Tumor Suppression by DNA Base Excision Repair

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Abstract: Base excision repair (BER) is the main pathway for repair of endogenous DNA damage. It was expected that different tumor types could derive from BER defects but to date this link is elusive. *In vitro* and molecular epidemiology studies may be used to unravel this issue.

Key Words: DNA base excision repair, molecular epidemiology, oxidative DNA damage, 8-oxoguanine, glycosylase, mutation, *in vitro* neoplastic transformation, chemotherapy.

INTRODUCTION

Among various DNA repair mechanisms, base excision repair (BER) is the main pathway that removes endogenous damage. Although its protecting function from neoplastic transformation would seem logic, this is far from being established. Both *in vitro* and molecular epidemiology approaches may be used to investigate this so far putative link.

1. DNA BASE EXCISION REPAIR (BER)

BER is so called because the first step of the pathway involves recognition and removal of an altered base (reviewed in [1-3]) (Fig. **1**). Frequent types of alterations are oxidation, deamination and ring fragmentation. There is also a certain level of endogenous methylation of DNA bases, due to some physiological methylating agents such as S-adenosylmethionine. BER can also be initiated by "spontaneous" base loss that occurs at a rate of several thousands events/day/genome. According to the kind of lesion, the damaged base is removed by a monofunctional glycosylase [e.g. uracil (U)-DNA glycosylase] that only detaches the altered base (Fig. **1** – left pathway), or by a bifunctional glycosylase (e.g. hNTH1) that also cleaves the abasic (AP) site by an associated AP lyase activity (Fig. **1** – right pathway). 5' or 3' termini left after AP site incison in either branch have to be modified by a number of still partially characterized activities in order to make them suitable substrates for the repair polymerase [DNA polymerase (pol) β in most instances] that usually incorporates just one nucleotide to reconstitute a normal sequence. The repair patch is eventually sealed by a DNA ligase (I or III). Most BER components interact with XRCC1, a scaffold protein that is essential for the coordination and stimulation of the whole process [4]. Two polymorphisms have been found in the XRCC1 gene: the Arg194Trp polymorphism which resides in the linker region separating the pol β domain from the PARP interacting domain and the Arg399Gln polymorphism which resides within the BRCT (BReast cancer proteins C Terminus-like) domain [5].

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A number of repair patches are longer than one nucleotide, in the so-called long-patch BER (Fig. **1** – bottom left pathway). In this alternative pathway, several replicative proteins are involved [PCNA, DNA polymerase δ/ε, DNAase IV (FEN1)] and the suggestion has been made that this pathway could be replication-coupled [6].

Oxidized bases are further repaired at reduced efficiency by the nucleotide excision repair (NER) pathway that may act as a backup system [7]. NER is particularly important for repair of a subset of lesions formed by aldehydes derived from lipid peroxidation, such as 6-(1-hydroxyhexanyl)-8-hydroxy-1,N(2)-propano-2'-deoxyguanosine (4-HNE-dG) [8] and malondialdehyde (MDA) – DNA adducts [9].

Mutations in BER genes probably affect viability at great variance. For instance, it is unlikely that marked AP site repair defects can be observed in human pathological tissues. In bacteria, yeast and rodents, substantial reductions in AP site incision capacities seriously affect viability [10-12] and human cells, even if tumoral, may not escape this rule [13]. On the contrary, defects in glycosylases may more likely be sustained and underlie some forms of human pathology. Glycolytic enzymes usually have a specific and not essential role and base removal is in some instances the rate-limiting step of the repair process [14,15].

Development of mouse knockout strains is currently pursued in order to define the role of BER *in vivo* [3]. Deletion of BER activities leads to various phenotypic consequences ranging from arrest of embryonic development (such as in the cases of mice deficient in the major AP endonuclease APE/HAP1 [11], DNA polymerase (pol) β [17] or XRCC1 protein [18]) to mild (strains deficient in 3-alkyl-N-purine glycosylase [ANPG – 19,20]), poly (ADP) ribose polymerase [PARP – 21], 8–oxoG DNA glycosylase [OGG1 – 22], U DNA glycosylase [UNG – 23] or minimal (strains deficient in the endonuclease III homologue [NTH1 – 24] effects thus opening new questions on the significance and the backup supply of the different BER activities. Despite the complexity of this emerging picture, it is most likely that endogenous le sions escaping the "cleaning" activity of BER may contribute to spontaneous mutagenesis/carcinogenesis [9, 25-27]. In particular, some lesions with elevated miscoding properties [8-oxo-7,8-dihydroguanine (8-oxoG) and 4,6-

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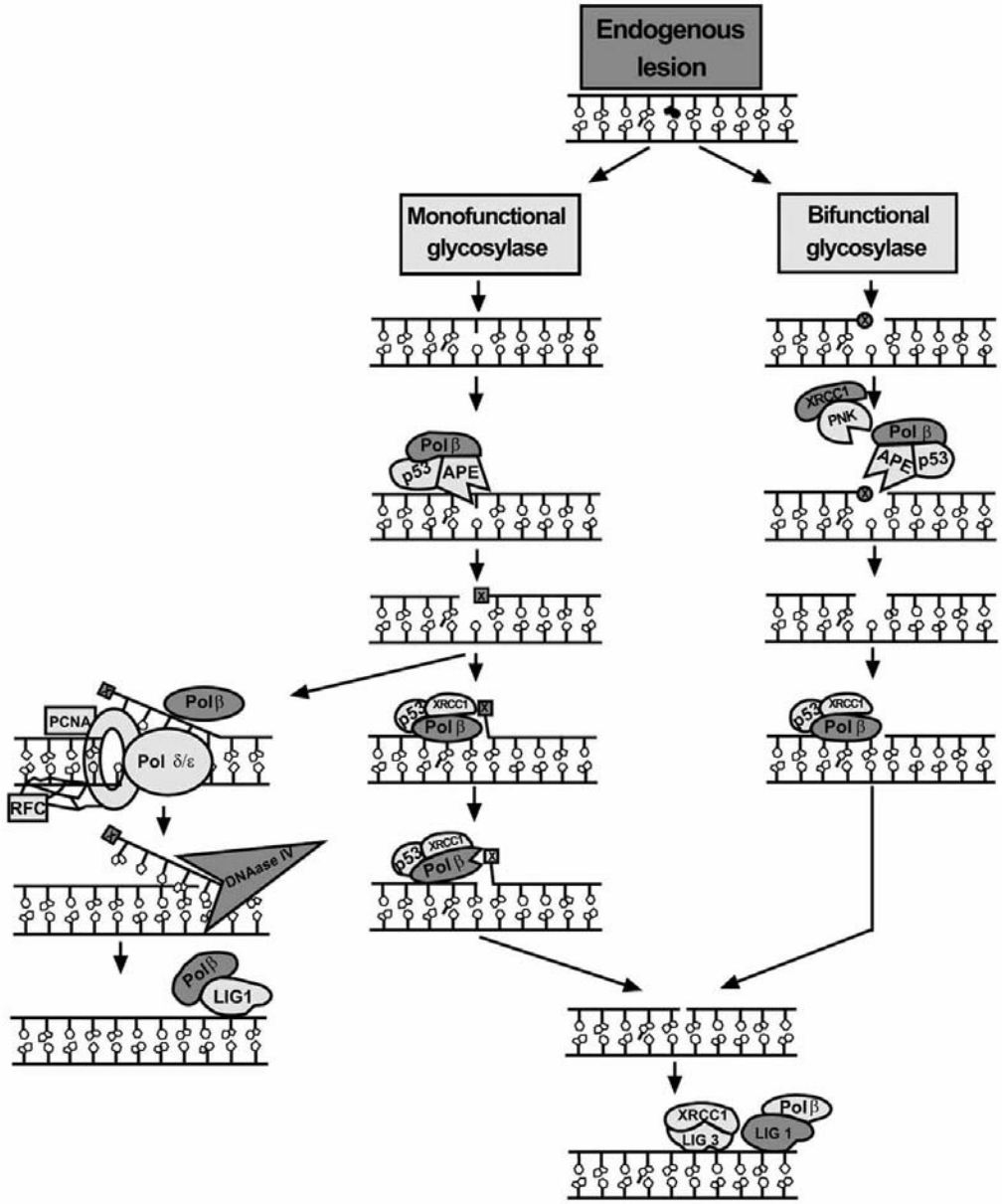

Fig. (1). Outline of the DNA BER pathways in mammals. Altered bases are removed by either monofunctional or bifunctional DNA glycosylases. Monofunctional glycosylases (left-hand pathway) only remove the base leaving a natural AP site. The latter is incised in 5' by the major APE/Ref-1 hydrolytic AP endonuclease that leaves a 5'-terminal dRP residue and a 3' OH priming terminus. DNA pol β inserts in most cases one nucleotide and the dRP group is removed by its N-terminal dRpase activity. p53 interacts with both APE/Ref-1 and pol β and stabilizes the latter on DNA. The complex DNA ligase III/XRCC1 or DNA ligase I seals the interruption. A number of repair patches is longer (2-10 nucleotides) and require participation of proliferating cell nuclear antigen (PCNA - bottom left-hand pathway). Both pol β and the PCNA-dependent polymerases δ/ε (pol δ/ε) are involved in the long patch pathway. The damaged 2-10 nucleotides long DNA fragment is displaced during polymerization and removed by DNAase IV (FEN1). DNA ligase I is the main sealing activity in the long-patch pathway. In the case of bifunctional glycosylases (right-hand pathway), the AP site generated by the glycosylase activity is further incised in 3' by an associated AP lyase. The 3'-blocking fragment left by AP lyases is trimmed in human cells by the 3' phosphodiesterase activity associated to APE/Ref-1 or by the complex PNK-XRCC1. Synthesis is performed *via* pol β only and ligation proceeds as for the short-patch pathway initiated by monofunctional glycosylases (from [16] with permission - http://www.tandf.co.uk/journals).

diamino-5-formamidopyrimidine (Fapy Ade)] are repaired with low efficiency in human cells [28,29].

The repair system for 8-oxoG deserves a special mention as this repair seems particularly important with respect to human health [30]. 8-oxoG forms at a rate of ~ 1000 lesions/cell/day [26] and mispairs with adenine (A) during DNA replication [31] thus producing GC to TA transversions [32]. *In vivo* measurements indicate that insertion of an A opposite 8-oxoG occurs in human cells at a frequency of 16-17% of replication events [33]. 8-oxoG mutagenicity is

counteracted in humans by three different mechanisms [34]. First, 8-oxoG is recognized by the hOGG1 protein, a sluggish bifunctional DNA glycosylase that removes specifically the lesion when coupled to cytosine (C) (pre-replicative lesion). In this case the repair process eventually leads to reconstitution of a normal G:C base pair. Second, the hMYH protein removes misincorporated A from 8-oxoG:A base pairs originated after passage of the replication fork (post-replicative lesion) [35]. hMYH is a monofunctional DNA glycosylase that starts a BER process that leads to reconstitution of an 8-oxoG:C base pair that in turn is a suitable substrate for hOGG1. hMYH is associated with the replication foci, indicating a role in replication-coupled repair [36] and interacts with AP endonuclease, PCNA and RPA suggesting its involvement in long patch BER [37]. Third, hMTH1 sanitizes the triphosphate cellular pool by hydrolyzing 8-oxodGTP (pre-incorporation lesion) to 8-oxodGMP, thus preventing insertion of anomalous precursors into nascent DNA. All of the above genes have been cloned by homology to *E.coli* or *S. cerevisiae* counterparts. The existence of a complex and evolutionarily conserved system to counteract 8-oxoG hints at the dangerous properties of this oxidized lesion.

2. TUMOR SUPPRESSION BY BER *IN VITRO*: SPONTANEOUS TRANSFORMATION OF MOUSE EMBRYONIC FIBROBLASTS AS A MODEL SYSTEM.

2.1. Stimulating DNA Repair of Endogenous Damage to Delay the Onset of Spontaneous Transformation

Most human cancers may be considered "spontaneous" in nature as no evident specific inducing agent is usually identified. Development of cancer is linked to a number of genetic alterations caused by both endogenous and exogenous factors. Those alterations are continuously selected for improved proliferation according to a Darwinian process. This phenomenon is fortunately very long and development of frank malignancies may take decades. An increased efficiency of protective mechanisms may delay the threshold accumulation of cancerous events beyond the average human lifespan. In particular, the ability of mammalian cells to repair endogenous lesions may be increased by overexpression of one or more rate-limiting BER activities [38]. For instance, the bacterial homologue formamidopyrimidine DNA glycosylase (FPG) is 80-fold faster than human OGG1 in repairing mutagenic oxidative lesions [39]. Cell culture studies have shown that FPG can be expressed in mammalian cells where it accelerates DNA repair and abates mutagenicity of a wide range of DNA damaging agents (reviewed in [40]). The question arises whether accelerated repair of endogenous damage may diminish the rate of spontaneous carcinogenesis. The development of new strategies to investigate this point may take advantage of simple and more convenient systems than traditional animal studies. *In vitro* neoplastic transformation of mouse embryonic fibroblasts (MEF) is a possible surrogate system [41].

Most primary animal cells exhibit a limited life span in culture and eventually undergo senescence, during which time the cells cease to proliferate with resultant cell death [43]. With varying frequency, especially dependent on the species of origin, a few cells survive the senescent crisis and acquire unlimited proliferative potential. At the same time, measurable in months, they also become neoplastic spontaneously, displaying increasing capacity to grow in soft agar and induce tumors in nude mice (Fig. **2**). A number of comprehensive reviews on *in vitro* spontaneous transformation have been produced in the past [44-49] and for a detailed description of the phenomenon we refer to them. Transformation of cultured rodent fibroblasts has been used until recently to assess the carcinogenic properties of various drugs and metabolites [50,51] but exploitation of this phenomenon to investigate new strategies to prevent or reverse the spontaneous cancer phenotype has declined. This is somewhat surprising given the important achievements that have been made in understanding the molecular changes that underlie spontaneous *in vitro* transformation and the parallels between this phenomenon and human carcinogenesis. Spontaneous *in vitro* transformation may be conveniently used to investigate the possible protecting role of accelerated BER, the main pathway that repairs endogenous damage in mammalian cells.

2.2. Spontaneous Transformation in Rodent and Human Cells

When embryonic cells are taken from a mouse and placed in culture, they usually divide a limited number of times (10-15 population doublings) after which most cells die [44,52,53]. Some cells survive this crisis and become immortal, i.e. capable of indefinite growth. Cells that survive crisis and become immortal are relatively frequent with rodent cell cultures, with an immortalization rate of 1-10 x 10^{-6} per cell per generation [54,55]. Variants that survive crisis display aneuploidy, chromosomal aberrations and mutations in a number of tumor suppressor genes [56-59] thus indicating significant genotypic alterations, but still have very limited proliferation capacity and no ability to grow in soft agar or induce tumors in nude mice [60]. Within a period measurable in months, cells slowly acquire improved proliferation potential and a number of characteristics that are typical of neoplastic cells i.e. increased colony forming ability, loss of contact inhibition, elevated saturation density, ability to grow in soft agar and to induce tumors in nude mice [44,45,47,49] (Fig. **2**). The time-course of this phenomenon has been described in detail ([42] – Table **1**): crisis usually occurs after a couple of weeks (average 16 days) while the capacity to grow at elevated cell density, acquisition of 25% anchorage-dependent and 0.5% anchorage-independent colony forming ability take average periods of 255-290 days [42]. The process clearly involves continuous selection. Spontaneous immortalization and transformation is more frequent in mice than in rats but can be considered a general feature of rodent cells [47].

Unlike rodents, spontaneous *in vitro* transformation of human cells or avian cells is a very rare event [61]. Three cases of spontaneous transformation of human fibroblasts have been reported [62-64] together with a few other cases with other cell types such as epidermal keratinocytes [65] or mammary epithelial cells [66]. The genuine derivation of transformed cells from diploid normal parent cells has even been questioned in some of the above cases [46]. Spontaneous immortalization is more frequent in normal cells from patients with Li-Fraumeni syndrome who carry inherited mutations of the p53 gene [67-69]. It is clear that the combi-

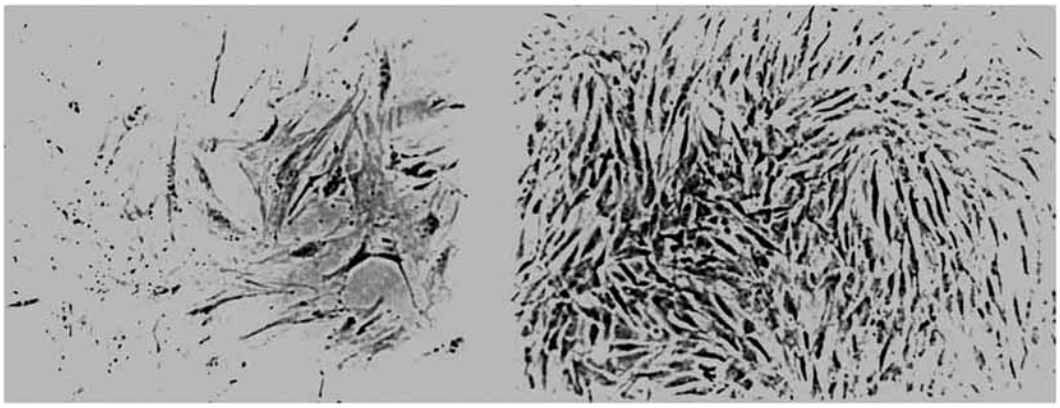

Fig. (2). MEFs before (left) and after (right) spontaneous transformation]. 600,000 CD-1 MEF cells were seeded in 60 mm dishes and photographed after 48 hours. Cells had been previously grown for 12 (left) or 120 (right) days starting with preparation (from [42] with permission).

nation of events that lead human fibroblasts to spontaneously immortalize and subsequently transform in culture is extremely rare in comparison to rodent cells. A possible explanation for this is that the number of mutational events required to confer immortality on human cells is higher than the number required for rodent cells [48,70-72]. For example, human fibroblasts control the number of cell divisions by telomere shortening, a mechanism that is not present in mice [73,74]. Further, rates of spontaneous mutation are lower in humans [75]. This may be linked to their more elevated repair capacity (demonstrated for NER but probably applying to repair of endogenous damage as well) and slower metabolism [76-78]. As a consequence, no human cell can acquire a sufficient number of alterations necessary for indefinite growth before the onset of crisis.

2.3. How Similar are Spontaneous Transformation of Cultured Rodent Cells and Human Carcinogenesis?

Spontaneous *in vitro* transformation of rodent cells resembles human carcinogenesis for some aspects. First, like most human cancers it occurs in the absence of any intentional or known treatment. Second, a major agent responsible for the spontaneous malignant transformation of MEFs is atmospheric oxygen [79]. Lowering the concentration of oxygen from 18% to ~ 1% markedly reduces the phenomenon [79]. Addition of catalase to the culture medium decreases the incidence of chromosomal aberrations and delays or prevents the onset of neoplastic transformation of mouse fibroblasts thus indicating that H_2O_2 and/or the derivative ·OH are factors involved [80]. The proliferative effect of superoxide radicals varies with the stage of neoplastic progression [81]. Some indications point to a role of oxygen in human cancer too. Roughly three decades ago it was observed in pioneering epidemiological studies that there is little contribution of industrialization and general pollution on the spontaneous rate of occurrence of cancer and that oxygen metabolism may play a role [82,83]. Many subsequent evidences have confirmed this notion and have pointed to endogenous damage as a factor in the aetiology of cancer, with particular reference to products of oxygen-metabolism (reviewed in [25,27,84,85]). A small, but probably steady production of carcinogenic radicals is a price to be paid to aerobic metabolism. Third, the spontaneous transformation of MEFs is accompanied by inactivation of tumor suppressor genes with frequencies and characteristics similar to those found in human tumors. For example, mutations in the tumor suppressor genes p53 and INK4a are common, albeit not sufficient, events in the spontaneous immortalization/transformation of normal fibroblasts [56-58,86,87] and those are precisely the two most frequently inactivated tumor suppressor genes in human cancer, irrespective of tumor type, site, and patient age [88,89]. Fourth, cultured murine fibroblasts steadily increase their proliferation capacity, reminding of tumor progression [90,91]. The process of spontaneous neoplastic progression *in vitro* has been described in detail by Kraemer *et al.* [60] and Cram *et al.* [92]. The process could be divided into four stages that correlated with a steady progression in karyotypic instability including aneuploidy and chromosomal aberrations of marker chromosomes, likewise

Table 1. Times of Spontaneous Transformation in CD-1 MEFs*

	MEF1	MEF2	MEF3	MEF4	X ± S.D.
Days elapsed at occurrence of crisis	14	14	19	16	16 ± 2
Days elapsed at 10^5 cells/cm^2 density	325	225	300	225	269 ± 45
Days elapsed at 25% anchorage-dep CFA	310	235	270	205	255 ± 39
Days elapsed at 0.5 % anchorage-indep CFA	340	255	345	220	290 ± 54

* From [42] with permission

what occurs in most malignancies. Further, most others indicators of *in vitro* progression, such as saturation density, criss-cross and piling up growth pattern, anchorage-independent growth [60], ability to undergo apoptosis [93], alterations in extracellular matrix components [94], amplification potential [95] correlated with tumorigenicity i.e. the better cells grow in the Petri dish, the better they also grow *in vivo* producing tumors in nude mice. Fifth, transformed MEFs and tumors (e.g. 3-methylcholantrene-induced mouse sarcomas) can share common antigens against which lymphoid cells mediate both primary and secondary immune reactions [96] and immunization with transformed MEFs may protect in some cases mice from subsequent challenge with live tumor cells [97]. There are also important specific features that differentiate spontaneous neoplastic transformation *in vitro* from human tumourigenesis. Most influences of tissue architecture, blood and lymphatic circulations, cell-cell interactions and a myriad of factors (e.g hormonal) present in the *in vivo* extracellular milieu are lost in the Petri dish. It is established that cell density influences the rate of spontaneous transformation namely cells transform faster if cultured at high density. An epigenetic origin for this phenomenon has been proposed as an adaptive response of cells to conditions of moderate growth constraint rather than selection among genetically altered cells [98,99] although this view has been challenged [100]. Senescence in cultured mouse cells is not linked to telomere shortening and telomerase activation is not required for transformation, unlike what occurs in human tumors [73,74]. Planning transfection experiments, a further drawback of MEFs is that these slowly-growing primary cells may have low transfection frequencies and the occurrence of crisis may hamper the recovery of a sufficient number of clones.

The above specificities of MEFs undoubtedly represent serious problems in extrapolation of results to the *in vivo* process of carcinogenesis when factors that prevent or correct the neoplastic phenotype are investigated. Yet, some biases (e.g. those linked to cell density) may be significantly attenuated with appropriate controls. Care should be taken of using MEFs from mouse outbred strains (e.g. CD-1) with no infection of tumor viruses (e.g. MuMTV) in order to minimize possible influences of inbreeding and virus particles [45]. Finally, reagent kits that allow efficient transfection of MEFs have been developed and are commercially available [87].

3. TUMOR SUPPRESSION BY BER *IN VIVO*: MOLECULAR EPIDEMIOLOGY STUDIES

Notwithstanding the conceptual framework that endogenous damage contributes to human degenerative pathologies [1,101-103], links between BER defects and human cancer have been elusive so far [16,104,105]. A recent accumulation of data indicating the protective role of BER from some tumoral forms is discussed here.

3.1. Major Cancers

3.1.1. Lung Cancer

Lung cancer is the paradigm of a tobacco-induced cancer. However, genetic susceptibility to such carcinogenesis is also an important determinant, because only 10-15% of cigarette smokers develop smoking-related lung cancer [106]. Some indications point to reduced repair capacity as a susceptibility factor to lung carcinogenesis [107]. Theoretically, even slight defects in repair of oxidation damage might have serious consequences in an organ exposed to elevated oxygen fluxes. Elevated levels of 8-oxoG have been found in urines, PBL and tumor tissues of lung cancer patients in comparison to matched control individuals [108-110]. The issue of the levels of DNA oxidation damage in human tissues is a highly controversial and contentious area, mainly for technical reasons [111,112]. However, animal studies indicate that in some cases accumulated oxidation damage may indeed reflect a reduced repair capacity [22,113]. Mutagen-sensitivity is often used as an indirect measurement of repair capacity as well [114]. In a number of case-control studies, bleomycin-induced chromatid breaks were significantly more common in the lymphocytes of lung cancer cases than in controls [115-118]. Bleomycin is a radiomimetic chemical whose damage is in part repaired *via* BER [119]. Similarly, DNA repair of damage induced by benzo(a)pyrene - a xenobiotic present in tobacco smoke whose damages are repaired *via* either NER or BER [120] - was significantly reduced in untreated patients with various histopathological types of lung cancer [117, 121].

Analyses of the sequence changes in the p53 tumour suppressor gene showed that in lung cancer there is a bias in favour of GC to TA transversions [122]. As mentioned above, this type of mutations would be expected in cells incapable of eliminating 8-oxoG from their DNA. Levels of 8-oxoG have been found elevated in cells from lung tumors [123]. Consistently, Asami et al. [124] have reported that 8-oxoG levels were higher in lymphocytes of smokers and that 8-oxoG repair activity was higher, presumably positively induced, in smokers than in complete non smokers. The smoking status may elevate in human cells the level of oxidative damage that, in turn, may contribute to tobacco-induced carcinogenesis. That defective BER of 8-oxoG may play a role in predisposition to lung cancer may be inferred by a number of studies reporting a positive association with variations in the hOGG1 gene (Table **2**). Substantial variations in the statistical power of this kind of studies can be observed in the literature, with the number of recruited patients ranging in one order of magnitude. This can be a seriously confounding factor especially in those pilot epidemiological investigations were recruitment is very limited [125]. However in the hOGG1 case, significantly increased frequencies of either chromosomal rearrangements or SNP or point mutations have been repeatedly and consistently reported thus indicating that variations in this gene probably predispose to lung cancer. Importantly, an association between low hOGG1 activity and risk of lung cancer has been described [126]. hOGG1 activity was lower in peripheral blood lymphocytes (PBL) from patients than in matched controls. The estimated relative risk of lung cancer for smokers with an hOGG1 activity of 6.0 and 4.0 U/μg protein (lower than the "normal" value 7.0 U/μg) were 34 and 124 fold, respectively. This steep "gene dosage" effect may reflect partial compensation of limited hOGG1 deficiencies by backup systems such as NER and amplification of the risk with more severe defects. It was proposed that low hOGG1 activity and smoke may have cumulative effects on the risk

Table 2. BER Variations in Lung Cancer Patients*

Gene Studied	Variation Studied	Positive Association[a]	Negative Association[b]	No Association[c]	Ref.
APE/ Ref-1	Point mutations			√	[136]
APE/ Ref-1	Catalytic activity			√	[137]
APE/ Ref-1	Asp148Glu SNP			√	[138]
APE/ Ref-1	Asp148Glu SNP			√	[131]
APE/ Ref-1	Asp148Glu SNP + Smoking	√			[131]
APE/ Ref-1	Asp148Glu SNP + XRCC1	√			[131]
APE/ Ref-1	Arg399Gln SNP + Smoking	√			[131]
DNAase IV/FEN-1	Point mutations			√	[135]
hMYH	Point mutations			√	[139]
hOGG1	Rearranged chromosomal region 3p25/26	√			[235]
hOGG1	Rearranged chromosomal region 3p25/26	√			[236]
hOGG1	Rearranged chromosomal region 3p25/26	√			[237]
hOGG1	LOH	√			[238]
hOGG1	LOH	√			[239]
hOGG1	LOH	√			[123]
hOGG1	LOH	√			[240]
hOGG1	Point mutations	√			[211]
hOGG1	Ser326Cys SNP	√			[239]
hOGG1	Ser326Cys SNP	√			[123]
hOGG1	Ser326Cys SNP	√			[241]
hOGG1	Ser326Cys SNP	√			[242]
hOGG1	Ser326Cys SNP	√			[136]
hOGG1	Ser326Cys SNP	√			[243]
hOGG1	G→T transition in 5' non-coding region	√			[244]
hOGG1	Catalytic activity	√			[126]
PARP pseudo gene	Deletions	√			[129]
Pol β	Gene deletions	√			[128]
XRCC1	Arg194Trp SNP	√			[134]
XRCC1	Arg194Trp SNP		√		[245]
XRCC1	Arg194Trp SNP + high antioxidants		√		[132]

(Table 2. Contd….)

Gene Studied	Variation Studied	Positive Association[a]	Negative Association[b]	No Association[c]	Ref.
XRCC1	Arg194Trp SNP + XPD codon 751 SNP	√			[133]
XRCC1	Arg194Trp SNP + XPD codon 751 SNP	√			[134]
XRCC1	Arg399Gln SNP	√			[246]
XRCC1	Arg399Gln SNP	√			[247]
XRCC1	Arg399Gln SNP		√		[248]
XRCC1	Arg399Gln SNP			√	[131]
XRCC1	Arg399Gln SNP			√	[245]
XRCC1	Arg399Gln SNP			√	[134]
XRCC1	Arg399Gln SNP+ smoking			√	[131]
Repair gene for εA εC	Catalytic activity	√			[130]

[a] Increased risk of pathology in the presence of the indicated variation.

[b] Decreased risk of pathology in the presence of the indicated variation.

[c] Unchanged risk of pathology in the presence of the indicated variation.

* From [16] with permission.

of lung cancer and that smoking cessation may significantly reduce this danger. Those conclusions have been yet subsequently questioned [40,127]. The evidence for involvement of variations in other BER genes is weaker. Positive associations have been reported in single studies for pol β mutations [truncated forms, possibly arising from splicing errors [128], a PARP pseudogene [129] and an activity involved in repair of 1,N(6)-ethenoadenine (εA) and 3,N(4)-ethenocytosine (εC) [130]. In the latter two cases, the repair defects were particularly associated to inflammation-derived lung adenocarcinomas. This may be linked to the elevated amounts of ROS released during the inflammation process.

Inconsistent results have been obtained in six different laboratories with respect to the role of XRCC1 Arg194Trp and Arg399Gln SNPs in lung cancer risk (Table **2**). It is difficult to reconcile those data although the effect of a repair polymorphism could depend on the level of population's exposure to genotoxicants. Gene-environment interactions have been described between smoking and the codon 399 polymorphism [131] and between antioxidants levels and the codon 194 polymorphism [132]. In two studies, the risk of lung cancer has beeen found to increase more than additive for individuals carrying the XRCC1 194Trp genotype and another high risk genotype at codon 751 in the NER gene Xeroderma Pigmentosum D (XPD) [133,134]. The combined polymorphisms in XRCC1 and XPD genes may confer an increased risk of lung cancer affecting different repair pathways.

No associations have been found for Flap endonuclease (DNAase IV/FEN-1 [135]), Ape/Ref-1 [136-138] and hMYH [139]. Gene-environment interactions with smoking have been found for the Ape/Ref-1 Asp148Glu polymorphism [131].

3.1.2. Gastric Cancer

Gastric cancer is the leading cause of cancer death in China and other countries in eastern Asia. It is a disease of complex aetiology involving dietary, infectious, environmental, occupational and genetic factors. Evidence has been provided for a human model of gastric carcinogenesis with the following sequential stages: chronic gastritis; atrophy; intestinal metaplasia; and dysplasia [140]. The initial stages of gastritis and atrophy have been linked to *Helicobacter pylori*-driven inflammation during which elevated amounts of ROS are released at the lesion sites [141]. The functionality of BER might be important at this stage to counteract ROS genotoxicity in gastric cells.

Six studies have investigated the variations of BER genes in gastric cancer patients (Table **3**). Genes studied included hOGG1, XRCC1, pol β and thymine-DNA glycosylase. In most instances, no associations with gastric cancer were found. A positive association was reported in one study [142], but only for gastric cardia cancer. The current evidence does not suggest that BER variations may underlie an overall increased risk of gastric cancer.

3.1.3. Intestinal Cancer

Different conclusions may be drawn for a subset of colorectal tumors (Table **4**). Elevated levels of oxidative damage have been reported in PBL and tumor tissues of colon cancer patients [143]. In 1992, Wang *et al.* [144], reported on polymerase β truncating mutations in a number of human colorectal cancers. The data were confirmed and extended in 1997 [145]. It was suggested that truncated pol β may act as a dominant negative mutant thus facilitating accumulation of mutations and expression of a mutator phenotype in tumor cells. Later on, mutations in the mismatch-specific DNA glycosylase MBD4 (MED1) have been found in human colorectal cancers with microsatellite instability [146]. MBD4 is a still poorly characterized glycosylase/lyase that binds to fully and hemimethylated DNA and interacts with other mismatch repair proteins such as MLH1. XRCC1 polymorphisms have not been found implicated in colorectal carcinogenesis [147].

Table 3. BER Variations in Gastric Cancer Patients*

Gene Studied	Variation Studied	Positive Association	Negative Association	No Association	Ref.
hOGG1	Gene mutation			√	[249]
hOGG1	Ser326Cys SNP			√	[249]
hOGG1	Ser326Cys SNP			√	[250]
Pol β	Gene mutation			√	[251]
Thymine-DNA glycosylase	LOH			√	[252]
XRCC1	Arg194Trp SNP	√ (gastric cardia)		√	[142]
XRCC1	Arg194Trp SNP	√ (gastric cardia)		√	[253]
XRCC1	Arg194Trp SNP	√ (gastric cardia)		√	[142]
XRCC1	Arg194Trp SNP	√ (gastric cardia)		√	[253]

* From [16] with permission.

In 2002, observations of mutational spectra in the polyps of siblings in a family with multiple adenomas and carcinomas [148] and in those from seven unrelated patients with polyposis [149] led to hypothesize defective BER of oxidative damage (reviewed in [150]).Those patients lacked inherited mutations of the adenomatous polyposis coli gene (APC) that is associated with familial adenomatous polyposis thus indicating failure of other tumor-suppressors. The mutations identified in the adenomas were G:C-T:A transversions, that are induced as a consequence of formation of a number of

Table 4. BER Variations in Intestinal Cancer Patients*

Gene Studied	Variation Studied	Positive Association	Negative Association	No Association	Ref.
hMYH	Gene mutation	√			[148]
hMYH	Gene mutation	√			[149]
hMYH	Gene mutation	√			[151]
hMYH	Gene mutation	√			[152]
hMTH	Gene mutation			√	[148]
hMTH	Gene mutation			√	[151]
hMTH	Gene mutation			√	[152]
hOGG1	Gene mutation			√	[148]
hOGG1	Gene mutation			√	[151]
hOGG1	Gene mutation			√	[152]
MBD4 (MED1)	Gene mutation	√			[146]
Pol β	Gene mutation	√			[144]
Pol β	Gene mutation	√			[145]
XRCC1	Arg194Trp SNP			√	[147]
XRCC1	Arg399Gln SNP			√	[147]

* From [16] with permission.

oxidized lesions including 8-oxoG. Analysis of mutations in the hOGG1, hMYH and hMTH genes showed a significantly increased mutation frequency of hMYH in multiple colorectal adenomas and carcinomas. Compound heterozygotes in which both missense mutations compromise function or homozygotes for truncating or missense mutations were identified [148,149]. This is an example of how the presence of a certain type of mutation (in this case an excess of somatic G:C-T:A transversions) may hint at the possible involvement of a specific lesion (in this case 8-oxoG) albeit in no way constitutes a signature of it. In a following study, Sieber *et al.* [151] screened for germ-line hMYH mutations in 152 patients with multiple (3 to 100) colorectal adenomas and 107 APC mutation-negative pro-bands with classic familial adenomatous polyposis (> 100 adenomas). Changes in the related genes hMTH1 and hOGG1 were also analysed and adenomas were tested for somatic APC mutations. Six patients (3.9 %) with multiple adenomas and eight patients (7.5 %) with polyposis had biallelic germline hMYH variants. In another study [152], among 614 british families with polyposis, 25 (4%) had biallelic mutations of the hMYH gene. The incidence of this BER-defective syndrome is thus around 5% of polyposis patients. This compares to an estimated 5-7% colorectal cancers caused by mismatch repair (MMR) deficiencies [153]. Both missense and nonsense mutations have been found and the mutation spectra were very similar in the two groups of patients. In the tumors of carriers of biallelic mutations, all somatic APC mutations were GC-TA transversions. No pathogenetic mutations in the hMTH1 or hOGG1 genes have been identified. It is concluded that germ-line hMYH mutations predispose to a recessive phenotype, multiple adenomas or polyposis coli. For patients with multiple colorectal adenomas in which no germ-line APC mutation has been identified and the family history is compatible with recessive inheritance, genetic testing of hMYH should be carried out for diagnosis and calculation of the level of risk in relatives. Two mutational hot spots were identified in the hMYH gene [148,149,151]. Of the 36 germ-line mutations identified in hMYH alleles of white European patients, 31 (86%) were represented by the amino acid substitutions Tyr165Cys and Gly382Asp. 14 of 18 patients with these substitutions (78%) were either homozygous (Tyr165Cys-Tyr165Cys or Gly382Asp-Gly382Asp) or compound heterozygous (Tyr165Cys-Gly382Asp) [34]. The Tyr165Cys and Gly382Asp mutations affect amino acid residues that are evolutionarily conserved and substantially reduce the enzymatic activity of the bacterial protein [148]. The other missense mutations either affect conserved amino acid residues or lie close to conserved regions encoding structural motifs of hMYH.

3.1.4. Breast and Ovary Cancer

32 % of female tumours develop in breast and during her first 39 years of life, one in 228 women faces this disease [154]. What causes this elevated and early incidence is unknown. More than 75% of women with newly diagnosed breast cancer have no identifiable risk factors [155]. Elevated levels of oxidative damage (in particular 8-oxoG) have been found in breast cancer tissues [156-158] although some earlier determinations might have suffered of technical problems [156] and negative results have also been reported [159]. During the last decade, several studies have indicated reduced DNA repair capacity as a predisposing factor in breast cancer, in particular familiar forms caused by mutations in the BRCA1 and BRCA2 genes [160-162]. The role of the latter gene products in DNA repair has been repeatedly indicated [163-167] and some reports initially suggested a possible requirement for them in BER (Table **5**). Briefly, i) the BRCA gene products were found to be required for transcription-coupled BER of oxidized bases [168,169]; ii) BRCA2-null cells exhibit a severe defect in ligation of BER patches [170]; iii) the BRCA2 gene product is important for resistance to methylmethane sulfonate [171] a chemical inducing damages mainly processed *via* BER; iv) the C-terminus sequence of the BRCA1 protein contains a domain (so-called BRCT module) that is common to several DNA BER proteins such as XRCC1 and DNA ligase III [172,173]. However, the report by Gowen *et al.* [168] was subsequently retracted [174] and subsequent studies have in fact implicated BRCA proteins in homology-directed DNA repair rather than BER [175-178]. BRCA proteins would mediate homologous recombination in close connection with Fanconi anemia (FANC) proteins (BRCA2 itself is identical to FANCD1 and perhaps FANCB) [179]. It remains to reconcile this model with the severe defect observed in BRCA2 null cells in ligation of BER patches [170], a process that does not require recombination.

Ten studies have investigated BER defects/polymorphisms in sporadic forms of breast cancer (Table **5**). Positive associations have been found in two of them for pol β gene mutations [180] and the XRCC1 Arg399Gln and Arg194Trp SNPs [181,182]. Further, the protein expression pattern of APE/Ref-1 was found altered in two studies [183,184]. A protective effect has been reported for the Arg194 Trp SNP [185]. The remaining studies performed on the same or different variations indicate no association [181,182,186-188]. It is paradigmatic of the difficulties encountered in these investigations, that three different results were obtained in three different laboratories, concerning the predisposing role of the XRCC1 Arg194Trp SNP to breast cancer [181,182, 185]. Those discrepancies might in part be explained by a gene-environment interaction with folate levels [189].

In conclusion, defects in homology-directed recombinational repair and the ligation step of BER are present in familial forms of breast and ovary cancer originated by alterations in the BRCA/FANC pathway. This witnesses the central role of BRCA/FANC gene products in the repair machinery of human cells, including BER. On the contrary, the current evidence for BER defects in sporadic breast cancer is limited.

3.1.5. Prostate Cancer

The preventive efficacy of antioxidant compounds and the frequent inactivation of cellular components of the antioxidant defence system in prostate cancer suggest that oxidative damage may be particularly important for development of this neoplasm [190]. Four studies investigate variations of BER genes in prostate cancer (Table **6**). Three of them indicate a positive association. The genotype frequency of two sequence variants of the hOGG1 gene (the Ser326Cys variant and a 11657A/G variant) was significantly different be-

Table 5. BER Variations in Breast/Ovary Cancer Patients*

Gene Studied	Variation Studied	Positive Association	Negative Association	No Association	Ref.
BRCA1/BRCA2	Reduced transcription-coupling and ligation in mutant cells	√			[169]
BRCA1/BRCA2	Reduced transcription-coupling and ligation in mutant cells	√			[170]
APE/Ref-1	Catalytic activity			√	[186]
APE/Ref-1	Gene mutation			√	[187]
APE/Ref-1	Protein expression pattern	√			[183]
APE/Ref-1	Protein expression pattern	√			[184]
hOGG1	Gene mutation			√	[187]
Pol β	Gene mutation	√			[128]
XRCC1	Arg399Gln SNP	√			[181]
XRCC1	Arg399Gln SNP			√	[182]
XRCC1	Arg399Gln SNP			√	[188]
XRCC1	Arg194Trp SNP			√	[181]
XRCC1	Arg194Trp SNP	√			[182]
XRCC1	Arg194Trp SNP		√		[185]
XRCC1	Arg194Trp SNP + high folate		√		[189]

* From [16] with permission.

tween cases of prostate cancer and controls [191]. This was observed in both a population study on sporadic prostate cancer and in a family-based study on hereditary prostate cancer families [191]. A positive association was also found for the XRCC1 Arg399Gln SNP when associated with an XPD SNP [192]. In contrast, a somewhat lower prostate cancer risk of men with one or two copies of the variant alleles at the XRCC1 codons 194 and 399 in comparison to those homozygous for the common allele was reported by van Gills *et al.* [193]. Prostate cancer risk was highest among men who were homozygous for the common allele at codon 399 and had low dietary intake of vitamin E.

Marked increase in Ape/ref-1 nuclear staining was observed in prostatic intraepithelial neoplasia and in prostatic cancer as compared with benign hypertrophy [194].

Table 6. BER Variations in Prostate Cancer Patients*

Gene Studied	Variation Studied	Positive Association	Negative Association	No Association	Ref.
Ape/ Ref-1	Increased protein expression	√			[194]
hOGG1	Ser326Cys SNP	√			[191]
hOGG1	11657 A/G SNP	√			[191]
XRCC1	Arg399Gln SNP		√		[193]
XRCC1	Arg194Trp SNP		√		[193]
XRCC1	Arg399Gln + XPD Asp312Asn SNP	√			[192]

* From [16] with permission.

3.1.6. Haematopoietic System Malignancies

Data on endogenous damage levels and BER capacity in haematopoietic system disorders are sparse. A number of oxidized lesions were found at increased levels in PBL of acute lymphoblastic leukemia (ALL) patients as compared to matched controls [195] while in other studies, no variations in urinary levels of oxidized bases have been found in patients with different hematological disorders including lymphomas and acute leukemia [110].

An extensive oligonucleotide chip analysis performed by Alcalay and coworkers [196] indicated that functionally homogenous groups of genes were coherently regulated by leukemogenic fusion proteins deriving from chromosomal translocations and that, in particular, a number of BER genes were repressed. The oncogenic potential of leukemogenic aberrant transcription factors may thus be exerted in part through deregulated BER.

An association of polymorphisms in the XRCC1 gene with therapy-related acute myeloid leukemia (AML) was reported by Seedhouse *et al.* [197]. The distribution of the XRCC1 Arg399Gln genotype was significantly different when comparing the therapy-related AML and control groups. The data provided evidence of a protective effect against AML in individuals with at least one copy of the variant XRCC1 399Gln allele compared with those homozygous for the common allele. No association between this polymorphism and risk of malignant lymphoma was found by Matsuo *et al.* [198].

BER is inhibited in human cells infected with the human T-cell leukemia/bovine leukemia group retroviruses which cause hematopoietic cancers. Inhibition of BER is linked to expression of the TAX gene. In these cells, damage induced by oxidizing agents is repaired with decreased efficiency, while repair induced by deoxyribonuclease I or psoralen is normal [199].

3.2. Other Cancers

3.2.1. Head and Neck Cancer

The association between squamous cell carcinoma of the head and neck and the Arg194Trp and Arg399Gln XRCC1 polymorphisms has been investigated in two studies (Table **7**). In the first one, Sturgis *et al.* [200] had reported that lack of the Arg194Trp aminoacid substitution was a significant risk factor specifically for cancers of the oral cavity and pharynx. Increased risk was also caused by homozygosity of the XRCC1 allele that causes the Arg399Gln substitution. Synergistic effects of the two polymorphisms were observed. Analysis of the same two polymorphisms in a second study from a different laboratory gave opposite results: a weak elevation in risk was associated with the Arg194Trp polymorphism and a decreased risk with the Arg399Gln polymorphism, especially when the latter was in homozygosity [201]. Positive associations have been found between the hOGG1 Ser326Cys polymorphism and risk of orolaryngeal cancer in smokers and alcohol drinkers [202].

3.2.2. Bladder Cancer

Some evidence of a protective effect from bladder cancer for subjects that carry at least one copy of the Arg194Trp variant allele of the XRCC1 gene, relative to those homozygous for the common allele, has been observed by Stern *et al.* [203] (Table **7**). For the codon 399 polymorphism (Arg399Gln), the data suggested a protective effect of the homozygous variant genotype, relative to carrier of one or two copies of the common allele. Those data were not confirmed by Matullo *et al.* [204] that in a case control study of 124 bladder cancer patients and matched hospital controls found no variations in risk associated to the XRCC1 polymorphism Arg399Gln.

DNA pol β gene mutations have been observed in 4 out of 24 cases of human bladder cancer by Matsuzaki and coworkers [205]. In three cases, pol β mutations were accompanied by mutations or loss of heterozigosity in other tumor suppressors (p16, RB, p53 or APC). No evidence of somatic mutations or deletions was observed in bladder cancer patients by Thompson *et al.* [206]. These authors observed however an elevated frequency of splice variants leading most frequently to loss of exon 2.

3.2.3. Esophageal Cancer

The XRCC1 polymorphisms at codons 194, 280 and 399 (Arg194Trp, Arg280His and Arg399Gln) were investigated for association with esophageal cancer [207] (Table **7**). The distribution of the three genotypes was not significantly different among patients with esophageal cancer and controls but, among alcohol drinkers, the Arg399 homozygous genotype was more frequently found in patients.

The Ser326Cys polymorphism in the hOGG1 gene has been found associated to esophagus cancer [208]. Homozygosity for the Cys/Cys genotype significantly increased the risk of developing esophageal squamous cell carcinoma. Although smoking alone also significantly increased the risk, no interactions between smoking and polymorphism were found.

3.2.4. Pancreatic Cancer

The polymorphism Arg399Gln of the XRCC1 protein was analyzed in 309 cases of pancreatic adenocarcinoma and 964 controls in the San Francisco Bay area. This allele was found to be a potentially important determinant of susceptibility to smoking-induced pancreatic cancer [209] (Table **7**). This association was stronger among women than men.

3.2.5. Kidney Cancer

Abnormal levels of 8-oxoG have been found in renal cell carcinomas *vs*. non cancerous tissue [210]. Chevillard *et al.* [211] have used denaturing gradient gel electrophoresis (DGGE) to screen 15 kidney tumours for alterations in the hOGG1 cDNA (Table **7**). The study revealed a base substitution mutation in one of those tumors. The surrounding normal tissue was wild type. An extension of this analysis to 99 renal tumours detected somatic missense mutations of the hOGG1 gene in 4 of the 99 tumor samples [212]. One of those mutations was later found to affect the mitochondrial localization of hOGG1 [213]. This mutation disrupts a putative mitochondrial targeting sequence of hOGG1 but does not affect the enzymatic activity of the enzyme. Loss of mitochondrial repair capacity may thus occur by enzyme relocalization during development of kidney cancer.

Table 7. BER Variations in Other Cancers*

Gene Studied	Variation Studied	Positive Association	Negative Association	No Association	References
Head and Neck					
hOGG1	Ser326Cys SNP	√			[202]
XRCC1	Arg194Trp SNP		√		[200]
XRCC1	Arg194Trp SNP	√			[201]
XRCC1	Arg399Gln SNP	√			[200]
XRCC1	Arg399Gln SNP		√		[201]
Bladder					
Pol β	Gene mutation	√			[205]
Pol β	Gene mutation			√	[206]
XRCC1	Arg194Trp SNP		√		[203]
XRCC1	Arg399Gln SNP		√		[203]
XRCC1	Arg399Gln SNP			√	[204]
Esophagus					
hOGG1	Ser326Cys SNP	√			[208]
XRCC1	Arg194Trp SNP			√	[207]
XRCC1	Arg399Gln SNP			√	[207]
XRCC1	Arg399Gln SNP + alcohol	√			[207]
	Arg280His SNP			√	[207]
Pancreas					
XRCC1	Arg399Gln SNP	√			[209]
Kidney					
hOGG1	Gene mutation	√			[211]
hOGG1	Gene mutation	√			[213]
Cervix					
Ape/ Ref-1	Protein expression			√	[215]
Skin					
XRCC1	Arg399Gln SNP		√		[216]

* From [16] with permission.

3.2.6. Cervical Cancer

Oxidative damage levels are high in cervical dysplasia, compared to normal tissues [214]. After analysis of 88 samples of cervical cancer, no correlation was found between Ape/ref-1 expression and survival or between Ape/ref-1 and hypoxia-inducible factor (HIF)-1alpha [215] (Table **7**).

3.2.7. Skin Cancer

The XRCC1 homozygous variant 399Gln genotype has been related to a significantly reduced risk of both basal cell and squamous cell carcinoma by Nelson and coworkers [216] (Table **7**). These authors further noticed a statistically significant multiplicative interaction of this XRCC1 polymorphism and lifetime number of sunburns in squamous cell carcinomas. Thus, the etiology of sunburn-related squamous cell carcinomas may be significantly different by XRCC1 genotype.

4. PATHOLOGIES IN BER KNOCKOUTS

Mouse knockout strains have been developed for a number of BER activities (reviewed in [3,217]. As aforemen-

tioned, the phenotypic consequences are very different, according to the step of the BER pathway involved. Arrest of embryonic development occurs after knockout of central proteins of BER, such as the major AP endonuclease APE/HAP1 [11], the pol β [17,218] and the XRCC1 protein [18]. This may be linked to deletion of important associated functions other than repair (e.g. APE/Ref-1 is endowed with an important redox function maintaining transcription factors in an active reduced state [219]). On the contrary, knock-out mice deficient in a number of DNA-N-glycosylases (APNG [19,20,220]; OGG1 [22]; UDG [23]; NTH1 [24]; NTH1+ OGG1 [221]), PARP [21] and MBD4//MED1 [222] do not show severe abnormalities associated with accumulation of DNA damage and mutation. In some instances, mismatch repair defects may be associated [222]. Extracts from these mice are able to support removal of substrate lesions from DNA at reduced efficiency (20-30% as compared to normal extracts) [24,223,224] and accumulation of significant amounts of DNA damage can be observed. For instance, the amount of 8-oxoG in kidney DNA from OGG1 -/- mice treated with $KBrO_3$ is approximately 70 times that of +/+ mice [224] and UNG -/- cells accumulate approximately 2000 U residues per cell [223]. Despite this, the knockout mice show only small increases in mutation frequencies and no overt cancer-proneness. This paradox could be explained at least in part by the observations that some endogenous lesions such as 8-oxoG can be removed specifically from transcribed lesions in hOGG1$^-$ cells [169] and that redundant repair pathways keep within certain limits the oxidative damages in the presence of a single gene knockout [113]. The existence of important mutation-avoidance mechanisms other than DNA repair can also be hypothesized.

5. RESPONSE TO CANCER CHEMOTHERAPY

BER may be a useful pharmacological target through which tumor cells can be sensitized to alkylating therapeutic agents. Most cancer chemotherapy consists of oxidizing and alkylating agents, whose damages are in part repaired *via* BER. Inhibition and/or imbalancing of BER may sensitize cells to chemotherapeutic regimens [225].

A significant enhancement of the antitumor effect of temozolomide was observed in human colon cancer xenografts by methoxyamine, a drug which binds abasic sites thus acting as an inhibitor of BER [226]. The main effect of methoxyamine is a significant increase of temozolomide-induced single strand breaks resulting from persistence of methoxyamine-reacted AP sites that are not further processed [227]. In MMR-deficient cells methoxyamine further potentiates temozolomide cytotoxicity by formation of large double-strand DNA fragmentation and subsequent apoptotic signalling [227]. Methoxyamine enhances the antitumor activity of BCNU as well [228].

The PARP inhibitors PD128763, 3-aminobenzimide and 6-aminonicotinamide increase the sensitivity of cancer cells to temozolomide [229,231]. The enhancing effect was probably caused by inhibition of the repair of N-methylpurines produced by temozolomide. The enhancing effect of PARP inhibitors was particularly evident in glioma cells characterized by defective expression of MMR since these cells are tolerant to O^6methylguanine damage and show low sensitivity to temozolomide. Association of temozolomide and PARP inhibitors was also found of benefit in treatment of leukaemia resistant to triazene compounds. Median effect plots analysis indicated a high degree of synergy between temozolomide and methoxyamine or PD128763 [229]. In this study the BER inhibitors had little effect on the therapeutic index of the crosslinking agent BCNU. PARP inhibitors together with methoxyamine can thus increase specifically the sensitivity of cancer cells to therapeutic alkylating agents whose damages are mainly removed *via* BER.

Overexpression of APNG in nuclei of breast cancer cells causes an increase in DNA damage and increased cytotoxicity of MMS, as well as increased apoptosis levels [232]. APNG expression was further targeted to mitochondria using the human manganese superoxide dismutase mitochondrial targeting sequence. This led to dramatic increases of the sensitivity of cells to MMS. APNG overexpression may thus sensitize cancer cells to therapeutic alkylating agents by imbalancing the BER pathway in nuclei and, with much greater effects, in mitochondria [232].

U DNA glycosylase (UDG) and dUTPase have profound effects on the efficacy of agents that target thymidilate biosynthesis. UDG removes any U residues that may arise in DNA while dUTPase is an enzyme that plays a pivotal role in regulating cellular dUTP pools. Under normal conditions, U is precluded in DNA by the combined action of UDG and dUTPase. However, during thymidilate synthase inhibition (e.g. during methotrexate treatment), dUTP pools may accumulate, resulting in repeated cycles of U misincorporation and detrimental repair, leading to strand breaks and cell death [233]. UDG overexpression may thus sensitize cancer cells to treatments that target *de novo* thymidilate metabolism.

Ape/Ref-1 is expressed at high levels in some germ cells tumors, as demonstrated by immunohistochemistry. It has been suggested that elevated expression of Ape/Ref-1 may result in resistance to certain chemotherapeutic agents, such as bleomycin and, to a lower extent, gamma radiation [119].

6. CONCLUDING REMARKS

Despite use of different investigational approaches, the link between BER defects and human carcinogenesis remains elusive. Marked defects in the pathway could be simply not compatible with life so that only limited BER deficiencies, usually difficult to determine, may underlie some forms of tumour susceptibility. The functional redundancy between proteins of BER and of other repair pathways is consistent with this essential role. For instance, most oxidized purines and pyrimidines can be repaired by more than one glycosylase [234]. Notwithstanding the above, some links start to emerge. In lung cancer a number of variations in BER genes are found with polymorphic frequencies, and mutations and LOH of genes involved in repair of oxidation damage often occur. Functional defects have been further reported, although their significance still is an open question. Evidence of defects in BER of oxidative damage have been also disclosed in some forms of intestinal cancer where oxidation-induced mutations accumulate detectably. Finally, BER contributes significantly to resistance to a number of

chemotherapeutic agents and its modulation has been proven to significantly sensitize cancer cells to antitumor drugs. Thus, BER may represent in some cases a therapeutic target.

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ABBREVIATIONS

A	=	Adenine
ALL	=	Acute lymphoblastic leukemia
AML	=	Acute myeloid leukemia
ANPG	=	3-alkyl-N-purine glycosylase
AP	=	Abasic
APC	=	Adenomatous polyposis coli
BER	=	DNA base excision repair
BRCT	=	BReast cancer proteins C Terminus
C	=	Cytosine
DGGE	=	Denaturing gradient gel electrophoresis
DNAase IV/FEN-1	=	Flap endonuclease-1
εA	=	1,N(6)-ethenoadenine
εC	=	3,N(4)-ethenocytosine
FANC	=	Fanconi anemia
Fapy Ade	=	4,6-diamino-5-formamidopyrimidine
FPG	=	Formamidopyrimidine DNA glycosylase
HIF	=	Hypoxia-inducible factor
MEF	=	Mouse embryonic fibroblasts
MMR	=	Mismatch repair
NER	=	Nucleotide excision repair
NTH	=	Endonuclease III
OGG1	=	8–oxoG DNA glycosylase
8-oxoG	=	8-oxo-7,8-dihydroguanine
PARP	=	Poly (ADP) ribose polymerase
PBL	=	Peripheral blood lymphocytes
pol	=	Polymerase
U	=	Uracil
UNG	=	U DNA glycosylase
XP	=	Xeroderma Pigmentosum

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