks and gaps (Ahel *et al.*, 2006). APTX is also responsible for the repair of typically endogenous damage produced by reactive oxygen species on 3′ DNA ends, including 3′-PUA and 3′-P (Takahashi *et al.*, 2007). APTX acts preferentially on adenylated nicks and DSBs rather than on SSBs. Moreover, APTX has been found to act in BER, specifically in the removal of adenylates that arise from abortive ligation reactions that take place at incised AP-sites in DNA, and may have a general proofreading function in DNA repair, removing DNA adenylates as they arise during SSBR, DSBR, and in BER (Rass *et al.*, 2007).

Flap endonuclease activity (FEN-1) possesses (*i*) 5′→3′ exonuclease activity which is involved in maturation of Okazaki fragments during mammalian DNA replication, and (*ii*) endonuclease activity which removes 5′-dRP-containing flap during LP-BER (Garg & Burgers, 2005; Liu *et al.*, 2005). *Fen1*$^{-/-}$ knockout mice are not viable (Friedberg & Meira, 2004).

Recently, it has been found that the high-mobility group box 1 protein (HMGB1) specifically interacts with a BER intermediate. HMGB1 possesses weak dRP-lyase activity and stimulates AP-endonuclease and FEN1 activities on BER substrates (Prasad *et al.*, 2007).

DIFFERENT BER SUB-PATHWAYS

BER proceeds further *via* two alternative subpathways (Fig. 2): short-patch (SP), which involves replacement of one nucleotide, or long-patch (LP), which involves replacement of several nucleotides (at least 2, often 6–13 nucleotides).

SP-BER

Oxidized and ring-saturated bases are recognized and removed from DNA by the bifunctional DNA *N*-glycosylases/AP-lyases. Next, APEs remove 3′-PUA and 3′-P (for more details see above) leaving 3′-OH and 5′-P ends suitable for filling by mammalian Pol β or *E. coli* Pol I and for end-sealing by mammalian LIG3α or bacterial ligase I. In contrast, alkylated and deaminated bases as well as some types of mismatches, are recognized and removed from DNA by the monofunctional DNA *N*-glycosylases. In this process the N-glycosydic bond connecting the aberrant base to the sugar-phosphate backbone is cleaved and an AP-site is created (Krokan *et al.*, 1997). The AP-site is recognized and processed by the APEs (Taylor & Weiss, 1982) that hydrolyze the phosphodiester DNA backbone at the 5′ side of the AP-site, leaving 3′-OH and 5′-dRP ends flanking the gap. From this point, the choice of the pathway depends on the ability of the enzymes to remove the 5′-sugar phosphate. In mammalian cells both pathways are initiated by Pol β, which inserts one nucleotide into the repair gap. In SP-BER Pol β also removes 5'-dRP by its 5'-dRPase activity, and finally DNA LIG3α–XRCC1 complex seals the ends. Additionally, Pol λ may partially backup Pol β, since it has a 5'-dRPase activity. XRCC1 is a platform protein and was shown to interact with Pol β, LIG3α, PNK, APE1 and PARP-1 (Fig. 3). The lesions removed by bifunctional DNA glycosylases are processed mainly by SP-BER, since the 3'-OH and 5'-phosphate ends may be readily filled in by Pol β. In *E. coli*, 5′-dRP is removed by Fpg, Nei, or RecJ or by the 5′→3′ exonuclease activity of Pol I, and the resulting gap is filled in by Pol I and sealed by DNA ligase I.

LP-BER

In human cells modification of the 5′-dRP moiety by oxidation or reduction prevents its excision by Pol β and the lesion is further processed by LP-BER. First, Pol β falls off and PCNA (replication sliding clamp) is recruited together with Pol δ or Pol ε. The polymerase adds a few nucleotides to

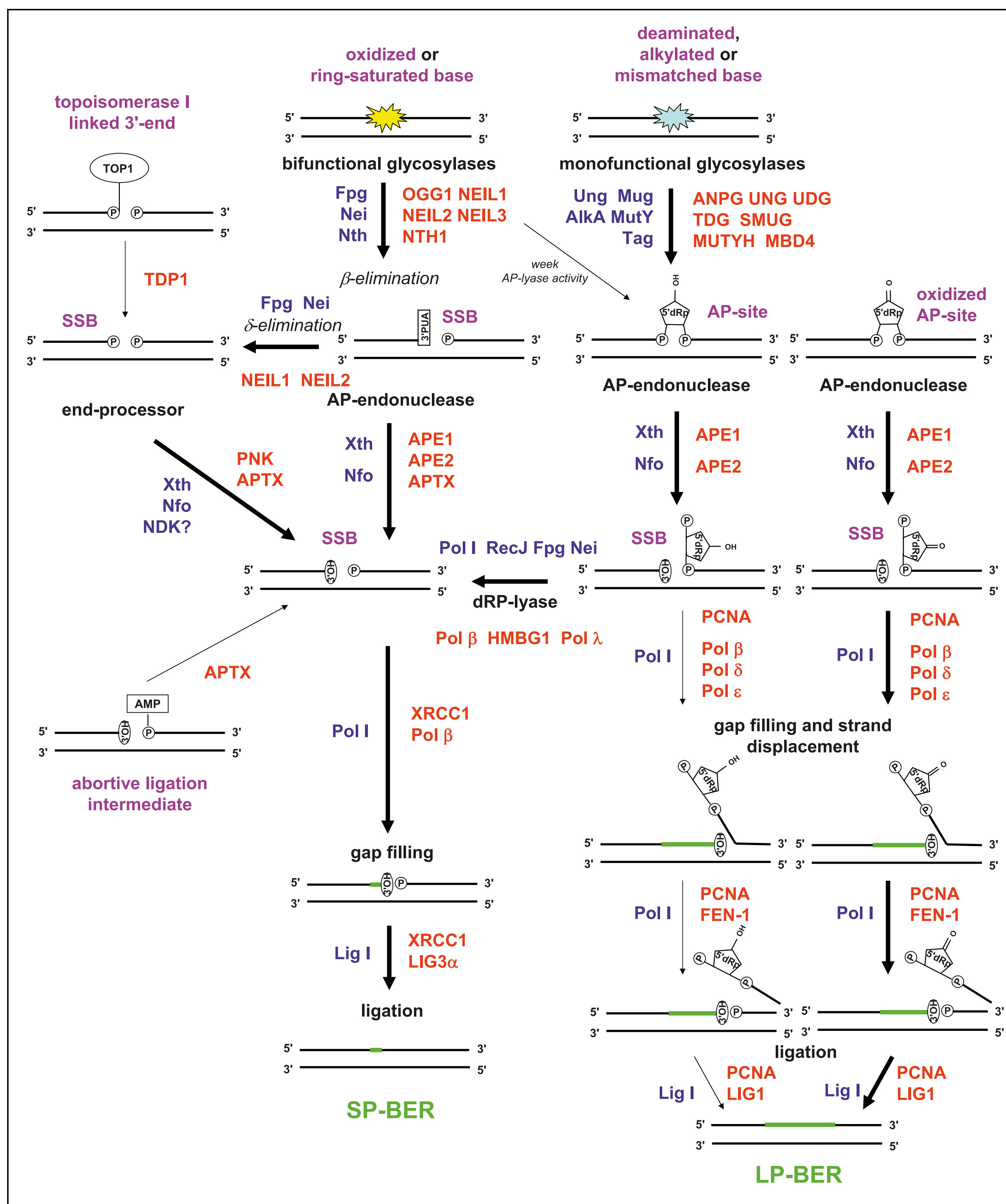

Figure 2. Model for the BER and SSBR subpathways.
P, phosphate; OH, hydroxyl group; 3'PUA, 3'-unsaturated aldehyde; 5'dRp, 5'-deoxyribose phosphate; AMP, adenylate group; TOP1, topoisomerase I-linked 3'-end.
The types of DNA lesions repaired by common subpathways of single strand breaks repair and base excision repair are marked in purpure. *Escherichia coli* enzymes are on left, and are in blue, human enzymes shown on right, are in red.

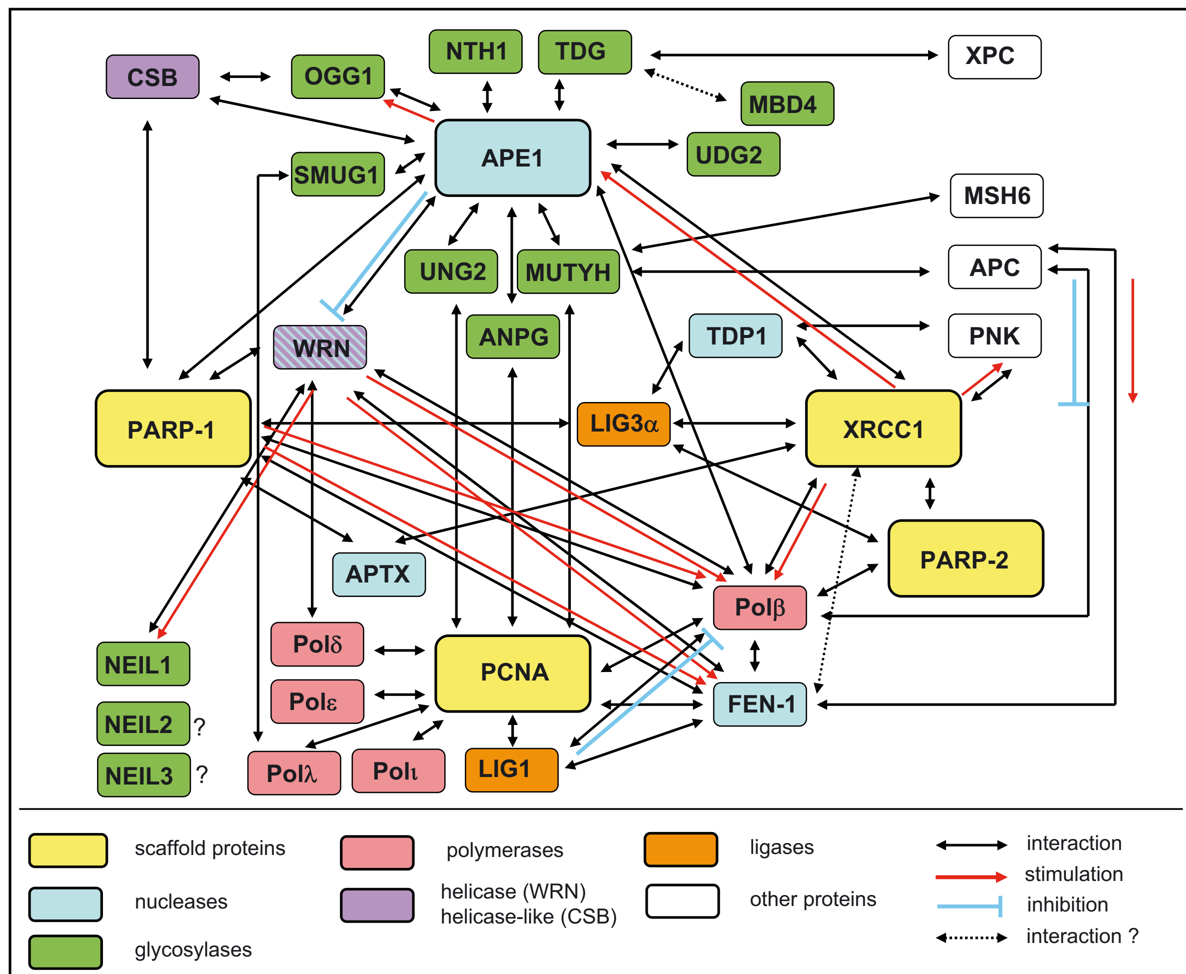

Figure 3. Scheme of interaction between the main proteins involved in human BER and SSBR.
Cartoon is based on: for APE1 interaction: (Bennett *et al.*, 1997; Privezentzev *et al.*, 2001; Vidal *et al.*, 2001b; Yang *et al.*, 2001; Kavli *et al.*, 2002; Marenstein *et al.*, 2003; Xia *et al.*, 2005), for XRCC1 interaction: (Caldecott *et al.*, 1995; Vidal *et al.*, 2001a; Whitehouse *et al.*, 2001; Plo *et al.*, 2003; Clements *et al.*, 2004; Dianova *et al.*, 2004; Caldecott, 2007), for PARP interaction: (Allinson *et al.*, 2003; Leppard *et al.*, 2003; von Kobbe *et al.*, 2003; von Kobbe *et al.*, 2004; Thorslund *et al.*, 2005), for PCNA interaction: (Klungland & Lindahl, 1997; Parker *et al.*, 2001; Xia *et al.*, 2005; Fortini & Dogliotti, 2007; Wilson & Bohr, 2007).

the 3'-OH end and generates a flap containing the 5'-dRP end, which is then removed by FEN-1 and finally the ends are sealed by DNA ligase I (LIG1). PCNA interacts not only with the polymerase, but also with FEN-1 and LIG1 (Fig. 3). Furthermore, replication protein A (RPA), which interacts with the MUTYH and UNG2 glycosylases, is required by Pol δ and Pol ε for DNA synthesis, and may stimulate LP-BER. Pol δ requires also replication factor C (RF-C; which loads the PCNA sliding clamp on the double helix) and PCNA for efficient synthesis, while Pol ε is highly processive in the absence of PCNA (reviewed by: Krokan *et al.*, 1997; Nilsen & Krokan, 2001; Dianov *et al.*, 2003; Slupphaug *et al.*, 2003; Sung & Demple, 2006). If in *E. coli* cells the 5'-dRp residue is not removed prior to repair synthesis, Pol I displaces the dRP-containing strand *via* a strand displacement reaction (Mosbaugh & Linn, 1982) during filling of the gap. The displaced strand is cleaved by the 5′→3′ exonuclease activity of Pol I (Xu *et al.*, 1997; Xu *et al.*, 2001), and 2 to 8 or even more nucleotides are removed and replaced, leading to so-called long-patch BER (LP-BER) (Radicella *et al.*, 1993; Sung & Mosbaugh, 2003). Furthermore, the length of repair synthesis may also be determined by the availability of DNA ligase I, its lack leading to longer repair patches *in vitro* (Sung & Mosbaugh, 2003).

In mammalian cells 8-oxoG is repaired *via* a 2–6-nucleotide patch, since the hOGG1 3′-AP-lyase activity is 10 times lower than its *N*-glycosylase activity, and repair proceeds *via* LP-BER (Sattler *et al.*, 2003). Furthermore, APE1 has been shown to

increase hOGG1 turnover on damaged DNA and stimulate its excision activity (Hill *et al.*, 2001). BER is further complicated by other proteins which interact with its components (Fig. 3). PARP-1 binds to SSB immediately after its formation and dissociates after self-poly(ADP-ribosyl)ation. PARP-1 has been proposed to prevent cleavage of the strand break ends by nucleases, and was also shown to stimulate LP-BER strand displacement synthesis by Pol β (Dianov *et al.*, 2003; Parsons *et al.*, 2005). Furthermore, Werner syndrome protein (WRN) stimulates Pol β strand displacement DNA synthesis *via* its helicase activity, and provides proofreading of 3'-mismatches *via* its 3'→5' exonuclease activity (which is absent in Pol β) (Harrigan *et al.*, 2006). Additionally, Cockayne syndrome group B (CSB) functions in the catalysis of 8-oxoG excision by BER and in the maintenance of efficient hOGG1 expression (Tuo *et al.*, 2002).

MUTAGENESIS IN *E. COLI* CELLS CAUSED BY DYSFUNCTION OF BER PROTEINS

DNA guanine is frequently oxidized to 8-oxoG, which, if unrepaired, can be bypassed by DNA polymerases and pair with its cognate C as well as noncognate A, leading to GC→TA transversions. *E. coli* has evolved a complicated strategy to avoid mutations from this commonly oxidized base. Fpg (also called MutM), removes 8-oxoG paired with C in DNA, while the MutY protein removes A mispaired with 8-oxoG. Finally, the MutT protein, an 8-oxodGTPase, removes oxidized dGTPs from the nucleotide pool, preventing their misincorporation opposite adenine (reviewed by Arczewska & Kusmierek, this issue). *E. coli* mutants defective in Fpg or MutY, and double mutants lacking both proteins, exhibit higher than wild type spontaneous mutation frequencies (Au *et al.*, 1988; Cabrera *et al.*, 1988; Boiteux & Huisman, 1989; Michaels *et al.*, 1991; Fowler *et al.*, 2003; Speina *et al.*, 2005b; Hamm *et al.*, 2007). Mutants lacking the MutT protein also exhibit high spontaneous mutation frequencies (Akiyama *et al.*, 1989). Oxidized pyrimidines are repaired in *E. coli* by Nth (endo III) and Nei (endo VIII). The *nth* mutants exhibit a small mutator phenotype, while *nei* mutants exhibit no mutator phenotype. Double mutants, lacking both proteins, exhibit spontaneous mutation frequency higher than the wild type (Saito *et al.*, 1997). Surprisingly, triple mutants lacking Fpg, MutY, and Nei and quadruple mutants lacking all four DNA glycosylases, Fpg, MutY, Nei, and Nth, exhibit significant synergistic effects, suggesting an overlap in the substrate specificities of the "pyrimidine-specific" and "purine-specific" enzymes (Blaisdell *et al.*, 1999). Moreover, the *nth nei* double mutants are hypersensitive to ionizing radiation and hydrogen peroxide but not as sensitive as APEs mutants *xth nfo*. Single *nth* mutants exhibit wild-type sensitivity to X rays, while *nei* mutants are consistently slightly more sensitive than the wild type. Additionally, *ung* cells are not able to initiate base excision repair of uracil-containing DNA. These mutants have a high GC→AT mutation rate because they are not able to repair deaminated cytosine residues. Uracil residues also accumulate in the DNA of *ung* mutants as a consequence of the occasional biosynthetic incorporation of uracil into DNA in place of thymine (Duncan & Weiss, 1982). The *mug* mutant does not show a mutator phenotype in dividing *E. coli*, and is only a modest mutator in stationary phase cells (Jurado *et al.*, 2004). It is possible that this lack of a strong phenotype is caused by the presence of alternative enzymes in *E. coli* that process the promutagenic lesion U and the T:G mispair. However, *E. coli mug* mutant is sensitive for agents causing etheno-adducts (Maciejewska, unpublished; Borys-Brzywczy *et al.*, 2005). Moreover, *E. coli* possesses two different DNA repair glycosylases, Tag and AlkA, which have similar ability to remove the alkylation product 3-meA from dsDNA. These enzymes have quite different activities for the excision of 3-meA from ssDNA, AlkA being 10–20 times more efficient than Tag. AlkA may have an important role in the excision of base damage from single-stranded regions transiently formed in DNA during transcription and replication (Bjelland & Seeberg, 1996). All bacterial DNA *N*-glycosylases are summarized in Table 1. The double *xth nfo E. coli* strain devoid of BER is very sensitive to H_2O_2 and MMS. Moreover, the triple mutant for the DNA repair genes *xth nth nfo*, chronically induces the SOS response (Janion *et al.*, 2003). Bacterial nucleases are summarized in Table 2.

PROCESSES CONTROLLED BY DNA GLYCOSYLASES IN HUMAN CELLS

The sources of uracil in DNA are spontaneous or enzymatic deamination of cytosine (U:G mispairs) and incorporation of dUTP (U:A pairs), inducing CG→TA transitions during DNA replication (Duncan & Weiss, 1982). Uracil is usually an inappropriate base in DNA, but it is also a normal intermediate during somatic hypermutation (SHM) and class switch recombination (CSR) in adaptive immunity. In B-cells cytosine is actively deaminated to uracil by activation-induced cytosine deaminase (AID), which leads to numerous CG→TA transitions in the immunoglobulin (Ig) *Ig* locus. This process increases immunoglobulin diversity. Paradoxically, proteins involved normally in error-free base excision repair and mismatch repair, seem to be co-opted to facilitate SHM and CSR, by recruiting error-prone transle-

sion polymerases to the DNA temple containing dU created by AID (Neuberger *et al.*, 2003; Samaranayake *et al.*, 2006).

Mammalian cells posses at least four enzymes with UDG activity, namely UNG, TDG, SMUG1 and MBD4. The major ones are nuclear UNG2 and mitochondrial UNG1 encoded by the *UNG* gene (Nilsen *et al.*, 1997) and SMUG1 that also removes oxidized pyrimidines. The other ones are TDG that removes U and T from mismatches arising after deamination of C and 5-meC, respectively, and methyl binding domain IV (MBD4) that removes U from CpG contexts. UNG2 is found in replication foci during the S-phase and has a distinct role in the repair of U:A pairs, but it is also important in U:G repair, a function shared with SMUG1. Humans lacking UNG2 suffer from recurrent infections and lymphoid hyperplasia, and have skewed SHM and defective CSR, resulting in elevated IgM and strongly reduced IgG, IgA and IgE. UNG-defective mice also develop B-cell lymphoma late in life. The Phe251Ser UNG2 variant protein has been found to be mistargeted to mitochondria, resulting in deficient nuclear activity and increased uracil genomic content (Akbari *et al.*, 2007; Kavli *et al.*, 2007).

5-meC is normally present in DNA and constitutes up to 30% of total number of cytosines in the mammalian cell and at CpG sequences 5-meC is involved in silencing of gene expression (Li *et al.*, 1992; Yoder *et al.*, 1997). In humans, G:T mispairs arise from replication errors, which are handled by the mismatch repair pathway, or from the deamination of 5-meC to T. Because cytosine methylation occurs at CpG dinucleotides, G:T mispairs caused by 5-meC deamination are found at CpG sites. It has been shown that TDG is active for G:T mispairs with a 5′ C:G pair, suggesting that a predominant biological role of the enzyme is to initiate the repair of CpG:T lesions. However, the U:G mispair is the most efficiently processed physiological substrate for TDG (Gallinari & Jiricny, 1996; Hardeland *et al.*, 2001; Cortazar *et al.*, 2007). Epigenetic silencing through methyl-CpG (mCpG) is implicated in many biological patterns such as genomic imprinting, X chromosome inactivation, and cancer development as well as the silencing of repetitive genetic elements. According to the facts described above, TDG could contribute to tumor suppression in a number of different ways: it may (*i*) help maintain genomic stability through the repair of mutagenic DNA base damage (e.g. deamination of C or 5-meC); (*ii*) provide epigenetic stability through the excision of erroneously methylated Cs in gene regulatory sequences; (*iii*) and/or it may assure proper cell differentiation and control the number of stem cells and/or tumor progenitor cells in certain tissues by its ability to cooperate with nuclear receptors and other transcription factors that integrate differentiation signals (Cortazar *et al.*, 2007).

Another human DNA glycosylase, mentioned earlier, MBD4, exhibits specificity for G:T mispairs at CpG sites and also plays a role in the integrity of CpG sites (Hendrich *et al.*, 1999). It has been shown that MBD4 binds to hypermethylated promoter of the *MLH1* gene (MLH1 is a MMR protein). These results suggest that also MBD4 is one of the essential components involved in epigenetic silencing and its repair activity is necessary for the maintenance of hypermethylated promoters (Kondo *et al.*, 2005).

Taking it all together, in human cells a few mechanisms exist that regulate the level and activity of DNA glycosylases by post-translational modifications (reviewed by: Tudek, 2007). Also UNG2 expression is up-regulated during S-phase of the cell cycle where the protein associates with PCNA and RPA at replication foci, implicating a role for this glycosylase in the removal of misincorporated U during DNA replication. Conjugation of SUMO to TDG induces glycosylase dissociation from DNA (Baba *et al.*, 2006). Cells entering S-phase eliminate TDG through the ubiquitin-proteasome pathway. Degradation of TDG is critical for S-phase progression and cell proliferation. Strikingly, TDG levels decline just when UNG2 expression goes up and *vice versa*, suggesting that uracil repair is handled by distinct pathways throughout the cell cycle that are coordinated by the ubiquitin-proteasome system. The inability of TDG to discriminate between the parental and newly synthesized DNA strands would fix C→T transition mutations in cases where the T is in the parental strand. In addition, TDG-induced postreplicative G:T repair in the parental DNA strand, particularly in the parental lagging strand, could destabilize the replication fork and thereby impede the replication process. Thus, G:T correction during DNA synthesis should be left to the postreplicative mismatch repair system, which is designed to correct the error in the newly synthesized DNA strand (Hardeland *et al.*, 2007).

Expansion of CAG trinucleotide repeats encoding polyglutamine has been identified as the pathogenic mutation in at least nine different genes associated with hereditary neurodegenerative disorders, including Huntington's disease (HD), dentatorubral pallidoluysian atrophy (DRPLA), spinal and bulbar muscular atrophy (SBMA), and the spinocerebellar ataxias: SCA1, SCA2, SCA3 (also known as Machado-Joseph disease), SCA6, SCA7, and SCA17 (Adachi *et al.*, 2007; Underwood & Rubinsztein, 2007; Walker, 2007). Also, the two most common triplet expansion human diseases, myotonic dystrophy 1 and fragile X syndrome, are caused by expanded CTG/CAG and CGG/CCG repeats, respectively (Wang, 2007). Moreover, oxidative lesions are known to be

associated with ageing and neurological diseases (Olinski *et al.*, 2007). Recently it has been found that the age-dependent somatic mutation associated with Huntington's disease occurs in the process of removing oxidized base lesions (8-oxoG) and is remarkably dependent on OGG1. OGG1 was shown to initiate an escalating oxidation-excision cycle that leads to progressive CAG expansion. Age-dependent CAG expansion provides a direct molecular link between oxidative damage and toxicity in post-mitotic neurons through a DNA damage response and error-prone repair of SSBs (Kovtun *et al.*, 2007).

COULD APC BE A FACTOR DETERMINING THE PATCH SIZE DURING REPAIR SYNTHESIS?

The *adenomatosis polyposis coli* (APC) tumor suppressor is a multifunctional protein that is mutated in a majority of colon cancers. Close examination of the function of APC has shown that this multifunctional protein is involved in a wide variety of processes, including regulation of cell proliferation, cell migration, cell adhesion, cytoskeletal reorganization, and chromosomal stability. Clues to the different functions of APC have been provided by the identification of proteins interacting with several discrete motifs within APC. Each of these putative functions could link APC inactivation to cancerogenesis (reviewed by: Fodde *et al.*, 2001; van Es *et al.*, 2001).

Familial adenomatous polyposis (FAP) is caused by mutations in the *APC* gene. More than 800 mutations in the *APC* gene have been identified in families with classic and attenuated types of familial adenomatous polyposis. Most of these mutations cause the production of an APC protein that is abnormally short and nonfunctional. This short protein cannot suppress the cellular overgrowth that leads to the formation of polyps, which can become cancerous. The most common mutation in FAP is a deletion of five bases in the *APC* gene. This mutation changes the sequence of amino acids in the resulting APC protein beginning at positions 1309. Additionally, Ile1307Lys, Glu1317Gln, Asp1822Val, and other polymorphisms have been found. However, these kinds of polymorphism in *APC* gene are regional and population specific and are responsible together with environmental factors for the risk of colorectal cancer (Friedl *et al.*, 2001; Locker *et al.*, 2006; Guerreiro *et al.*, 2007). Also, the Ile1307Lys mutation has been found to be clearly associated with a somatic additional adenine insertion in the region of codons 1306–1309, but other mutations in the region of codons 1277–1348 were found to be no more prevalent in carriers than in noncarriers (Zauber *et al.*, 2005).

Recently it has been shown that human APC protein can interact with the human DNA Pol β-mediated one-nucleotide as well as strand-displacement synthesis of reduced abasic, nicked-, or 1-nt gapped-DNA substrates. APC also blocks strand-displacement synthesis of LP-BER and 5'-flap endonuclease as well as the 5'→3' exonuclease activity of FEN-1, resulting in the blockage of LP-BER. These studies will have important implications for understanding APC role in DNA damage-induced carcinogenesis and chemoprevention, especially critical APC role in several cellular processes (Narayan *et al.*, 2005; Jaiswal *et al.*, 2006).

Moreover, the fidelity of BER is dependent on the polymerization step, where the major BER Pol β incorporates nucleotide into the gap. Recent studies have indicated that expression of some Pol β variants or changes in expression of wild type Pol β protein, frequently found in cancer cells, can lead to DNA repair synthesis errors and confers to cells a mutator phenotype (reviewed by: Chan *et al.*, 2006). In this case, it can not be excluded that APC could act not only as a factor determining the patch size during repair synthesis in BER by Pol β but also as a factor limiting the spearing of incorrect incorporation by Pol β.

BER ENZYMES AS BIOMARKERS IN MOLECULAR EPIDEMIOLOGY

Oxidative DNA damage and DNA repair mediate the development of several human pathologies, including cancer. The major pathway for oxidative DNA damage repair is base excision repair. Functional assays performed in blood leukocytes of cancer patients and matched controls show that specific BER pathways are decreased in cancer patients, and may be risk factors (Olinski *et al.*, 1998). These include 8-oxoguanine (8-oxoG) repair in lung and head and neck cancer patients and repair of lipid-peroxidation-induced εA in lung cancer patients. Decrease of excision of lipid peroxidation-induced DNA damage εA and εC was observed in blood leukocytes of patients developing lung adenocarcinoma, a specific histological type of cancer related to inflammation and healing of scars (Gackowski *et al.*, 2003; Speina *et al.*, 2003; Speina *et al.*, 2005a). The activity of BER proteins depends on gene polymorphism, interactions among BER system partners, and post-translational modifications. Polymorphisms of DNA glycosylases may change their enzymatic activities, and some polymorphisms increase the risk of inflammation-related cancers, colorectal, lung and other types.

Alternative splicing of the human *OGG1* gene produces two major protein isoforms, α-OGG1 and

β-OGG1. β-OGG1 is transferred to mitochondria, while α-OGG1 is targeted to the nucleus. Both isoforms of human OGG1 exhibit the same catalytic activity. Several single nucleotide polymorphisms (SNP) are present in *OGG1* sequence, with Ser326Cys (C→G in exon 6) being the most frequent. The Cys326 variant has lower activity than Ser326 and is not stimulated by APE1. Since APE1 stimulates excision of 8-oxoG from DNA by OGG1, it seems reasonable that the activity of 8-oxoguanine DNA glycosylase is significantly affected by the Ser326Cys polymorphism (Collins & Gaivao, 2007). Therefore, the human OGG1-Cys326 variant has been proposed to increase the risk of lung cancer, prostate cancer, and nasopharyngeal carcinoma. Also the rare Arg154His (G→T) OGG1 polymorphism has been identified in sporadic colorectal cancers but did not segregate with cancer phenotypes. Two other less frequent OGG1 polymorphisms, Arg46Gln and Arg154His, also influence OGG1 activity and were detected in human lung and gastric cancers (reviwed by: Nohmi *et al.*, 2005).

Alternative splicing of the human *MUTYH* gene produces two major protein isoforms, type 1 (535 amino acids), which localizes in mitochondria, and type 2 (521 amino acids), which is transferred to the nucleus. Interestingly, type 2 protein has a higher glycosylase activity than type 1 protein. MUTYH interacts with a number of proteins, such as RPA, APE1, PCNA and MSH6 (Fig. 3), and its expression is increased during S phase. Thirty various mutations that are predicted to turncate the protein product have been reported in *MUTYH* gene, comprising 11 nonsense, 9 small insertion/deletion and 10 splice site variants. In addition, 52 missense variants and 3 small inframe insertion/deletions have been reported (reviewed by: Cheadle & Sampson, 2007). Gly382Asp and Tyr165Cys substitutions cover more than 70% mutations reported in *MUTYH* gene and are linked with higher cancer incidence. The Gly382Asp and Tyr165Cys MUTYH variant proteins that are devoid of glycosylase activity towards the 8-oxoG:A pair, have been found in familial polyposis. These mutations are associated with GC→TA transversions in the *APC* gene. Other *MUTYH* alterations which have been found in patients with colorectal tumors are missense Tyr90 or Glu466 to stop codon mutations (reviewed by: Nohmi *et al.*, 2005).

For other components of BER, the association of mutations in genes encoding proteins engaged in base excision repair with cancerogenesis appears less consistent. However, Pol β has been found to be overexpressed at both mRNA and protein level in about 30% of all tumors studied, with the overexpression being particularly frequent in uterus, ovary, prostate and stomach. Pol λ and Pol ι were also found to be overexpressed to a significant extent in a range of tumor types, albeit less frequently than Pol β (Albertella *et al.*, 2005). Additionally, approx. 30% of human tumors examined for mutations in *POLB* gene appear to express Pol β variant proteins (Starcevic *et al.*, 2004). Many of these variants result from a single amino-acid substitution. The Lys289Met and Ile260Met variants exhibit reduced polymerase fidelity and are observed in colon and prostate cancer, respectively (Lang *et al.*, 2004; 2007; Sweasy *et al.*, 2005). Moreover, the Glu295Lys gastric carcinoma Pol β variant acts in a dominant-negative manner by interfering with BER, which leads to an increase in sister chromatid exchanges and genomic instability indicating that BER is critical for maintaining genome stability and could therefore be a tumor suppressor mechanism (Lang *et al.*, 2007). The Pro242Arg and Lys289Met polymorphism of Pol β can be an auxiliary marker for breast cancer risk and cancer progression (Sliwinski *et al.*, 2007). Apart from the single substitution, several Pol β cancer-related variants were found, e.g. truncation and deletion mutants. The wild type and truncated forms of Pol β proteins are expressed in primary colorectal and breast adenocarcinomas and in a primary culture of renal cell carcinoma. Three types of deletion variants were detected in squamous, non-small, or large cell carcinomas. The most common variant was a deletion of 87 bp from *POLB* cDNA at a site corresponding to exon 11. In addition, a variant exhibiting deletions of 87 and 140 bp together with an insertion of 105 bp was identified in lung tumors (Bhattacharyya & Banerjee, 1997; Bhattacharyya *et al.*, 1999; Chen *et al.*, 2000; Bhattacharyya *et al.*, 2001; Bhattacharyya & Banerjee, 2003). Additionally, the 208–236 deletion variant found in many human tumors has been shown *ex vivo* to reduce BER capacity. *Pol* $\beta^{-/-}$ knockout mice are not viable and *Pol* $\beta^{+/-}$ haploinsufficient mice demonstrate higher level of SSBs and increased chromosomal aberrations (Cabelof *et al.*, 2003). Also a few SNPs in *POLL* and *POLI* genes were found, resulting in amino-acid substitutions within the Pol λ and Pol ι variant proteins, respectively. Mutation in *POLI* has been shown to be associated with NSCLC (Sakiyama *et al.*, 2005).

The Arg399Glu (G→A in exon 10) and Arg194Trp (C→T in exon 6) polymorphisms of the BER platform protein XRCC1 are connected with increased risk of tobacco-related cancers (Santella *et al.*, 2005; Shen *et al.*, 2005). In contrast, a lack of association of XRCC1 Arg399Gln polymorphism with chronic myelogenous leukemia has been observed recently (Deligezer *et al.*, 2007). *Xrcc1*$^{-/-}$ knockout mice are not viable (Friedberg & Meira, 2004).

Several amino-acid substitution variants were identified in the repair domain of human APE1. Functional characterization revealed that the variants, Leu104Arg, Glu126Asp and Arg237Ala, exhibited approx. 40–60% reductions in specific incision

activity. Moreover, the Asp283Gly and Asp283Ala variants were found to exhibit approx. 10% repair capacity. The most common substitution Asp148Glu had no impact on endonuclease and DNA binding activities, nor did the Gly306Ala substitution. The Gly241Arg variant showed a slightly enhanced endonuclease activity relative to the wild type. All reduced function variants may be associated with increased disease susceptibility (Hadi *et al.*, 2000). However, a significant association between the Asp148Glu (T→G in exon 5) polymorphism in *APE1* gene and lung cancer risk was found (De Ruyck *et al.*, 2007). *Ape1*$^{-/-}$ knockout mice are not viable (Friedberg & Meira, 2004).

Poly(ADP-ribose) polymerase 1 (PARP-1) modifies a variety of nuclear proteins by poly(ADP-ribosyl)ation, and plays diverse roles in molecular and cellular processes. PARP-1 is also a platform protein associated with SSBR and interacts with several DNA repair proteins (Fig. 3). The common Val762Ala polymorphism of PARP-1 in the catalytic domain is implicated in susceptibility to cancer. The PARP-1 Val762Ala polymorphism reduces the enzymatic activity (Wang *et al.*, 2007). PARP-1 deficiency causes mammary tumorigenesis in mice underlying the role of PARP-1 in suppressing mammary tumorigenesis *in vivo* and suggesting that dysfunction of PARP-1 may be a risk factor for breast cancer in humans (Tong *et al.*, 2007). Recently, all PARP-1 exons, intron-exon junctions and promoter sequences have been sequenced. Rare genetic variants of PARP-1, including Ser383Tyr (C→A), Arg452Arg (C→A), Lys940Arg (C→G) were detected in about 11% breast cancers. Interestingly, the Ala284Ala (T→C) PARP-1 variant was likely associated with loss of estrogen- and progesterone-receptor expression. This implies that genetic variants of PARP-1 may contribute to breast cancerogenesis and that the PARP-1 Ala284Ala variant protein may influence hormonal therapy of breast cancer (Cao *et al.*, 2007). *Parp-1*$^{-/-}$ knockout mice are viable. In contrast, double *Parp-1*$^{-/-}$ *Parp-2*$^{-/-}$ mice are not (Friedberg & Meira, 2004).

BER is also changed in tumors in comparison to unaffected surrounding tissues, and this change may be due to transcription stimulation, post-translational modification of BER enzymes as well as protein–protein interactions. Modulation of BER enzymes' activities may be, then, an important factor determining the risk of cancer and also may participate in cancer development (Tudek *et al.*, 2006; De Ruyck *et al.*, 2007; Tudek, 2007).

SUMMARY

As outlined above, the development of mutator phenotype is proposed to be an early step in carcinogenesis. The best known examples of such a situation are defects in the *MUTYH* gene which increase the G→T transversions in the *APC* gene in human colorectal cancers. Importantly, these mutations are frequently formed in hot spots of tumor suppressor genes or oncogenes, and thus further influence carcinogenesis. DNA-damaging agents may also preferentially modify hot spots of tumor suppressor genes or oncogenes. For instance, etheno-adduct-forming chemicals, such as vinyl chloride and urethane, have been shown to induce specific hot spot mutational patterns in *TP53* (Kowalczyk *et al.*, 2006) and *Ha-ras* in liver, lung or skin cancers in humans (occupationally exposed to vinyl chloride), rats, and mice (reviewed by: Barbin, 2000). Individual susceptibility is an important factor in cancer development that depends on carcinogen uptake, balance between metabolic activation and detoxification, DNA repair activity, and varying effects of genes involved in DNA repair, signal transduction pathways and regulation of the cell cycle.

Polymorphisms in genes encoding DNA repair functions can lead to varying capacities of defense against endogenous and environmental DNA damaging agents. Since variations in DNA repair genes may influence and modulate an individual's cancer susceptibility, screening for polymorphisms has become recently a promising area of research in molecular epidemiology. Moreover, this knowledge is necessary to allow a number of DNA repair inhibitors as potential anticarcinogenic compounds. However, the ability of the DNA repair inhibitors to prevent cancer development is difficult to interpret and is sure to depend upon the system used and the type of genotoxic stress.

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