Single nucleotide polymorphisms in DNA glycosylases: from function to disease

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Abstract

Oxidative stress is associated with a growing number of diseases that span from cancer to neurodegeneration. Most oxidatively induced DNA base lesions are repaired by the base excision repair (BER) pathway which involves the action of various DNA glycosylases. There are numerous genome wide studies attempting to associate single-nucleotide polymorphisms (SNPs) with predispositions to various types of disease; often, these common variants do not have significant alterations in their biochemical function and do not exhibit a convincing phenotype. Nevertheless several lines of evidence indicate that SNPs in DNA repair genes may modulate DNA repair capacity and contribute to risk of disease. This overview provides a convincing picture that SNPs of DNA glycosylases that remove oxidatively generated DNA lesions are susceptibility factors for a wide disease spectrum that includes besides cancer (particularly lung, breast and gastrointestinal tract), cochlear/ocular disorders, myocardial infarction and neurodegenerative disorders which can be all grouped under the umbrella of oxidative stress-related pathologies.

INTRODUCTION

DNA glycosylases are the catalysts of the first step of the base excision repair (BER), the primary repair mechanism for small base lesions arising from deamination, oxidation, methylation and replication-associated misincorporation. Their role in the control of genetic integrity is inferred from *in vitro* and *in vivo* studies and from human diseases, although rare, associated with germline mutations in their coding genes. Aside this evidence there is a plethora of studies where the effects of single nucleotide polymorphisms (SNPs) in DNA glycosylases have been evaluated in population studies and analysed for function, although not systematically. SNPs are the most common type of genetic variation among people (there are many millions) and usually occur in non-coding regions. Only when they are located within genes or their regulatory regions they may affect the gene function and thus play a more direct role in disease. In this review we will briefly introduce the structure, function and biological importance of DNA glycosylases as inferred from knock-out (ko) model mice and human diseases with germline mutations and then we will focus on the impact of SNPs on gene function and disease.

DNA glycosylases: structure, function and biological importance

Eleven DNA glycosylases have been identified in mammals so far. They can be divided into four structurally different superfamilies: the uracil DNA glycosylases (UDGs), the helix-hairpin-helix (HhH) glycosylases, the endonuclease VIII-like glycosylases, and the 3-methylpurine glycosylases (MPG). UDG family comprises nuclear (UNG2) and mitochondrial uracil DNA glycosylases (UNG1), single-strand-specific monofunctional uracil DNA glycosylase1 (SMUG1), and thymine DNA glycosylase (TDG). Although the methyl-binding domain glycosylase 4 (MBD4) presents an overlapping specificity with UDG members, MBD4 belongs to HhH family which also includes endonuclease III-like 1 (NTHL1), 8-oxoguanine DNA glycosylase1 (OGG1) and MutY homolog DNA glycosylase (MUTYH). Endonuclease VIII-like (NEIL) family includes NEIL1, NEIL2 and NEIL3 DNA glycosylases.

The family of the UDGs

UDGs are monomeric proteins that recognize and excise uracil base from DNA [1]. In mammalian cells nuclear UNG2 is devoted to the repair of incorporated uracil (U:A base pair) whereas UNG2, SMUG1, TDG and probably MBD4 all contribute to the repair of

uracil in the U:G base pair (formed by deamination of cytosine) [2]. All UDGs share a common $\alpha-\beta$ fold structured catalytic domain [3]. UDGs, except SMUG1 [2] and MBD4 [4] are cell cycle regulated. In particular, UNG1 and UNG2 increase in late G1/early S with UNG2 most highly expressed in S phase whereas TDG is highly expressed in G1 and to lower levels in G2 and M phase [2].

Humans and mice have two different UNG isoforms, UNG1 and UNG2 that are localized in the mitochondria and nucleus, respectively [5]. These isoforms derive from transcription from two distinct start sites as well as from alternative splicing of the mRNAs transcribed from the *ung* gene [5]. The role of UNG1 in the processing of uracil at mitochondria is not well defined and needs additional studies [6,7]. UNG2 is the nuclear DNA glycosylase [8] and its turnover is regulated by cell-cycle specific phosphorylations by cyclin-dependent kinases [9,10] and by a TP53-dependent phosphatase [9,10]. UNG2 associates with replication complexes [11-13], interacting, among others, with PCNA and RPA [14] that target UNG2 to its main function, i.e. the removal of uracil misincorporated opposite adenine during replication. In B cells UNG2 plays also an important role in somatic hypermutation (SHM) and class switch recombination (CSR), presumably by removing uracil generated by cytosine deaminase (AID). Recently UNG2 has been involved in DNA demethylation in mouse zygotes, where TDG, the DNA glycosylase devoted to demethylate DNA in CpGs islands (see below), is poorly expressed and dispensable in DNA demethylation [15].

Ung deficient mice accumulate uracil residues in proliferating cells but do not exibit any relevant increase of spontaneous mutation frequency [8]. Nevertheless, old mice (>18 months) develop B-cell lymphoma [16]. The cancer specificity of *ung* ko mice testifies the key role of this DNA glycosylase to generate immunoglobulin diversity (reviewed in [17]) a role that is conserved in humans.

Homozygous patients for recessive mutations of UNG2 are defective in both CSR and SHM processes and display a hyper-IgM syndrome with recurrent infections [18].

SMUG1 has a nuclear localization and a preference for single stranded DNA substrates [19]. It is able to remove the uracil in both U:A and U:G mispairs. Since SMUG1 has a lower K_M than UNG [20], this results in a higher efficiency at repairing rare lesions in non-replicating DNA regions [21]. In addition, SMUG1 is involved in the removal of 5-hydroxymethyluracil (5-hmU) from RNA in the nucleolus [22].

Smug1 ko mice breed normally and both health and survival up to 1 year are not compromised despite the complete ablation of the 5-hmU removal in different tissues [23]. However, when the ablation of *smug1* is combined with that of *ung* and *msh2*, the triple ko mice shows an increased cancer predisposition, predominantly lymphoid tumors, indicating that also SMUG1 contributes to antibody diversity and both UDGs synergize with mismatch repair (MMR) in the adaptive and innate immunity response [23].

TDG removes thymine in G:T mispairs which spontaneously derives from 5-methylcytosine (5-mC) deamination within CpG islands and the uracil in U:G mismatches. TDG has a large hydrophobic catalytic pocket accomodating a broad range of lesions as those resulting from oxidation, alkylation and deamination of C, 5-mC, and A leading to uracil, thymine and 6-hydroxypurine (alias hypoxanthine), respectively. After base removal TDG binds tightly to the produced abasic site and the rate of dissociation from the abasic product is the rate-limiting step of the glycosylase reaction. The interaction of the catalytic domain with APE1 significantly increases the rate of dissociation from the AP site, thus allowing further processing of the lesion [4].
TDG has also a role in active demethylation at CpG islands [24], regions with a high frequency of CpG sites, typically occurring at or near gene promoters [25]. The mechanism of DNA demethylation by TDG has been recently clarified and reconstituted *in vitro* [26]. It proceeds by oxidation of 5-meC by TET dioxygenases which generate substrates for TDG-mediated BER thus leading to 5-mC replacement with a cytosine. This highly coordinated system is able to work on both strands at symmetrically modified CpGs in a sequential manner thus preventing DNA double strand breaks (DSB) formation but leading to increased C>T transitions [26,27].
Loss of *tdg* in mice causes embryonic lethality [28]. This is in contrast with all the other DNA glycosylases whose targeted gene deletion in transgenic mice models is associated with a viable and fertile phenotype. This dramatic phenotype is consistent with the essential function of TDG in driving the proper epigenetic program during embryo development as depicted above. Moreover, the control and the maintenance of locus specific DNA methylation pattern are supposed to be essential for both the genome reprogramming required during cell differentiation and the maintenance of the function specificity.

The HhH glycosylases

MBD4 recognizes not only methylated CpG dinucleotides but also T:G mismatched sites generated by spontaneous deamination of 5-mC. Besides the removal of T and U paired with G, MBD4 shows a broad substrate specificity, overlapped with TDG, including 5-fluorouracil, 5,6-dihydroxy-5,6-dihydrothymine, the so-called thymine glycol (Tg) and 5-bromouracil opposite G, and unique substrates such as thymine erroneously incorporated during replication across O^6methylguanine [4,29].
Recently the crystal structure of MBD4 complexed with ^{5m}CG/^{5m}CG and ^{5m}CG/TG has revealed that the features of the DNA interface of MBD4 may account for its dual base specificities [30]. The C-terminal of MBD4 contains the glycosylase domain which belongs to the HhH DNA glycosylase family [4] and which contains ten α-helices that form a cleft in the middle [31]. The crystal structure of MBD4 bound to an abasic site analog paired to G [32] has revealed that MBD4 binds to the minor groove of DNA at the target site. The opposing G remains intrahelical and makes several electrostatic interactions with residues of the active site. These contacts are not compatible with A, explaining the high preference for excising T from G:T versus A:T base pairs [32].
Mbd4 mutant mice develop normally and do not show any aberrant phenotype although a 3 fold higher mutation frequency at CpG sites at the *lacI* locus in spleen and intestinal epithelium was reported. Moreover, the inactivation of MBD4 activity in the cancer prone model mouse *apc* -/+ led to an increase in gastrointestinal (GI) tumors. At molecular level the GI tumors showed an increase in C>T transitions at the CpG sites of the wild type *apc* allele. This study supports the notion that MBD4 inactivation is not tumorigenic *per se* but can influence cancer progression in predisposing genetic backgrounds [33,34].
Mutational screening of several human cancers characterized by microsatellite instability (MSI) showed that the MBD4 coding region is often mutated in the “repeated” tracks, the so called mutator’s mutations [35].

NTHL1 (endonuclease III-like 1) is devoted to the removal of ring fragmented purines or oxidized pyrimidine residues like Tg, 2,6-diamino-4-hydroxy-5-formamidopyrimidine (FapyG), 4,6-diamino-5-formamidopyrimidine (FapyA), 5-hydroxycytosine (5-hC), 5-hydroxyuracil (5-hU) [36,37], and 8-oxo-7,8-dihydroguanine (8-oxoG) opposite a purine [38].
NTHL1 utilizes an internal lysine residue as the active site for β-elimination reaction, generating a 3’ phospho α,β-unsaturated aldehyde [1]. NTHL1 localizes to both the

nucleus and mitochondria and contains an iron-sulfur center which is redox-active and is possibly involved in DNA damage sensing [39]. NTHL1 is upregulated in S phase [39]. Two independent studies showed that *nthl1* deficient mice exhibit no overt abnormalities likely due to the broad but largely overlapped substrate specificity of NTHL1 with other DNA glycosylases (see below) [40,41].
It is of note that a loss-of-function germline homozygous mutation (268C>T that leads to Gln90> stop codon) in *nthl1* has been recently described in individuals presenting adenomatous polyposis and colorectal cancer [42].

OGG1 is the primary enzyme responsible for the excision of 8-oxoG. Human OGG1 is present in different isoforms [43] the most important being α-OGG1 and β–OGG1 that are expressed in all human tissues and localize to nuclei [44] and to mitochondria [44,45], respectively. OGG1 is a bifunctional DNA glycosylase but with an inefficient AP lyase activity that can be replaced by direct cleavage by APE1. APE1 can also stimulate the AP lyase activity of OGG1 by preventing its reassociation to the AP site [46]. OGG1 activity is inhibited by the nucleosomal structure and this inhibition is relieved by chromatin remodeling factors. Oxidative stress induces the recruitment of OGG1 to euchromatin regions, suggesting that post-translational modifications of OGG1 and of other structural nuclear proteins could affect their mutual affinity [47]. Similarly to TDG, OGG1 has been recently involved in the DNA demethylation induced by oxidative stress. The proposed model involves OGG1 interaction with TET1 and its recruitment to 8-oxoG lesions followed by oxidation of 5-mC adjacent to 8-oxoG [48]. It is of relevance that OGG1 is able to initiate expansion of CAG trinucleotide during BER leading to age-dependent CAG expansion in somatic cells in mouse models of Huntington disease (HD) [49]. *Ogg1* is therefore a candidate gene predicted to alter both somatic instability and age of onset in HD patients. Moreover, the recognition of 8oxoG by OGG1 has been shown to play a regulatory role in transcription and signal transduction with potential relevant implications for human disease (see review by B. Epe and coworkers in this issue).
Although 8-oxoG is the most common and mutagenic oxidized DNA lesion, homozygous *ogg1* ko mice are viable and healthy into adulthood. They accumulate 8-oxoG in tissue with a low level of proliferation (liver) and show a moderate increase of spontaneous mutation frequency without any development of malignancies [50]. The multiple levels of protection from oxidatively-induced DNA damage that characterize bacterial as well as mammalian cells are likely to account for this mild phenotype (see below). Interestingly,

ogg1 ko mice, under high fat diet, show an obese phenotype associated to several tissue dysfunctions which concur to the metabolic syndrome [51] such as impaired glucose tolerance, insulin resistance and increased hepatic steatosis but they lack the hepatic inflammatory response. These data are consistent with studies which suggest that OGG1 deficiency can be protective versus oxidative stress-induced inflammation [52] and also to allergic immune responses [53].

MUTYH postreplicatively excises the misincorporated A opposite 8-oxoG thus facilitating the removal of 8-oxoG. Two different MUTYH isoforms differing in their localization (mitochondrial for type1 protein and nuclear for type 2 protein) have been described in humans [54]. MUTYH is endowed with a catalytic domain and a C-terminal domain separated by a linker region [55]. The N-terminal domain contains the HhH element and is followed by a (Gly/Pro)-rich loop and by an aspartate residue (Asp222), which is essential for the catalytic activity. This domain interacts with the DNA strand containing the substrate adenine residue that is then completely extruded from the DNA helix and inserted into an extra-helical pocket. Moreover this domain contains a [4Fe-4S] cluster that is probably involved in damage recognition, transmitting the redox signal [56]. The C-terminal domain interacts with the 8-oxoG containing strand, allowing 8-oxoG recognition [55]. MUTYH interacts with proteins belonging to several DNA repair pathways [57-59] such as APE1 that stimulates its glycosylase activity and promotes its turnover [58], MMR proteins and PCNA that assure its coupling to DNA replication [60,61] and the damage sensor clamp heterotrimer, Rad9-Rad1-Hus1 [62].
Similar to *ogg1* deficient mice, *myh* ko mice were originally reported to be cancer-free [63] but were later shown [64] to present an increased frequency of intestinal tumors, when analysed in a large cohort after 18 months, testifying that the loss of MUTYH activity *per se* leads to spontaneous tumorigenesis. When both *myh* and *ogg1* are defective the double ko mice show a clear increase in the frequency of tumors, predominantly lung and ovarian tumors, and lymphomas [63]. In an independent study [65] the *myh ogg1* double ko mice showed an age dependent accumulation of 8-oxoG in the majority of tissues and an increased incidence of lung and small intestine cancer.
It is of note that the cancer prone *myh ogg1* double mutant mouse does not present mitochondrial dysfunction neither increased mitochondrial DNA mutagenesis [66] indicating that it is specifically the nuclear function of these two DNA glycosylases that is causally linked to cancer prevention. Interestingly, a recent study shows that *myh ogg1*

double ko mice present increased activity and decreased anxiety with impaired learning ability suggesting a broad role for these glycosylases that encompasses behaviour and cognition [67]. In humans, biallelic germline mutations in *myh* are associated with recessive inheritance of multiple colorectal cancers (MYH-associated polyposis) [68] and monoallelic germline mutations seem to increase risk of malignant brain tumors [69].

The endonuclease VIII-like glycosylases

NEIL1 repairs ring-fragmented purines, saturated pyrimidines and several oxidative lesions including Tg, FapyG, FapyA, 8-oxoG, 5-hU and 5-hC [1]. The structure of human NEIL1 has been solved by X-rays crystallography [70]. NEIL1 contains a structural motif composed of two antiparallel β-strands that mimick the antiparallel β-hairpin zinc-finger found in other Nei family members with the relevant difference of lacking the loops that harbor the zinc-binding residues (zinc-less finger). This motif is necessary for the DNA glycosylase activity of NEIL1 as a single nucleotide amino acid substitution (i.e. Arg277Ala) in this zinc-less finger motif reduces the substrate cleavage [70]. NEIL1 can cleave lesions present in single strand, double strand and bubble DNA structures [71]. After base removal, NEIL1 cleaves the abasic site by a β–δ-elimination mechanism, which requires the polynucleotide kinase (PNK) protein to generate the 3'-OH terminus and thus is APE1-independent [72]. NEIL1 interacts with and is stimulated by the replication proteins Polδ, RF-C, Lig1 and FEN1 and is preferentially involved in replication-coordinated BER [73]. Moreover NEIL1 interacts with several BER proteins such as Polβ, DNA Ligase III (LigIII), PCNA and XRCC1 via its C-terminal domain [1]). NEIL1 stimulates OGG1 excision activity [74] and, in turn, it is stimulated by the checkpoint complex Rad9-Rad1-Hus1 (9-1-1) [75] and by the Werner helicase [76].

*Neil*1 ko mice are viable and do not show any obvious immediate postnatal defects [77]. Only a slight increase of lung adenomas and hepatocarcinomas incidence was reported in aged animals. In contrast, a clear cancer prone phenotype was observed in *neil1 nth1* double ko mice which are characterized by pulmonary and hepatocellular carcinomas and C>T activating mutations in the *k-ras* gene in their pulmonary tumors [78]. These findings not only confirm the overlapping substrate specificity between NEIL1 and NTHL1, but indicate that lesions other than the well-known procarcinogenic 8-oxoG are involved in tumor initiation. It is of note that *neil1* ko mice spontaneously develop late-onset obesity associated to hyperleptinemia, hyperinsulinemia, hepatic steatosis and increased mitochondrial DNA damage [77].

In humans, inactivating mutations of *neil1* have been found in a subset of primary gastric cancers (GC) suggesting that low NEIL1 activities may be involved in GC pathogenesis [79].

NEIL2 shares the same substrates of NTHL1 and NEIL1. The NEIL2 protein structure has not been solved by crystallography yet. It presents two domains: the N-terminal and the C-terminal that contain the typical H2TH motif and an unusual zinc finger motif necessary for DNA binding and catalysis respectively [80,81]. The AP site generated after the base removal is cleaved by a $\beta-\delta$-elimination mechanism similar to that of NEIL1 [82]. NEIL2, like NEIL1, has an efficient dRP-lyase activity [83].
NEIL2 seems to have a crucial role in the repair of oxidized bases in active genes (transcription-coupled BER, TC-BER) as suggested by its interaction with RNA polymerase II, TFIIH, CSB and LIGIII both *in vitro* and *in vivo* [84,85]. In addition NEIL2 has a back-up function in pre-replicative DNA repair by NEIL1 [73]. Recently it has been shown that both NEIL1 and NEIL2 cooperate with TDG during base excision, stimulating TDG-substrate turnover [86]. Moreover, NEILs function as AP lyase during oxidative DNA demethylation [86].
Neil2 ko mice do not present an overt phenotype or spontaneous tumorigenesis although the depletion of *neil2* leads to telomere loss and genomic instability and induces innate inflammation [85]. Only middle aged to old animals accumulate oxidative DNA damage mostly in transcribed regions of their genome [85] as expected from a role of NEIL2 in TC-BER.

NEIL3 mainly operates as a monofunctional DNA glycosylase [87] and excises hydantoin lesions in both single-stranded and double-stranded DNA and, although less efficiently, 5-hC and 5-hU in single-stranded DNA. *Neil3* gene is cell cycle-regulated and is induced in early S phase with the highest levels in G2 phase [88]. The N-terminal half of NEIL3 contains the H2TH motif and the C terminal contains the zinc finger motif for DNA binding. In the conserved N-terminus, a valine substitutes the catalytic proline found in most of Nei family members [88].
Studies on *neil3* deficient mice [89,90] show that these animals are viable, fertile and healthy into adulthood and do not show genome instability. Nevertheless, aged *neil3* ko mice show an impairment of differentiation of the neural progenitor cells associated to a reduced learning and memory, demonstrating that NEIL3 is pivotal for maintaining adult

neurogenesis [89,90]. Recently, a role for NEIL3 in atherogenesis in balancing lipid metabolism has been hypothesized on the basis of the promotion of atherosclerosis by *Neil3* deficiency in Apolipoprotein E ko mice on hig fat diet [91]. This finding adds evidence to the involvement of DNA glycosylases (see also OGG1 and Neil1) in the regulation of energy metabolism.

N-methylpurine DNA glycosylase

MPG is a monofunctional glycosylase which recognizes several alkylated and etheno-modified bases. Its expression is cell-cycle dependent [92] and localizes both in the nucleus and in mitochondria [93]. MPG activity is enhanced by XRCC1 and the Nucleotide Excision Repair (NER) factor HR23B [94,95]. Moreover, MPG binds PCNA and is stimulated by APE1 by displacement from the abasic site [96,97]. MPG consists of a single mixed α/β domain that differs from any other known protein and the active site is lined with aromatic amino acids for binding to the electron-deficient alkylated bases that it recognizes [98,99].

Mpg deficient mice do not display an obvious phenotype but are more susceptible to chronic inflammation induced colon tumorigenesis [100] and alkylation-induced retinal degeneration [101].

In conclusion, the knowledge derived from mouse model systems and human diseases indicates that inactivation of DNA glycosylases is mostly causally associated with increased cancer risk, particularly of the gastrointestinal tract, but also with increased susceptibility to other adverse phenotypes such as obesity related metabolic dysfunctions and neurodegeneration (Table 1).

SNPs: function and disease

In this section the studies currently available in the literature on the function of SNPs are reported in conjuction with their association with disease. The description of the SNP-disease association studies is focused on large size epidemiological studies and/or meta-analysis of published studies when available. It should be taken into consideration that the conclusions of all the other studies summarized below are hampered by several factors including limited sample size.

The family of UDGs

Recently, the UNG2 Arg88Cys (rs151095402) variant has been reported in humans [102]. This single nucleotide substitution abolishes the binding to RPA and the recruitment of UNG2 to single-stranded DNA. This SNP together with missense variants in NEIL2 and TDG was identified in patients with familial colorectal cancer, but not in 188 healthy controls [103].
The SNP analysis of several BER genes in a large series of BRCA1/2 mutation carriers [104] identified an association of the rs34259 in UNG2 with ovarian cancer risk but the function of this polymorphism is unknown.
In a hospital based case-control study aimed to evaluate the association between SNPs in UNG and the development of esophageal squamous cell carcinoma (ESCC) a total of 380 cases and 380 controls were recruited. When the UNG rs246079 GG homozygote genotype was used as the reference group, the GA genotype was associated with a significantly decreased risk for ESCC. In stratification analyses, the decreased risk of ESCC was evident among women, younger patients and never-smokers and never-drinkers. However, because of the limited sample size and lack of tissue-specific biological characterization further studies are required to confirm this finding [105].
A potential role of the rs2337395 polymorphism of UNG and of its combination with the SMUG1 rs3087404 SNP has been proposed in the pathogenesis of age-related macular degeneration (AMD), an eye disease that results in progressive and irreversible loss of central vision [106]. Moreover UNG polymorphisms rs3219218 and rs246079 have been involved in the development of rheumatoid arthritis (RA) in the Taiwan's Han Chinese population [107].

The TDG Gly199Ser (rs4135113) variant is found in 10% of the global population. Gly199 contributes to the stabilization of the flipped abasic nucleotide into the DNA glycosylase active pocket and blocks its retrograde flipping back into the helix but does not change variant catalytic activity [108]. The mutation of the Gly199 to a larger and nucleophilic Ser strenghtens TDG interaction with both the abasic site and the substrate. The persistence of abasic sites in cells expressing this variant leads to the induction of DSB, genomic instability and cellular transformation [109]. A recent genome-wide association study (GWAS), for ESCC in a Chinese population showed that the most significant SNP for cancer risk is the Gly199Ser of TDG [110].
Non-melanoma skin cancer (NMSC) is the most common human cancer [111] and is associated with a broad spectrum of malignancies, suggesting that NMSC is a marker of a

cancer-prone phenotype [112]. The SNP Val367Met (rs2888805) in TDG seems to contribute to the NMSC-associated increase in overall cancer risk [113].
The rs167715 and rs4135087 were shown to associate with ovarian cancer risk in a large series of BRCA1/2 mutation carriers [104].

The TDG Arg66Gly (rs369649741) variant was identified in patients with familial colorectal cancer but not in 188 healthy control [103].
Significant associations between risk of ESCC and gastric cancer (GC) and SNPs in TDG and SMUG1 emerged from the analysis of the associations between DNA repair pathway genes and risk of cancer [114]. In this study 1942 ESCC cases, 1758 GC cases and 2111 controls were genotyped for 1675 SNPs in 170 DNA repair-related genes. The SMUG1 rs202916 and the TDG rs4135054 SNPs were significantly associated with risk of ESCC [114]. It is of note that TDG is located in a region of high loss of heterozygosity in GC [115].

The HhH glycosylases
The MBD4 variants Asp568His and Cys61Arg show reduction of both catalytic activity and binding affinity for its substrates T and U paired to G within a CpG context [4]. These variants were identified in gastric tumors with MSI [116].
Variants Ala273Ser/Thr, Ser342Pro and Glu346Lys are located within the long spacer domain, which interacts with several proteins including the two major components of the HDAC-dependent pathway, Sin3A and HDAC1 [117].
In a case-control study the SNP Glu346Lys was found to be a significant predictor for the risk of ESCC in a Chinese population [118]. The same polymorphism was associated with significantly decreased risk of cervical cancer in a Chinese population [119].
Using the Illumina SNP genotyping platform, three SNPs (rs2311394, Glu346Lys/rs140693, and rs2005618) of MBD4 have been selected and genotyped in a case-control study in a Chinese population. The data suggested that only the genetic variant of MBD4 Glu346Lys was associated with decreased lung cancer risk suggesting a protective role of this SNP [120,121].

Downregulation of NTHL1 has been reported in eight GC cell lines and in 36% (18/50) of primary GC [122]. In these cancers NTHL1 was predominantly localized in the cytoplasm in contrast to the nuclear localization in non-cancerous tissue. The low NTHL1 expression in the GC cell line AGS was functionally associated with inefficient repair of Tg. In this

same study two novel genetic polymorphisms, c.-163C>G and c.-241_-221del, were identified in the *nthl1* promoter region. They were shown to associate with reduced promoter activity, but not with risk of GC in a case-control study [122].
Recently, the Asp239Tyr variant of NTHL1 has been described in 6,2% of the global population. Expression of this variant in mammary epithelial cells induces genomic instability and cellular transformation suggesting its involvement in cancer susceptibility [123].

The most common polymorphic variant of hOGG1 is Ser326Cys (rs1052133), with the 326 residue located in the C-terminal domain of the protein. Homozygous carriers of the hOGG1 Ser326Cys variant present reduced ability to remove 8-oxoG [124,125] and to complete the repair synthesis step [125]. Moreover, under oxidizing conditions, this variant is characterized by lower catalytic activity [124,125] and higher proneness to dimerize [125]. The same occurs under oxidizing conditions that mimick inflammation: nitric oxide (NO) [126] and TNFα [127] both induced a reduction of the repair capacity of the Ser326Cys hOGG1 variant. In addition repair inhibition by NO causes an increase in genetic instability in cell expressing the hOGG1 Ser326Cys variant [127]. The reduced 8-oxoG repair of this variant determines genetic instability in cells in culture [124]. It has been proposed that because of a change in the phosphorylation status its localization to the nucleoli during the S phase of the cell cycle would be inhibited [128].
Other OGG1 variants such as OGG1 Arg154His, Ogg1 Arg46Gln and Ogg1 Asp322Asn have significantly lower activity compared to that of the wild type OGG1 [129,130]. Two OGG1 SNPs (Ala53Thr and Ala288Val) identified in brain tissues of Alzheimer's Disease (AD) patients [131] present lower catalytic activity. In addition, the Ala53Thr SNP has lower substrate binding and the Ala288Val SNP has reduced AP lyase activity. Both SNPs lead to a decrease in OGG1 binding to BER proteins such as PARP1 and XRCC1 [131]. Furthermore *ogg1*$^{-/-}$ murine embryo fibroblasts (MEFs) expressing Ala53Thr or Ala288Val SNPs are more sensitive to oxidatively induced DNA damage [132].
The association between SNPs in OGG1 and disease has been addressed by a large number of studies (summarized below) that taken together provide convincing evidence that genetic variants of this DNA glycosylase are susceptibility factors for a large spectrum of oxidative stress-associated diseases that span from cancer to cochlear/ocular disorders, cardiovascular diseases and neurodegeneration.

Epidemiological studies convincingly show that the activity of OGG1 is a biomarker of susceptibility for cancers such as non–small cell lung cancer [133] and head and neck cancer [134]. The association between hOGG1 Ser326Cys polymorphism and risk of lung cancer, although not fully consistent in the available literature, is strongly suggested by several studies. The most relevant are summarized below. An updated meta-analysis of 20 studies (8739 cases and 10385 controls) stratifying by ethnicity, control sources, cell histotypes, and smoking status showed a significant correlation of the hOGG1 Ser326Cys polymorphism with increased lung cancer susceptibility in Caucasians and, regarding the histopathologic category, with lung adenocarcinoma [135]. In order to eliminate as confounding factor the smoking habits, several studies have investigated the association of hOGG1 Ser326Cys polymorphism with lung cancer in non-smoking female population. A follow-up study of 610 non-small cell lung cancer (NSCLC) patients showed that patients with this OGG1 variant have poor overall survival compared with those with the homozygous wild type genotype, especially in the subgroups of female patients, adenocarcinoma histology, early stage, light smokers and without family history of cancer [136]. The hOGG1 Ser326Cys polymorphism seems also to increase the risk of lung adenocarcinoma in Chinese non-smoking females when exposed to cooking oil fumes [137] that are one of the major indoor air pollutants and are recognized as an important risk factor for lung cancer [138]. Finally, a recent meta-analysis provides additional evidence that hOGG1 Ser326Cys polymorphism may contribute to lung cancer risk, particularly in Asian populations, not only in heavy smokers but also in never smokers [139]. This common variant seems to lead to an increased susceptibility to breast cancer in a Spanish and in a Chinese population [140,141] and to ovarian cancer in Polish women [142].

In a large SNP analysis study conducted in BRCA1/2 mutation carriers addressing whether the common genetic variation in BER genes are associated with cancer risk the rs2304277 in OGG1 turned out to be associated with ovarian cancer risk [104]. The same OGG1 SNP has been shown to determine a significant hOGG1 downregulation, which exerts a synergistic effect together with BRCA1 or BRCA2 mutations on DNA damage and telomeres shortening [143].

Variants of OGG1 (rs2072668 and Ser326Cys), in combination with the APEX1 Asp148Glu SNP have been associated with increased susceptibility to breast cancer in a Korean population ([144]). Interestingly, the combination of the hOGG1 Ser326Cys variant allele with the same APE1 Asp148Glu SNP and also with XRCC3 (Thr241Met) has been

reported to modulate the frequency of chromosomal aberrations as measured in peripheral blood lymphocytes from healthy subjects [145].

The OGG1 Ser326Cys polymorphism has also been associated with increased colorectal cancer (CRC) [146-149] and bladder cancer risk in Belarus Chinese and in Caucasian population [150,151]. The analysis of gene-gene interaction revealed a significant increase of the risk of CRC particularly for the genotype combinations of the Ser326Cys of OGG1 and the Gln324His of MUTYH [148]. Moreover, the OGG1 rs159153 SNP, located 5'-upstream of *ogg1* gene, was shown to modify the effect of smoking on colorectal adenoma risk [152].

Other studies associate hOGG1 Ser326Cys polymorphism with risk of other types of cancer such as hepatocellular carcinoma (HCC), [153], cholangiocarcinoma (CCA) [154], upper aerodigestive tract cancer (UADT, [155]), nasopharyngeal carcinoma [156-159] and prostate cancer [160] but they rely on a small sample size which leads to a considerable lack of statistical power and ethnic and geographic differences that may account for the discrepancies observed. This polymorphism seems also to associate with myelodysplastic syndrome (MDS) and modulate acute myeloid leukemia (AML) transformation in MDS patients influencing survival of MDS and AML patients [161].

Several lines of evidence indicate the pathogenic role of oxidative stress in ocular disorders such as glaucoma. The most frequent type of glaucoma is primary open-angle glaucoma (POAG), which represents over 50% of diagnosed glaucoma cases in the developed countries [162]. One study demonstrates an association between the OGG1 Ser326Cys polymorphism and progression of POAG [163].

Cataracts are the leading cause of blindness worldwide. Opacity of the lens is a direct result of oxidative stress [164]. An association between OGG1 Ser326Cys polymorphism and age-related cataract was reported [165,166]. This polymorphism has been also associated with the susceptibility to AMD [167].

Underlying the classic set of cochlear pathologies that occur as a result of noise exposure including Noise-Induced Hearing Loss (NIHL) are increased levels of reactive oxygen species (ROS) that play a significant role in noise-induced hair cell death [168]. The hOGG1 Cys/Cys genotype was statistically significantly associated with Noise-Induced Hearing Loss (NIHL) in Chinese populations. Moreover, synergistic effects between the hOGG1 Ser326Cys polymorphism and noise exposure time, noise exposure level, smoking status, and drinking status on NIHL were observed [169].

The brain is particularly vulnerable to oxidative stress due to its high oxygen consumption, weakly antioxidative systems and the terminal-differentiation characteristic of neurons. Thus, oxidative stress elicits various neurodegenerative diseases. Carriers of at least one copy of the Cys326 allele of OGG1 showed a significantly earlier Huntington disease (HD) onset than Ser326 carriers. This finding suggests a possible role of the OGG1 Ser326Cys polymorphism in the HD phenotype [170,171]. However, this association has not been confirmed in 419 German HD patients [172]. No association between OGG1 Ser326Cys and sporadic Alzheimer disease (AD) was observed in two independent analysis [173,174]. An association between cognitive performance and OGG1 Ser326Cys polymorphism has also been reported [175].
Myocardial infarction (MI) due to coronary artery atherosclerosis is a leading cause of morbidity and mortality worldwide [176]. The underlying pathology of atherosclerosis constitutes a multifactorial process where oxidative stress plays a major role [177,178]. The hOGG1 Ser326Cys polymorphism has been found to be associated with coronary artery disease in a Turkish population [179] and with the development of coronary ectasia in Chinese population [180].

Estimated susceptibility due to inherited multiple low-penetrant genetic variants accounts for about 35% of variance in CRC risk and MUTYH has been identified as a possible contributor to the inter-individual variation in CRC and other cancer predisposition [181]. Several human MUTYH variants essentially due to missense or insertion /deletion mutations have been functionally characterized [182-186]. Usually, MUTYH variants have a severe reduction of the DNA glycosylase activity and show residue substitution in the catalytic domain or in the substrate recognition region. The most common MUTYH variant is Tyr165Cys (rs34612342). The Tyr165 residue directly intercalates into the DNA duplex between 8-oxoG and the nucleoside 5' to 8-oxoG [55]. In the variant, the smaller Cys substitutes Tyr, producing dramatic structural changes among which a reduction in both stacking interaction and inter-residue hydrogen bonding capability [55]. On the contrary, the variants Val22Met and Gln324His have a residue substitution located far from the catalytic domain. The Gln324His MUTYH variant is found in over 40% of people in some populations [187]. When expressed in insect cells, it has a lower 8-oxoG:A repair than the wild type protein [188]. More recently, it has been reported that the Gln324His variant presents a normal substrate binding and DNA glycosylase activity but displays a reduced affinity for Hus1 of the Rad9-Rad1-Hus1 complex [189]. The variant MUTYH Gln324His,

has been associated with increased risk of lung cancer [190] and CRC [191-193]. On the basis of its low repair activity and association with increased cancer risk this variant should be considered a cancer risk susceptibility gene [188]. Moreover, cells expressing the variant Gln388His show an increased 8-oxoG level, hypersensitivity to oxidants and accumulation in the S phase of the cell cycle [194].

The *MUTYH AluYb8* (rs10527342) is a common polymorphism due to insertion of an Alu element in the 15th intron of the *MUTYH* gene, causing an increase in genomic 8-oxoG levels [195]. Individuals homozygous for this variant have a reduced level of MUTYH type 1 (mitochondrial) protein expression and a decreased mitochondrial homeostasis which possibly explains the associated age-related diseases [196]. This polymorphism has been found to associate with early onset breast cancer risk and with GC in a Chinese population [197]. A chip-based TaqMan genotyping for the candidate genes performed on 227 bladder cancer patients and 260 healthy controls revealed that the SNPs rs3219493 in MUTYH is significantly associated with bladder cancer risk [198].

Individuals with a homozygous rs3219472 MUTYH variant present increased CCA risk. This SNP is proposed as biomarker for screening individuals at high risk [199]. Two rare catalytically impaired hMYH variants (hMYH Arg260Gln and hMYH His434Asp) were found in primary sclerosing cholangitis (PSC) patients [200]. PSC is often complicated by the development of CCA.

The endonuclease VIII-like glycosylases

NEIL1 polymorphisms with partial or full inactivation of the glycosylase activity have been described. The Gly83Asp (rs5745906) variant of NEIL1 is defective in the removal of 8-oxoG, Tg, FapyA, FapyG and dihydrothymine in duplex DNA, while it has a normal activity in the removal of 5-hydroxycitosine (5-hC) and 5-hydroxyuracil (5hU) in single stranded DNA [200] indicating that it is not completely devoid of glycosylase activity. Moreover, this variant is not able to perform δ-elimination [201]. Gly83 is located in the N-terminal domain, in a loop within a groove of NEIL1, which is believed to be involved in the binding to DNA. The Cys136Arg (rs5745907) variant does not exhibit glycosylase activity [201]. The folding of the protein is altered by this amino acid substitution, probably compromising the ability of the enzyme to bind flipped nucleotides. The glycosylase activity of other two variants, Ser82Cys (rs5745905) and Asp252Asn (rs5745926) was reported to be very similar to that of the wild type enzyme [201]. In another study [202] substrates specificity was analysed for the NEIL1 variants Ser82Cys, Pro208Ser, and ΔE28. The Pro208Ser variant presented

a wild type-like activity on all the substrates tested, while Ser82Cys and ΔE28 variants were defective in the Tg excision. This finding is in contrast with what reported by Roy and coworkers [201] for the Ser82Cys variant. The NEIL1 variant Gln282Stop-type protein (rs1128987) is prevalently localized in the cytoplasm, possibly due to a loss of the nuclear localization signal (NLS) and has a lower ability to suppress the onset of mutations [203]. If functional studies have identified NEIL1 SNPs with impaired activity the association studies with disease are scanty. Two PSC patients with CCA were found to be heterozygotic for NEIL1 Gly83Asp SNP [200], however the small number of individuals analysed does not allow drawing any conclusion on the association with CCA. The NEIL1 rs4462560 SNP was reported to be associated with MDS [161].

Two SNPs in the 5'UTR (rs74800505 and rs8191518) of NEIL2 have been shown to lower its expression levels when present together, suggesting their role in disease susceptibility. This down-regulation probably prevents the binding of essential transcriptional factors and determines an increase in mutagen sensitivity in cultured lymphocytes heterozygous or homozygous for the rs74800505 SNP [204].
Two other polymorphic variants, Arg103Gln (rs8191613) and Arg257Leu (rs8191664), frequently observed in lung cancer patients, have been characterized. The glycosylase activity was modestly lower only in Arg257Leu variant compared to the wt protein. However, when the glycosylase activity was measured in reconstituted repair assay containing wild type NEIL2 or Arg257Leu and Arg103Gln variants together with other DNA BER proteins (PNKP, Polβ, LigIIIα and XRCC1), a ~5 fold decrease in repair was observed with the Arg257Leu variant compared to the WT or Arg103Gln NEIL2, apparently due to lower affinity for other repair proteins, particularly Polβ [205]. The Arg257Leu variant may be a risk factor for certain histologically different types of lung cancer in the Chinese population, where occurrence of this SNP is very high in the population [205].
The SNPS rs1466785 in the NEIL2 gene showed an association with breast cancer risk in a large series of BRCA1/2 mutation carriers tested by SNP approach for variants in the BER pathway [104].
Finally, an increased risk for GC was detected in subjects from a Northern Jiangsu population with mutant alleles in NEIL2 (rs804270) [206] and the missense NEIL2 variant Pro123Thr (rs8191666) was identified in patients with familial CRC but not in 188 healthy controls [103].

A nested case–control study was conducted to evaluate the interaction between pesticide exposures and genetic variation in BER genes with respect to prostate cancer. The interaction between the pesticide fonofos and rs1983132 in NEIL3 was the most significant [207]. The NEIL3 SNP rs12645561 was shown to be associated with the risk of developing glioma [208] and glioblastoma [209]. The *neil3* rs12645561 SNP TT genotype was associated with increased risk of myocardial infarction [210]. A genome wide linkage analyses in a Korean families reported an association between the rs6850861, rs6823018, rs6830266 and rs2048077 SNPs in NEIL3 with fasting insulin level, overweight and type 2 diabetes [211].

N-methylpurine DNA glycosylase (MPG)

Two MPG polymorphic variant, Arg120Cys (rs2308313) and Arg141Gln (rs2308312), have been characterized. These variants have reduced enzymatic activity and, when expressed in mammalian cells, induce an increase in mutation frequency and in sensitivity to an alkylating agent compared to the wt MPG. The MPG variants have reduced affinity for 1,*N*6-ethenoadenine-containing DNA and exhibits slower turnover than the wt MPG [212]. A population-based case-control study has shown that increased MPG activity is associated with increased lung cancer risk, suggesting that an imbalance in DNA repair can cause cancer [213].

Concluding remarks: present and future perspectives

What emerges from this overview is that there is a clear association between SNPs in DNA glycosylases that are mostly involved in the repair of oxidatively-induced DNA lesions and susceptibility to diseases which all present as major risk factor oxidative stress. Notwithstanding the limits of the epidemiological studies, the scarce information on function of genetic variants and the limitation of studies exploring one or a few SNPs, the overall disease spectrum includes cancer (mostly lung, breast, GI tract), ocular and cochlear disorders, myocardial infarction and neurodegenerative disorders which can be all grouped under the umbrella of oxidative stress-related pathologies (Fig. 1). The phenotype of ko mice and the clinical features of the few human diseases with full inactivation of these DNA glycosylases support this conclusion (Table 1). Moreover, three DNA glycosylase (i.e. *ogg1, neil1 and neil3*) mutant mice indicate that obesity and

associated metabolic derangement may arise when these activities are defective. Further research should address the underlying mechanisms and the possible impact on human health. It is of interest that a large number of polymorphisms in DNA glycosylases are located in introns, often in exon-intron splice junctions (Table 2). This is also true for approximately 10% of all inherited pathological mutations [214]. This might be explained by the fact that introns represent a large mutational target and contain a multiplicity of functional elements that affect transcriptional activity or the splicing efficiency of their host genes and even of genes at distance. However, in most studies these polymorphisms are merely associated with impaired enzymatic activity and whether they are truly functional SNPs or a linkage disequilibrium effect remains to be addressed.

The advent of next-generation sequencing (NGS) has shown that considerable variation in human genome is still undiscovered and therefore a considerable number of rare variations that are related to disease susceptibility may still be unknown. NGS has allowed to strengthen the association between loss of function mutation in DNA glycosylases and cancer in the two human syndromes identified up to now. Genetic analysis of colon carcinomas and adenomas in the *nthl1* mutated patients showed a non-hypermutated profile enriched for C>T transitions that are expected on the basis of the mutation spectra observed in *nthl1/neil1* double ko mice [78]. Similarly, analysis of the somatic mutational landscape of adenomas of patients affected by MUTYH-associated polyposis revealed a moderate mutator phenotype (5 times higher than in FAP adenomas) and as dominant signature G>T transversions that are typically associated with the failure to remove misincorporated adenines opposite 8-oxoG [215]. NGS applied to tumor genome profiling has revealed that DNA damage response genes are often mutated in all cancer types. Inherited polymorphisms as well as inherited and somatic mutations or epigenetic changes can disrupt the cell capacity to respond to damages constantly caused by normal metabolic products and environmental factors and genes mutations are rapidly accumulated. Large scale studies performed by the Cancer Genome Atlas and the International Cancer Genome Consortium researchers have generated comprehensive catalogues of genomic abnormalities in 50 different cancer types and sub-types that show how among the hundreds of mutations accumulated by cancer cells only a few are driver mutations and point out how defects inactivating DNA repair genes constitute a clear cancer-specific signature. Interestingly, whereas homologous recombination alterations are diffused in most cancer types (breast, ovarian, colorectal and prostate), MMR is typically impaired in colorectal and endometrial cancer, NER in prostate cancer and

Fanconi Anemia genes in ovarian cancer [216]. The BER pathway does not present a specific cancer-signature but it is frequently mutated (>15% of patients analysed for each cancer type) in cancer such as bladder, colon, liver, lung and ovaries (data from [217]). It is of note that these are the cancer types most frequently associated with SNPs in DNA glycosylases (Table 2).

Although it is outside of the topics of our review, it should be mentioned that DNA repair gene alterations are often the result of epigenetic modifications in cancer. Inactivation, reduced expression by promoter methylation as well as increased expression by unmethylation of DNA repair genes are early events driving neoplastic transformation and can also confer resistance to chemotherapeutic treatments (reviewed in [218]). For instance promoter hypermethylation of *mbd4* is recognized as an early event in tumorigenesis of sporadic colorectal cancer [219] and aberrant promoter methylation of *neil1* has been reported in head and neck squamous cell carcinoma [220]. Finally, over the last decade defects in components of several DNA repair pathways have been recognized as etiopathological factors of novel disorders other than cancers such as immunological disorders, metabolic disease and neurodegenerative disorders. The variety of the BER-associated diseases that also emerges from the DNA glycosylase SNPs-disease association studies (Table 2) indicates the need of studying genomic variations in DNA repair pathways in a broader spectrum of diseases than cancer.

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Legend to Figure 1

A wide spectrum of diseases is associated with mutant DNA glycosylases.

GI: gastrointestinal