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Base Excision Repair Pathways

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1. Introduction

DNA repair is a process vital to the cell since the genetic material is the target of a multitude of daily attacks. Cells have evolved into possessing distinct but simultaneously intercalating ways of dealing with repair of DNA lesions. These repair pathways may include practices dealing with single strand damage (Base Excision Repair, Nucleotide Excision Repair, Mismatch Repair) or with double strand damage (Non-homologous End Joining and Homologous Recombination) as well as Direct Reversal Repair and Translesion Synthesis. The present chapter deals with one of these pathways (Base Excision Repair), which rectifies damage at the point of the single nucleotide.

2. Overview of base excision repair

Small non-helix distorting DNA alterations are very common in living organisms and they are due both to exogenous and endogenous sources. Endogenous damage can be summarised into the following categories: a) misincorporation of uracil in the genome or spontaneous deamination of cytosine (Sung and Demple, 2006) b) hydrolysis of all four bases or oxidation by reactive oxygen species (ROS), hormones, reactive nitrogen species, heme precursors and amino acids (Nilsen and Krokan, 2001; Wood et al., 2001) c) alkylation of purines and pyrimidines by lipid end-products (Sung and Demple, 2000) or other parameters (e.g. S-adenyl-methionine). Spontaneous abasic sites are also common lesions and 10000 purines are detached from DNA per human genome per day (Wilson and Kunkel, 2000; Nilsen and Krokan, 2001). Besides all these endogenous reactions, exogenous agents as xenobiotics and radiation are also able to cause similar damage. All these small, point lesions are rectified by Base Excision Repair (BER) (Krokan et al., 2000; Cabelof et al., 2002). BER was discovered by Tomas Lindahl in 1974 (Krokan et al., 2000), it is a tightly conserved pathway from bacteria to mammals (Izumi et al., 2003; Didzaroglu, 2005) and it must be preserved in a highly coordinated way to be effective (Moustacchi, 2000; Allinson et al., 2004).

BER is initiated by the cleaving of the damaged base by a specialized enzyme: a DNA *N*-glycosylase. The glycosylases implicated in BER fall into two main groups regarding their mechanisms of action: monofunctional and bifunctional glycosylases (Fortini et al., 1999; Krokan et al., 2000; Cabelof et al., 2002). In the case of the monofunctional glycosylases, an aspartic acid (Asp) residue activates a water molecule, which in its turn performs a nucleophilic attack on the *N*-glycosidic bond. In bifunctional glycosylases, the Asp residue

activates an amino group of a lysine (Lys) residue. The amino group forms a Schiff base ($\overset{R_2}{\underset{R_1}{>}}\!\!=\!\!N\!-\!R_3$) with C1' followed by β-elimination at the 3' side of the deoxyribose (Bailly et al., 1989; Nilsen and Krokan, 2001). In the case of a monofunctional glycosylase, the net result is an apurinic or apyrimidinic site (AP site) and in the case of a bifunctional glycosylase the net result are two single strand breaks: one strand with a 3'-α,β unsaturated aldehyde end (3'PUA) and another strand with a 5'-phosphate end. However, some of the bifunctional glycosylases (namely the bacterial Fpg and Nei and the mammalian NEIL1) are able to further process 3'PUA via δ-elimination bearing a 3'phosphate end (Nilsen and Krokan, 2001; Gros et al., 2002; Wiederhold et al., 2004).

The AP site created (as well as the SSB) must be quickly processed further since they are highly cytotoxic (Allinson et al., 2004) and mutagenic (Nilsen and Krokan, 2001). This is done by an AP endonuclease (APE1 for mammalian organisms) resulting in the formation of a 3'-hydroxyl end (3'OH) and a 5' abasic sugar phosphate end (5'dRP) (Memisoglu and Samson, 2000). AP endonuclease APE1 is also involved in the "trimming" of the blocked 3' end created by bifunctional glycosylases (Mitra et al., 2001; Cabelof et al., 2002; Izumi et al., 2003). However some researchers argue that the phosphatase activity of APE1 is low and that polynucleotide kinase (PNK) is the only enzyme that cleaves successfully the products of βδ-elimination (Mitra et al., 2002; Wiederhold et al., 2004).

The formation of SSB by APE1 is a critical point in the BER process since two sub-pathways may follow: the short-patch or the long-patch pathway (Christmann et al., 2003; Sung and Demple, 2006). The short patch may be initiated by *N*-glycosylases whereas the long-patch may be the pathway of choice for spontaneous hydrolysis of bases (Didzaroglu, 2005). Cell cycle stage may also affect the choice of sub-pathway (Krokan et al., 2000): bifunctional glycosylases point to a short-patch mode of action whereas damage rectified by monofunctional glycosylases may follow either pathway (Fortini et al., 1999). The long-patch process may have evolved as a more efficient or as a redundant mechanism for abasic moieties (Wilson and Thompson, 1997). In some cases these moieties are refractory to 5'phosphodiesterase activity. Indeed oxidized abasic sites do not give rise to deoxyribose phosphate (dRP) under physiological conditions. In this case the cleaving of the sugar-phosphate backbone must be done downstream towards the 3'end (Sung and Demple, 2006) and the same happens with reduced abasic sites (Zhang and Dianov, 2005).

No matter what the underlying reason for differentiation is, the two sub-pathways are substantially different. In the short-patch polymerase β attaches a single nucleotide to the trimmed 3'OH end, displacing the dRP at the 5'end (Wilson and Thompson, 1997; Schärer and Jiricny, 2001) and it also cleaves 5'dRP by its intrinsic lyase activity through a covalent Schiff intermediate (Sung and Demple, 2006). Ligase III/XRCC1 seals the gap and DNA integrity is restored (Wilson and Thompson, 1997; Cabelof et al., 2002). Polymerase β does not have proofreading abilities and sometimes it incorporates an incorrect nucleotide which is subsequently re-excised by APE1 (Noble, 2002). In the long-patch, polymerase β or polymerase δ/ε with the proliferating cell nuclear antigen (PCNA), add a few more nucleotides at the 3'OH end (Christmann et al., 2003). The number of extra nucleotides is according to researchers up to six (Schärer and Jiricny, 2001), up to ten (Christmann et al., 2003) or up to thirteen (Suttler et al., 2003). This action creates a flap at the 5'dRP end. This flap is then excised by flap endonuclease (FEN1) and afterwards PCNA/ligase I seals the gap (Christmann et al., 2003). A representation of BER pathways is depicted in Figure 1.

3. Common polymorphisms in BER and cancer risk

Given the crucial role of BER in DNA repair, it is expected that polymorphisms which alter enzyme activity may be linked with increased cancer risk. *In vitro* modified (increased or decreased) activity of mutated alleles is not always corroborated by similar *in vivo* activity and human studies are sometimes few and/or inconclusive. In other cases, however, a strong link between mutation and development or propagation of cancer has been verified.

The substitution of serine by cysteine in codon 326 (Ser326Cys) in OGG1 *N*-glycosylase (see subchapter 4) is one of the cases of questionable involvement in cancer; the imperative need for comprehensive human studies regarding this polymorphism which has been shown to be less efficient in oxidative lesion removal *in vitro* (Ishida et al., 1999; Yamane et al., 2004; Hill and Evans, 2006) has already been highlighted (Loft and Moller, 2006). Epidemiological studies of this polymorphism in relation to lung cancer have yielded mixed results showing a weak association between homozygous Ser326Cys and cancer development (Hatt et al., 2008). Two recent meta-analyses (statistical re-evaluations of separate but related studies) of 1925 and 3253 lung cancer patients showed indeed an increased risk in homozygous populations (Kohno et al., 2006; Hung et al., 2005 respectively). Furthermore, a meta-analysis of 6375 cases showed implications of Ser326Cys homozygous genotype in cancer development in non-smokers only (Li et al., 2008). Incrimination of this OGG1 polymorphism in lung cancer development is thus possible. Colorectal cancer is less strongly associated with this polymorphism; the Ser326Cys homozygous populations were at increased risk for colorectal cancer in certain studies (Moreno et al., 2006). The Ser326Cys homozygous populations were at increased risk for colorectal cancer, only when other incriminating factors (increased meat intake, cigarette smoking) were co-present (Kim et al., 2003). Other studies however have not found a correlation between this polymorphism and colorectal adenomas or carcinomas (Hansen et al., 2005).

On the contrary, mutations in the MYH gene (see also subchapter 4) have been proven without doubt to be able to cause an autosomal recessive form of familial adenomatous polyposis (Lindor, 2009). Individuals with biallelic inherited mutations of the MYH gene run a high risk of colorectal cancer that approaches 100% (Dolwani et al., 2007). Transversion mutations in MYH disrupt the normal base excision repair of adenines misincorporated opposite 7,8-dihydro-8-oxoguanine, a prevalent and stable product of oxidative damage to DNA, leading to hereditary colorectal neoplasms (Sampson et al, 2005). Patients with MYH-associated polyposis (MAP) present with clinical features similar to classic FAP (familial adenomatous polyposis). Patients typically present between the ages of 40–60 years with a variable number of colorectal adenomatous polyps, however, MYH mutation carriers do not usually present with multiple polyps before the age of 30 years (Kastrinos and Syngal, 2007).

Given the critical role of APE1 in BER a total of 18 polymorphisms in APE1 gene have been reported. The most extensively studied is the Asp148Glu; A meta-analysis of 12432 cases showed an increased risk of cancers, especially of colorectal cancer for this allele. Functional studies have shown that this variant may have altered endonuclease and DNA-binding activity and reduced ability to interact with other BER proteins (Gu et al., 2009) in order to form critical complexes for nucleotide excision/incorporation during the rectifying process. Besides its endonuclease activity, APE1 has been shown to stimulate the DNA binding activity of numerous transcription factors that are involved in cancer promotion and progression such as Fos, Jun, nuclear factor-κB and p53, thus is actively involved in redox regulation of oncoproteins (Kelley et al., 2010).

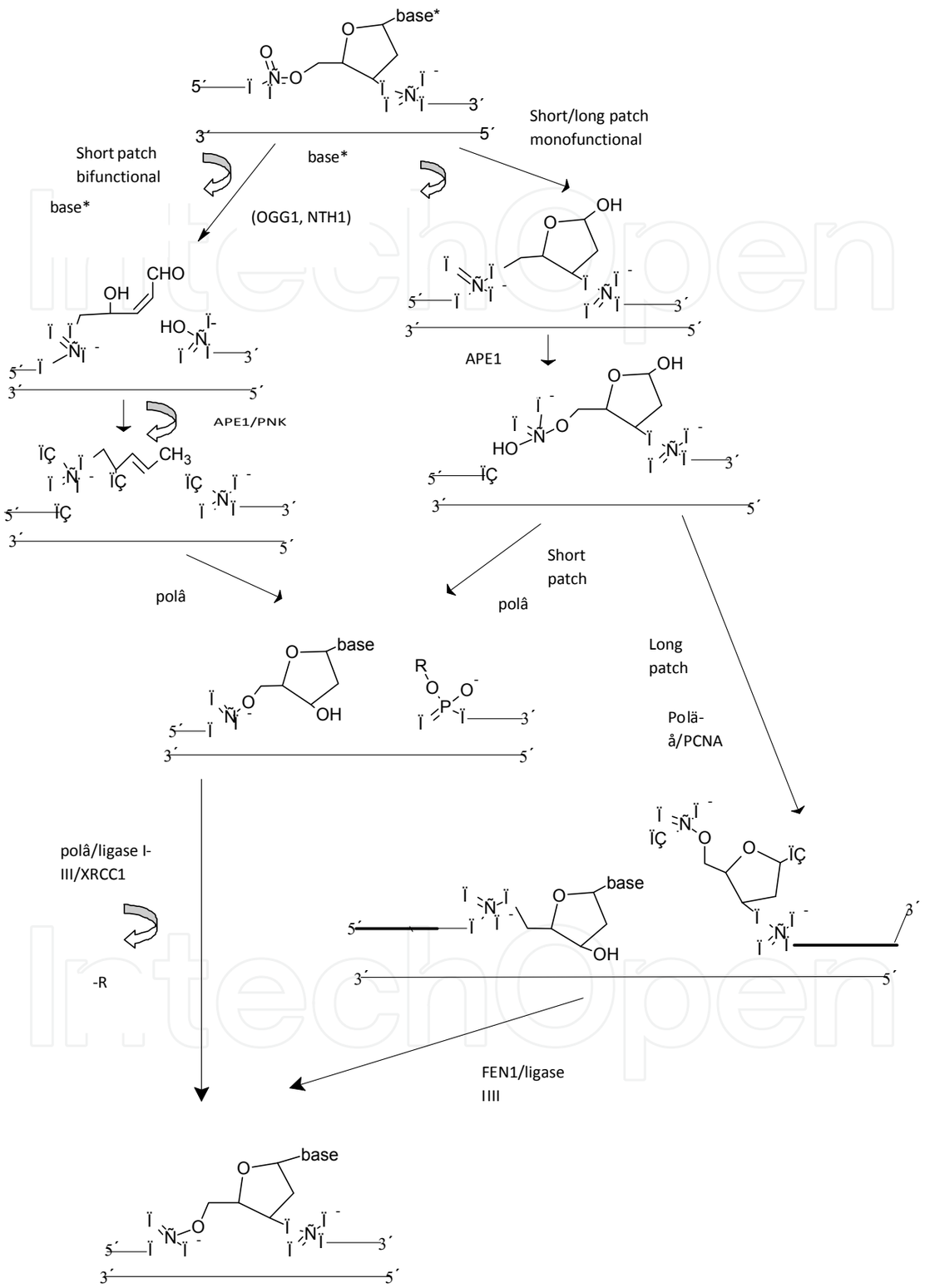

Fig. 1. Schematic representation of mammalian Base Excision Repair pathway (adapted from Wiederhold et al., 2004).

The XRCC1 protein plays a major role in facilitating the repair of single-strand breaks in mammalian cells, via an ability to interact with multiple enzymatic components of repair reactions (Caldecott, 2003). In BER, XRCC1 acts as a scaffold for DNA ligase III, polymerases and PAPR. Some of the most common XRCC1 polymorphisms are Arg194Trp, Arg280His and Arg399Gln (Xue et al., 2011). A meta-analysis of 40 studies regarding these three polymorphisms and breast cancer showed a recessive effect of Arg280His and Arg399Gln variants in Asians only (Li et al., 2009). However, no increase in gastric cancer risk for Arg194Trp, Arg280His and Arg399Gln has been noted (Geng et al., 2008; Xue et al., 2011). According to other studies, the Arg194Trp variant contributes to a reduced risk of various types of cancer (Goode et al., 2002; Hu et al., 2005). Indeed, the XRCC1 Arg194Trp and Arg280His variants were each associated with a reduced risk of lung cancer compared with common allele homozygotes (Hung et al., 2005). These last results are somewhat surprising since a common perception is that a change in amino-acid structure would be deleterious to function and would result in an increased risk of cancer. In the specific case of XRCC1, it is possible that a change to tryptophan would cause a transition from the positively charged arginine of the wild type to a hydrophobic tryptophan, which could positively affect binding to DNA and increase efficiency (Ladiges, 2006).

PCNA, another important component for BER polymerases scaffolding is also characterised as "the ringmaster of the genome". It interacts with p53-controlled proteins Gadd45, MyD118, CR6 and p21, in the process of deciding cell fate: proliferation, repair or apoptosis (Paunesku et al., 2001). A novel form of PCNA has been described in malignant breast cells. This unique form is not the result of a genetic alteration, as demonstrated by DNA sequence analysis but it is the product of post-translational modification. This example shows the diverse and multifaceted ways that BER enzyme variations may affect cancer frequency (Bechtel et al., 1988).

4. Specific BER N-glycosylases implicated in oxidised base removal

4.1 Prokaryotic organisms (*E.coli*)

i) Fpg (MutM): Formamidopyrimidine glycosylase (Fpg) is a glycosylase which excises 8-oxo-deoxyguanosine (8-oxo-dG) from 8-oxo-dG: C pairs (Beckman and Ames, 1997; Gros et al., 2002; Russo et al., 2006), but not from 8-oxo-dG: A mispairs because that would lead to a stable G-T transition (Wang et al., 1998). One of the most extensively studied glycosylases, Fpg has been also found in *Deinococcus radiodurans* (Gros et al., 2002), in yeast *Candida albicans* (Wallace, 2002) and in the plant *Arabidopsis thaliana* (Rosenquist et al., 2003). It is a globular monomer of 269 aminoacids and 30.2 kDa, which cleaves 8-oxo-dG, its opened ring form 2,6-diamino-4-hydroxy-5-formamidopyrimidine (Fapy) and a variety of pyrimidines (5-hydroxycytosine, 5-hydroxyuracil and thymine glycol) (Gros et al., 2002). Fpg possesses a C-terminal Zn finger motif, which stabilises the bound DNA and contributes to substrate interaction (Rosenquist et al., 2003). Fpg has an AP lyase activity performing βδ elimination of the abasic site (Gros et al., 2002; Russo et al., 2006).

ii) Nei (endo VII): Nei exhibits an overlapping substrate-specificity with Fpg. It comprises 263 amino acids and a C-terminal Zn finger motif (Gros et al., 2002; Rosenquist et al., 2003).

iii) MutT: MutT is a GTPase which sanitises nucleotide pools from 8-oxo-GTP by hydrolysing it to monophosphate, thus preventing its misincorporation in DNA (Beckman and Ames, 1997; Fortini et al., 2003). MutT deficient strains exhibit a strong mutator phenotype (Fortini et al., 2003).

iv) MutY: MutY excises A which is wrongly incorporated opposite 8-oxo-dG (Beckman and Ames, 1997; Vidal et al., 2001). MutY is a 39 kDa protein which can also excise A opposite to G, C and 8-oxo-dA (Le Page et al., 1999; Gros et al., 2002). Fpg/MutY double null strains exhibit a strong mutator phenotype (Wang et al., 1998; Russo et al., 2006).
v) Nth: Nth also excises Fpg substrates and it has a strong activity against thymine glycol and other oxidised pyrimidines (Gros et al., 2002; Izumi et al., 2003; Rosenquist et al., 2003). Nth possesses a β-lyase activity besides its *N*-glycosylase activity (bifunctional glycosylase) (Izumi et al., 2003). Nth mutants are not sensitive towards oxidative insult, however the double mutants *nth/nei* exhibit a mutator phenotype after exposure to ionising radiation or H_2O_2 (Gros et al., 2002).
The triad MutT, MutY and MutM (Fpg) comprise the so called GO system which suppresses effectively Guanine Oxidation via the concerted actions of sanitising of the nucleotide pool, excising misincorporated A and excising 8-oxo-dG from duplex DNA respectively (Beckman and Ames, 1997).

4.2 Eykaryotic organisms (mammals)

i) OGG1: hOGG1 is the functional analogue of Fpg in humans. Besides 8-oxo-dG, OGG1 has activity against Fapy (Nohmi et al., 2005) and very weak activity against 4,6-diamino-5-formamidopyrimidine (FapyA) (Wallace, 2002). The mammalian OGG1 contains a helix-hairpin-helix motif (HhH) with an Asp-activated Lys residue as an active site. The residue forms a Schiff base with the substrate and subsequently creates an AP site (Izumi et al., 2003). OGG1 is a bifunctional glycosylase, however it acts as a monofunctional *in vivo* since APE1 precludes the lyase activity of OGG1 (Vidal et al., 2001; Fortini et al., 2003). Given the crucial role of OGG1 in 8-oxo-dG control, it is rather surprising that *ogg1-/-* mice are viable and do not show malignant phenotype (Klungland et al., 1999; Gros et al., 2002). Implications of other glycosylases or even other pathways are probably some of the reasons for this incident (Izumi et al., 2003). However it has been shown in the same mice that the incidents of spontaneous lung carcinoma/adenoma and UV-induced skin tumours are elevated 1.5 years after birth (Sakumi et al., 2003). In humans OGG1 polymorphisms have been incriminated for certain cancer types, especially the mutation Ser326Cys as discussed earlier in this chapter. It is postulated that Cys mutants have lower 8-oxo-dG excision capacity than wild type cells (Nohmi et al., 2005).
ii) NEIL: 3 human and 3 mouse homologues of the bacterial Nei have been cloned, namely NEIL1, NEIL2 and NEIL3. They contain a helix-two turn-helix motif and NEIL 2 and 3 may also contain Zn finger motifs (Rosenquist et al., 2003). NEIL1 and NEIL2 perform a βδ elimination on their substrate with a 3' and a 5' phosphate strand as end products (Izumi et al., 2003). NEIL excises thymine glycol (TG), FapyG and FapyA but shows only nominal activity against 8-oxo-dG (Rosenquist et al., 2003). According to other researchers NEIL activity against 8-oxo-dG is significant and the tissue-specific high expression of NEIL3 may be a back up mechanism for removal of oxidised guanine (Slupphaug et al., 2003).
iii) MTH1: the mammalian homologue of MutT is MTH1. MTH1 sanitises the nucleotide pool from 8-oxo-GTP and it also degrades 2OH-dATP and 2OH-ATP (Slupphaug et al., 2003; Nohmi et al., 2005). *Mth-/-* mice showed an increased rate of point mutations (Nakabeppu et al., 2006). Some polymorphisms of MTH1 have been found in cancer patients but a correlation between cancer and MTH1 variations has not been established (Nohmi et al., 2005). However the polymorphism Val83Met was dominant in female Japanese patients with Type I diabetes mellitus (Miyako et al., 2004).

iv) MYH: the mammalian homologue of MutY is MYH. MYH removes A from 8-oxo-dG:A mispairs (Nagashima et al., 1997; Fortini et al., 2003). It also recognises A:G and A:C mispairs (Fortini et al., 2003; Izumi et al., 2003). It is mainly a monofunctional glycosylase with a weak AP lyase activity (Russo et al., 2006). Important variants of MYH were found in siblings afflicted by multiple colon adenoma and carcinoma and further studies proved its role in colorectal adenoma and carcinoma predisposition (Gros et al., 2002; Nohmi et al., 2005). Double mutants mice for MYH and OGG1 had increased tumours in lung, small intestine and ovaries (Russo et al., 2006). The unique action of MYH does not seem to have any back up from other glycosylases, which explain the importance of its mutations (Izumi et al., 2003).

v) NTH1: The mammalian homologue of nth is NTH1. NTH1 has similar substrate specificity with nth (Gros et al., 2002). It possesses both an *N*-glycosylase and an endonuclease activity but a product inhibition dissociates the two activities (Izumi et al., 2003; Marenstein et al., 2003). Double mutant embryonic cells still showed TG repair because of the accessory enzymes TGG1 and TGG2 (Gros et al., 2002). Furthermore, *nth1-/-* mice stayed healthy but exhibited a slower excision activity for NTH1 substrates (Izumi et al., 2003).

vi) OGG2: the novel glycosylase OGG2 has been found in human (Wang et al., 1998; Bohr and Dianov, 1999) and yeast (Nash et al., 1996) cells. OGG2 probably excises wrongly incorporated 8-oxo-dG opposite A, in a nascent strand (Izumi et al., 2003).

The triad MTH1, MYH and OGG1 together with other accessory proteins like OGG2 and NEIL comprise the mammalian GO system which suppresses effectively Guanine Oxidation. A representation of the GO system is given in Figure 2.

5. Specific BER N-glycosylases implicated in alkylated base removal

It has been estimated that 20,000 DNA lesions are produced per cell per day but the contribution of alkylation damage is not well established (Drabløs et al., 2004). However alkylation damage occurs frequently as part of the normal metabolism of the cell. It has been shown that the methyl donor *S*-adenyl-methionine can methylate spontaneously DNA to 3-methyl-adenine (3meA) (Seeberg et al., 1995). Also alkylation occurs as a consequence of lipid peroxidation and of nitrosocompounds in the gastrointestinal tract. Furthermore, there are naturally occurring 7-methylguanine (7meG) residues in the genome (Xiao and Samson, 1993). Exogenous sources of alkylation include chloromethane gas by plants, fungi and industrial uses, *N*-nitrosocompounds in tobacco smoke and alkylating anticancer drugs like temozolomide, carmustin and lomustine (Drabløs et al., 2004). Almost all the main mechanisms of DNA repair (direct damage reversal, BER, NER and recombination repair) are implicated in alkylation damage repair and almost all alkylating agents can form *O* and *N*-adducts in all bases and *O*-adducts in phosphodiesters (Drabløs et al., 2004). Regarding BER, a series of *N*-glycosylases have evolved especially for excision of alkylated bases.

5.1 Prokaryotic organisms (*E.coli*)

i) Tag: The bacterial Tag excises 3meA and 3meG from dsDNA only (Bjeeland and Seeberg, 1996) and it is not inducible (Seeberg et al., 1995). *E.coli* strains, which had enhanced 3meA glycosylase activity however, were more susceptible to mutations if they were simultaneously deficient in AP endonuclease activity (Taverna and Sedwick, 1996). The same happened with the functional homologue of *S. cerevisiae* when it was overexpressed in AP endonuclease

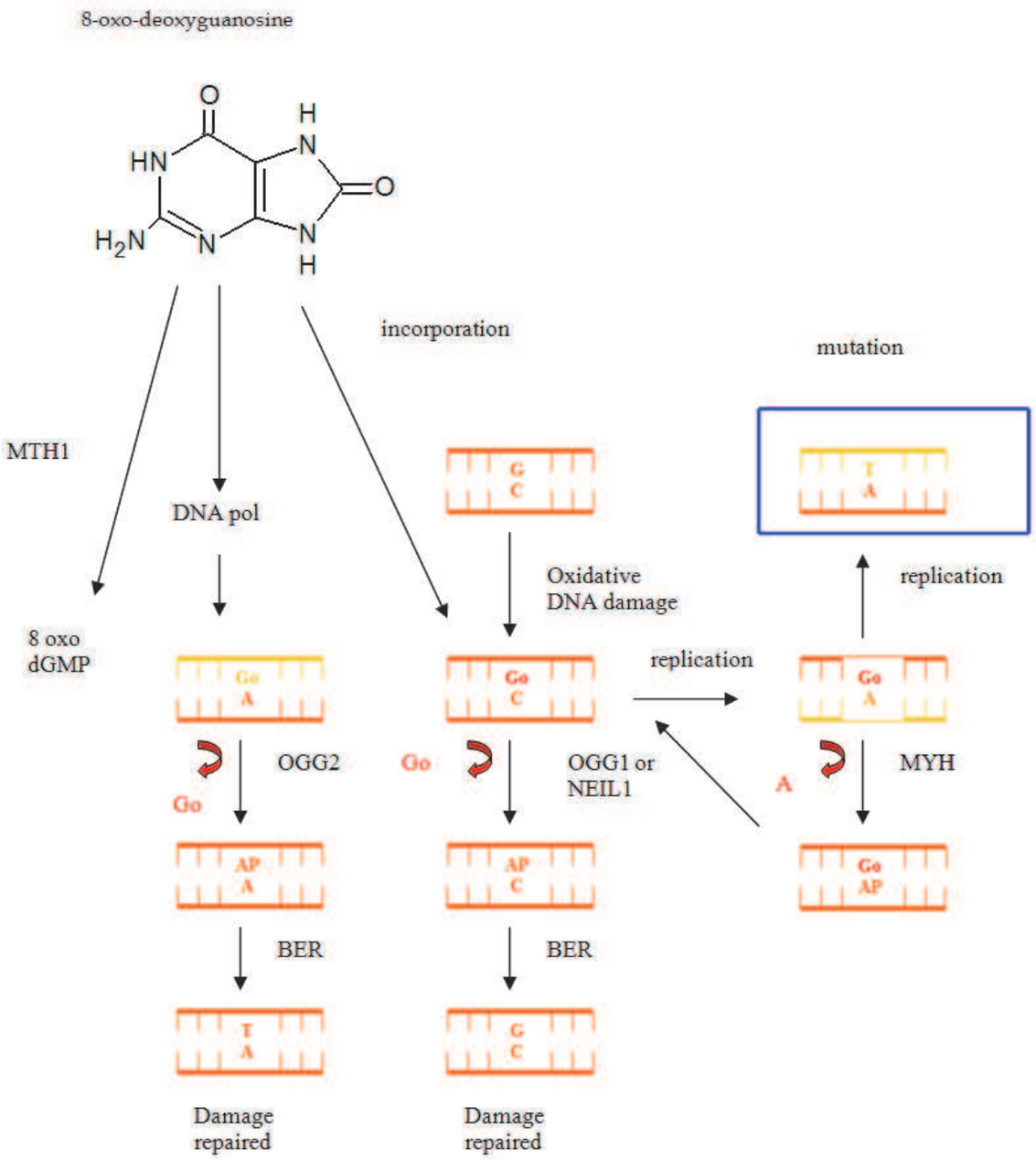

Fig. 2. Schematic representation of the "GO-system" in mammalian cells (adapted from Slupphaug et al., 2003).

deficient organisms (Xiao and Samson, 1993). These data suggest that the expression of Tag should be carefully controlled for achievement of optimal activity.

ii) AlkA: The bacterial AlkA excises 3meA, 7meA, 7meG, O^2 methylcytosine, O^2 methylthymine and hypoxanthine (Seeberg et al., 1995; Hollis et al., 2000; Drabløs et al., 2004). It is a monofunctional glycosylase (Labahn et al., 1996) with a HhH motif and an Asp328 as an active site. Also the active pocket of AlkA is rich in aromatic residues, which interact with the alkylated bases (Cunningham et al., 1997; Lau et al., 1998). AlkA is using a

base-flipping mechanism which projects the modified base into the active pocket of the enzyme. The charged, deficient bases may stack more tightly against the aromatic residues of AlkA than the uncharged bases (Hollis et al., 2000). Double mutant strains of *E. coli* for Tag and AlkA are extremely sensitive to alkylating DNA damage (Seeberg et al., 1995).

5.2 Eukaryotic organisms (mammals)

i) AAG (MPG, ANPG): The mammalian AAG shares the same broad specificity with the bacterial AlkA. It also removes intact guanines at very low frequencies but it cannot remove O^2-alkylated pyrimidines (Drabløs et al., 2004). However, AlkA and AAG bear little or no sequence similarity between them: the yeast MAG and AlkA possess some common sequence characteristics but there is no sequence analogy between AlkA and the plant or mammalian AAG (Labahn et al., 1996). The broad specificity of AAG is an interesting phenomenon. It is probable that AAG outstacks completely or partially nucleotides and scans along DNA searching for alkylation damage (Lau et al., 1998). Base flipping of the modified base is accompanied by its intercalation with Tyr162, its stabilisation and a nucleophilic attack by a water molecule deprotonated by Glu125 (Lau et al., 1998; Hollis et al., 2000).

As already mentioned. AAG is able to rectify exocyclic etheno adducts like εdA, 3,N^4-ethenodeoxycytidine (εdC), 1,N^2-ethenodeoxyguanosine (1,N^2εdG) and N^2, 3-ethenodeoxyguanosine (N2-3εdG) which are formed during lipid peroxidation or by vinyl chloride, vinyl fluoride, vinyl carbamate, urethanes and other carcinogens (Ham et al., 2004). *In vitro* AAG was the only enzyme able to repair these kinds of adducts, however experiments with *Aag* -/- mice showed that there is still a weak activity against etheno-adducts via other unknown enzymes or via other pathways (Ham et al., 2004). Overexpression of AAG may enhance the cytotoxicity of alkylating agents thus, protection from AAG or sensitization by AAG may be tissue-specific and its levels should be carefully controlled in order to achieve optimal activity (Drabløs et al., 2004). It is probable that enhancement of its glycosylase activity creates a surplus of abasic sites which are not properly processed by endonuclases leading to a repair imbalance.

6. Conclusion

Base Excision Repair pathway is a tightly conserved pathway, from prokaryotic organism to higher mammals. At the same time it is an adapting and flexible mechanism, which covers repair of a variety of small DNA lesions as evidenced by its diverse *N*-glycosylases. BER works both under normal conditions and during stressful incidents. The importance of BER in cell survival is highlighted by the fact that the most common genetic damages due to oxidative stress are rectified mainly through this pathway. Furthermore, polymorphisms of BER enzymes which compromise their activity may lead or contribute to neoplasias to a certain extent.

7. References

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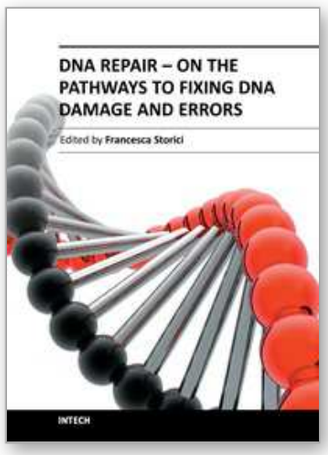

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DNA repair is fundamental to all cell types to maintain genomic stability. A collection of cutting-edge reviews, DNA Repair - On the pathways to fixing DNA damage and errors covers major aspects of the DNA repair processes in a large variety of organisms, emphasizing foremost developments, questions to be solved and new directions in this rapidly evolving area of modern biology. Written by researchers at the vanguard of the DNA repair field, the chapters highlight the importance of the DNA repair mechanisms and their linkage to DNA replication, cell-cycle progression and DNA recombination. Major topics include: base excision repair, nucleotide excision repair, mismatch repair, double-strand break repair, with focus on specific inhibitors and key players of DNA repair such as nucleases, ubiquitin-proteasome enzymes, poly ADP-ribose polymerase and factors relevant for DNA repair in mitochondria and embryonic stem cells. This book is a journey into the cosmos of DNA repair and its frontiers.

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