Chapter 19

DNA Base Excision Repair: Evolving Biomarkers for Personalized Therapies in Cancer

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Additional information is available at the end of the chapter

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1. Introduction

DNA repair is critical for maintaining genomic integrity. The DNA damage such as those induced by endogenous processes (methylation, hydroxylation, oxidation by free radicals) or by exogenous agents such as ionizing radiation, environmental toxins, and chemotherapy is processed through the DNA repair machinery in cells. At least six distinct DNA repair pathways have been described. A detailed discussion of individual pathways is beyond the scope of this chapter as several recent excellent reviews on DNA repair are available [1-6]. Briefly, direct repair is involved in the repair of alkylated bases (such as O^6 methyl guanine) by MGMT (O^6 methyl guanine DNA methyl transferases [7-10]. DNA mismatch repair (MMR) corrects base-base mismatches and insertion-deletion loops (IDLs) erroneously generated during DNA replication and by exogenous DNA damage [11-13]. Bulky DNA adducts are processed through the nucleotide excision repair pathway (NER) [14-16]. DNA double strand breaks are repaired through the homologous recombination pathway (predominantly during S-phase of cell cycle) [17-19] or the non-homologous end joining pathway (NHEJ), that operates outside the S-phase of the cell cycle [20-22]. DNA base damage is processed by the base excision repair (BER) machinery. In the current chapter we focus on BER. Evolving preclinical and clinical data suggests that BER factors are likely to be important prognostic, predictive and therapeutic targets in cancer.

2. Base excision repair pathway (BER)

Exogenous as well as endogenously derived reactive metabolites cause DNA damage such as base oxidation, deamination and alkylation. If the damaged bases are left unrepaired, then dur-

ing replication or transcription misincorporation of erroneous complementary bases usher mutagenesis. For example, reactive oxygen species (ROS) generated during cellular respiration, phagocytosis, inflammation and in tumour hypoxia milieu can lead to base oxidation and generation of oxidised bases such as 8-hydroxyguanine (8-oxoG) [23]. DNA polymerase inserts adenine opposite to 8-oxoG, resulting in GC to AT transversion mutations after replication. Similarly, pyrimidine oxidation leads to the formation of 5-hydroxycytosine (5-OHC) which leads to the insertion of a thymine creating a potential mutagenic lesion [24]. Purine deamination products such as hypoxanthine and xanthine generated from adenine and guanine respectively are highly mutagenic. Hypoxanthine in DNA can cause AT to GC mutations, whereas xanthine generate GC to AT mutations [25]. Deamination of cytosine generates uracil which can occur in DNA at a frequency of upto 100–500 per cell per day. Uracil misincorporation can induce CG to TA transition mutations [26]. Although endogenous *S*-adenosyl methionine (SAM) participates in targeted enzymatic DNA base methylation, non-enzymatic methylation of ring nitrogen of purine base adenine can be cytotoxic[26]. Exogeneous agents that cause base alkylation are common chemotherapeutic agents and include mono functional alkylating agents [27] (e.g. temozolomide, nitrosurea compounds, alkylsulfonates) and bifunctional alkylating agents (e.g. cisplatin, mitomycin C, nitrogen mustards). DNA bases damaged by oxidation, deamination and alkylation produce a non-helix distorting, non-bulky base lesion. Such lesions are the prime repair target of BER [6, 28-30].

BER is a complex process and utilizes a number of enzymes and accessory scaffold proteins (Figure 1). DNA glycosylases, AP endonuclease (APE-1) also called REF-1(Redox Effector Factor-1), DNA Polymerases, flap endonuclease (FEN-1), poly (ADP-ribose) polymerase 1(PARP-1) and DNA ligases are the key enzymes involved in BER. The core enzymes depend on accessory proteins such as X-ray cross complementation group 1 protein (XRCC1), proliferating cell nuclear antigen (PCNA), and protein 9-1-1 for coordinated action. DNA glycosylases initiate BER by excising the damaged base from DNA and generating an abasic site. APE1 hydrolyzes the phosphate bond 5′ to the AP site leaving a 3′-OH group and a 5′-dRP flanking the nucleotide gap. Polymerase β (pol β) excises the 5′-dRP moiety generating a 5′-P. Members of the poly (ADP-ribose) polymerase (PARP) family of proteins get activated by single strand DNA breaks induced by APE1 and catalyze the addition of poly (ADP-ribose) polymers to target proteins, affecting protein-protein interactions. PARP may also be involved in the coordination of BER. At this point, BER can proceed through the short-patch (SP-BER) where pol β introduces a single nucleotide with the help of XRCC1. Ligase-IIIα subsequently seals the DNA nick establishing the phosphodiester DNA backbone. The long patch (LP-BER) processes those lesions that cannot be handled by the short patch such as oxidised AP sites. PCNA mediated Polymerase δ/ε introduces two to eight nucleotides past the abasic site. The resulting overhang DNA is excised by FEN1 endonuclease and the nick is then sealed by DNA ligase I.[28-32]

2.1. BER factors are promising biomarkers in cancer

Prognostic factors are defined as patient and/or cancer characteristics that help to estimate patient survival independent of treatment. Conventionally these include patient age, fitness to withstand treatment toxicity (usually measured as performance status), tumour stage,

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histological grade, neuro-lymphovascular invasion by cancer cells, presence or absence of certain signal protein expression (for example Her-2 in breast cancer is a poor prognostic marker). Predictive factors are those factors that help estimate the probability of a patient responding to a specific treatment. For example BRAF V 600 gene mutation in patients with metastatic melanoma predicts the response to treatment with Vemurafenib [33].

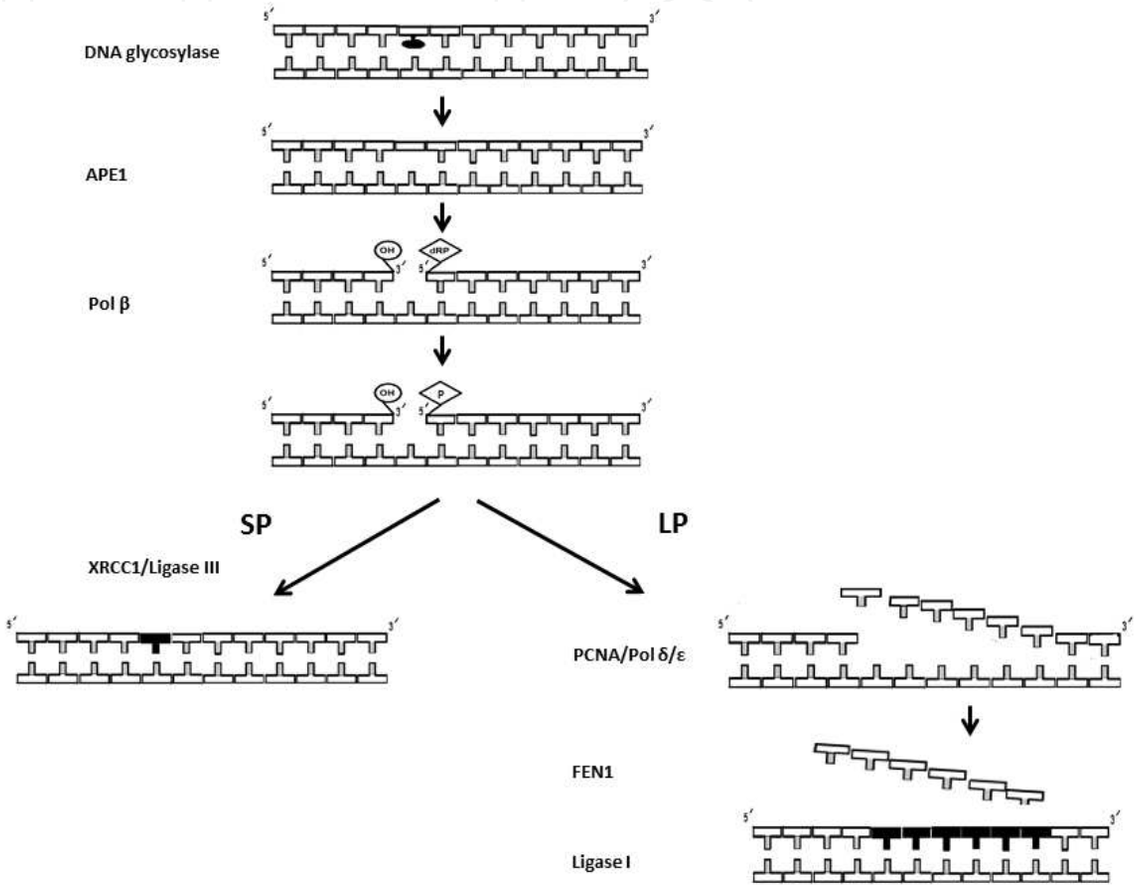

Figure 1. DNA glycosylase initiates BER by excising the damaged base from DNA and generating an abasic site. APE 1 nicks the phosphodiester bond and hydrolyzes the phosphate bond 5′ to the AP site leaving a 3′-OH group and a 5′-dRP flanking the nucleotide gap. Pol β excises the 5′-dRP moiety generating a 5′-P. The short-patch (SP-BER) where pol β introduces a single nucleotide with the help of XRCC1. Ligase-IIIα subsequently seals the DNA nick establishing the phosphodiester DNA backbone. The long patch (LP-BER) processes those lesions that cannot be handled by the short patch such as oxidised AP sites. PCNA mediated Polymerase δ/ε introduces two to eight nucleotides past the abasic site. The resulting overhang DNA is excised by FEN1 endonuclease and the nick is then sealed by DNA ligase I.

Chemotherapeutic agents and ionizing radiation achieve cellular cytotoxicity by inducing DNA base damages [34]. However proficient BER in cancer cells results in therapeutic resistance and adversely impact patient outcomes. BER factors, therefore, are emerging as important prognostic factors as well as predictors of response to cytotoxic therapy in patients. For example, Temozolomide is an effective treatment for patients with high grade brain tumours. It induces *O*6-meG, N3-meA and N7-meG base alkylation lesions which are processed by BER. [35]. Similarly, Melphalan which is used in the treatment of multiple myeloma induces N3-meA lesions that is processed through BER [36]. Thiotepa is used with or without total body irradiation

as a conditioning treatment prior to allogeneic or autologous haematopoietic progenitor cell transplantation in haematological diseases in adult and paediatric patients. Thiotepa produces formamidopyrimidine, 7-Methyl-formamidopyrimidine base lesions [37] which is repaired by BER. Dacarbazine is used in the treatment of patients with advanced malignant melanoma and Procarbazine is used in the treatment of Hodgkin's disease. They both produce *O*6-meG, N7-meG alkylation lesions which are targets of BER [38]. Streptozotocin generates *O*6-meG, N3-meA, N7-meG metabolites and is used in the treatment of neuroendocrine tumours of the gastro-intestinal (GI) tract.[39]. Platinating agents usually cause DNA inter-strand lesions which are repaired via NER, MMR and HR pathways (see table 1). Cisplatin is used in the treatment of advanced and metastatic non-small cell lung cancer (NSCLC), small cell carcinoma (SCLC), head and neck squamous cell carcinoma (HNSCC), germ cell tumour (GCT), gastric, pancreatic, bladder and cervical cancer. In addition to the DNA inter-strand lesions it also generates reactive oxygen species (ROS) that results in oxidative base damages. ROS derived base damages are also seen in patients with colorectal cancer (CRC) treated with Oxaliplatin. ROS induced base damages are also seen with anthracyclines (epirubicin and doxorubicin), used in the treatment of breast, gastric, ovarian, sarcoma and in haematological malignancy. The antimetabolite gemcitabine used in the treatment of NSCLC, pancreatico-biliary, bladder, breast and ovarian cancer also causes DNA base damage. Given the essential role of BER in cytotoxic therapy induced base damage, it is perhaps not surprising to note that several components of BER are promising prognostic and predictive factors. The following section will review individual markers and their relevance to cancer therapy.

2.2 APE1

Human apurinic / apyrimidinic endonuclease 1 (APE1) is a major endonuclease accounting for > 95% of the cellular AP endonuclease activity in most of the human cell lines [40]. It is also involved in redox regulation of transcription factors [41-43]. APE1 may be expressed in the cytoplasm and/ or in the nucleus of cancer cells. Although the precise sub-cellular localization and regulation is not clearly known, altered localization may have prognostic or predictive significance in patients. Table 2 summarizes the current knowledge regarding the association between APE1 and its role as a biomarker. We recently demonstrated that APE1 is over expressed in Ovarian, Gastro-oesophageal and pancreatico-biliary cancers [44]. In ovarian cancers, nuclear APE1 expression was seen in 71.9% of tumours and correlated with tumour type (P 0.006), optimal debulking (P 0.009), and overall survival (P 0.05). In gastro-oesophageal cancers previously exposed to neoadjuvant chemotherapy, 34.8% of tumours were positive in the nucleus and this correlated with shorter overall survival (P 0.005), whereas cytoplasmic localisation correlated with tumour de-differentiation (P 0.034). In pancreatico-biliary cancer, nuclear staining was seen in 44% of tumours. Absence of cytoplasmic staining was associated with perineural invasion (P 0.007), vascular invasion (P 0.05), and poorly differentiated tumours (P 0.068). [45]. In another study, a cohort of ninety one NSCLC patients treated with radical resection, tumour samples were analyzed for expression of APE1 protein. In patients with adenocarcinoma, cytoplasmic expression of APE1 was significantly associated with poor survival rate in univariate (P 0.01) and multivariate (P 0.07) analyses. In addition, a cytoplasmic

expression was also predictive of worse prognosis (log-rank test, P 0.02) in NSCLC patients with lymph node involvement, regardless of the histology [46]. In another study, high nuclear and cytoplasmic APE1 expression was demonstrated in prostate cancer biopsy samples [47].

	DNA damaging agents	DNA Lesions	DNA repair pathways [104, 105]
1	Mono-functional alkylators: temozolomide, nitrosurea, alkylsulfonates	Small alkyl base adducts	Direct reversal
		Non-bulky alkyl adducts, base oxidation, deamination, AP sites	BER
		Bulky alkyl adducts, helix distorting lesions	NER
		Mismatched base pairs, insertion deletion loops	MMR
		DS DNA break	HR
2	Bi-functional alkylators: cisplatin, mitomycin C, nitrogen mustards, psoralen	DNA cross-links	NER
		DS DNA break	HR
		Bulky adducts	NER, MMR
		Replication fork arrest	BER
3	Anti-metabolites: 5-Fluorouracil (5FU) Thiopurines Folate analogues	Base damages, replication fork arrest	BER
4	Topoisomerase inhibitors: Etoposide	Double-strand breaks Single-strand breaks Replication lesions	HR, NHEJ
5	Replication inhibitors: Hydroxyrea	Double-strand breaks, Replication lesions	HR, NHEJ
6	Ionising Radiation and Radiomimetics: Bleomycin	Single-strand breaks Double-strand breaks Base damage	NHEJ, HR,BER

Abbreviations: BER : base excision repair pathway, NER: Nucleotide excision repair pathway, MMR: mis match repair pathway, HR: homologous repair pathway, NHEJ: non homologous end joining repair pathway.

Table 1. Cytotoxic agents and DNA Repair pathways

	BER factor	Key findings	Year of publication	Ref
1	APE1	Profound deregulation of APE1 acetylation status in triple negative breast cancer	2012	[52]
2	APE1	Ape1 expression elevated by p53 aberration may be used to predict poor survival and relapse in patients with NSCLC.	2012	[53]
3	APE1, XRCC1,HOGG1	APE1 genetic variants may be associated with endometrial cancer in Turkish women.	2012	[54]
4	APE1	APE1 T1349G polymorphism may be a marker for the development of gastric cancer in the Chinese population	2012	[55]
5	APE1, XRCC1	APE1 allele and the 399Gln XRCC1 allele apparently increased the risk of colon cancer	2012	[57]
6	APE1	APE1-656 T "/> G polymorphism has a possible protective effect on cancer risk particularly among Asian populations	2011	[106]
7	APE1, XRCC, OOG1	Polymorphisms within BER genes may contribute to the tumorigenesis of lung cancer.	2011	[59]
8	APE1	Loss of APE1 expression causes cell growth arrest, mitochondrial impairment and apoptosis	2011	[107]
9	APE1	Genetic variant rs1760944 in APE1 was associated with gastric cancer survival in a Chinese population.	2011	[56]
10	APE1, OGG1, XRCC1	APE1 Asp148Glu and hOGG1 Ser326Cys polymorphisms might be associated with increasing risk of CRC in a Turkish population.	2011	[58]
11	APE1	Polymorphisms of APE1 may confer susceptibility to RCC.	2011	[60]
12	APE1	Cytoplasmic localization of APE1 is associated with tumor progression and might be a valuable prognostic marker for EOC	2011	[51]
13	APE1	Genetic variant in the APE1 promoter may modulate risk of glioblastoma.	2011	[61]
14	APE1	Changes in the expression of APE1 might contribute to lip carcinogenesis.	2011	[108]
15	APE1	APE1 inhibitors potentiated the cytotoxicity of alkylating agents in melanoma and glioma cell lines	2011	[109]
16	APE1	Ape1 promotes radiation resistance in pediatric ependymomas	2011	[110]
17	APE1	The APE1 expression had significant correlation with osteosarcoma local recurrence and/or metastasis.	2010	[111]
18	APE1	APE1 may be a potential therapeutic target of MM.	2010	[112]
19	APE1	APE1 is a potential drug target in ovarian, gastro-oesophageal, and pancreatico-biliary cancers.	2010	[44]

	BER factor	Key findings	Year of publication	Ref
20	APE1	Nuclear expression of APE1 in gastro-oesophageal cancer patients treated with neo-adjuvant chemotherapy is associated with poor prognosis.	2010	[45]
21	APE1	Polymorphism in APE1 gene may affect response to palliative chemotherapy in NSCLC.	2009	[113]
22	APE1	Altered APE1 expression found in platinum resistant ovarian cancer patients	2009	[114]
23	APE1	APE1 is up-regulated in the NSCLC	2008	[115]
24	APE1	APE1 activity promotes resistance to radiation plus chemotherapy in Medulloblastomas and primitive neuroectodermaltumours	2005	[116]
25	APE1, XRCC1	High APE1 and XRCC1 protein expression levels predict better cancer-specific survival following radical radiotherapy in bladder cancer.	2005	[77]
26	APE1	APE1 over expression corresponds to poor prognosis in osteosarcoma	2004	[117]
27	APE1	APE 1 activity mediates resistance to alkylating agents and radiation and may be a useful predictor of progression after adjuvant therapy in a subset of gliomas.	2004	[118]
28	APE1	Cytoplasmic localization of APE1 seems to confer a poor survival outcome in patients with lung adenocarcinoma. Cytoplasmic expression of APE1 is a poor prognostic marker in node positive NSCLC regardless of the Histology.	2002	[46]
29	APE1	Increased expression of APE1 is seen in GCT and may be responsible for resistance to treatment with chemotherapy and IR	2001	[119]
30	APE1	APE1 nuclear expression in HNSCC is directly related to resistance to chemoradiotherapy and poor survival	2001	[120]
31	APE1	Increased APE1 cytoplasmic staining in prostate carcinoma as compared to BPH	2001	[47]
32	APE1	APE1 expression in carcinompa of the cervix is a marker of radio-resistance	1998	[121]

Abbreviations: NSCLC: non small cell lung cancer, CRC: colorectal cancer, RCC: renal cell carcinoma, EOC: epithelial ovarian carcinoma, GCT: germ cell tumour, HNSCC: Head and neck Squamous cell carcinoma, BPH: benign prostatic hypertrophy.

Table 2. APE1

The commonly reported APE1 polymorphisms include Asp148Glu, Leu104Arg, Glu126Asp, Arg237Ala, Asp283Gly, Gln51His, Ile64Val, Gly306Glu and Thr141Gly [48-50]. In a cohort of epithelial ovarian cancer patients, cytoplasmic APE1 positivity was significantly associated with higher grade of tumour (P = 0.002), advanced stage (III + IV) compared to early stage (I + II) patients (40.7% vs. 11.8%; P = 0.002) and a lower survival rate compared to patients with cytoplasmic negative localization (P < 0.05) of APE1 [51]. Profound deregulation of APE1 acetylation status in triple negative breast cancer patients has recently been demonstrated. This may be a potential biomarker for breast cancer aggressiveness [52]. In another study, one hundred and twenty five lung tumour samples were analysed for APE1 protein and mRNA expression by immunohistochemistry and real-time RT-PCR respectively. Cytoplasmic APE1 overexpression and p53 aberration was shown to be a potential predictor of poor survival and relapse in patients with NSCLC[53]. In a case control study of one hundred and four endometrial cancer patients with aged matched normal controls, APE1 Asp148Glu genotypes were determined by PCR-RFLP assays. Frequencies of Glu+ and Asp/Glu genotypes of APE1 were found to be more prevalent in patients than controls. This may represent a future diagnostic biomarker in endometrial cancer [54]. In a study involving three hundred and thirty eight newly diagnosed gastric cancer patients and matched control, APE1 genotype T1349G polymorphism was assessed. Compared with the APE1 TT genotype, individuals with the variant TG/GG genotypes had a significantly increased risk of gastric cancer (OR 1.69, 95% CI 1.19-2.40). Further analyses revealed that the variant genotypes were associated with an increased risk for diffuse-type, low depth of tumour infiltration (T1 and T2), and lymph node metastatic gastric cancer. The APE1 T1349G polymorphism may be a biomarker for the development of aggressive gastric cancer [55]. Another cohort of nine hundred and twenty five gastric cancer patients was evaluated for the genetic variant rs1760944 in APE1. Survival analyses showed a statistically significant (P 0.025, log-rank test) differences in median survival time between gastric cancer patients with APE1 rs1760944 TT (55 months) versus those with GT/GG (78 months). These studies suggest that APE1 polymorphism is a potential biomarker in patients with Gastric cancer [56]. In another study, significant differences in the distribution of APE1 genotype were found between colon cancer patients and healthy individuals. The 148Asp APE1 allele apparently increased the risk of colon cancer (OR 1.9-2.3), suggesting it to be a biomarker in colorectal cancer (CRC) [57]. Polymorphisms of APE1 Asp148Glu (rs3136820) were determined by polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) methods in blood samples of seventy nine CRC patients at their initial staging and two hundred and forty seven healthy controls. Frequency of Glu allele of APE1 Asp148Glu was higher in CRC patients than in controls (P 0.006, OR 3.43; 95% CI 1.76-6.70)[58]. In a hospital-based case-control study of four hundred and fifty five lung cancer patients and four hundred and forty three controls, the single nucleotide polymorphisms (SNPs) of APE1 (Asp148Glu and -141T/G) were genotyped and analyzed. In a multi-

variate logistic regression model, individuals homozygous for the variants APE1 -141GG showed a protective effect for lung cancer (OR 0.62; 95% CI 0.42-0.91; p 0.02). This study indirectly suggests that polymorphism in APE1 genes may be a biomarker and contribute in the pathogenesis of lung cancer [59]. In a case-control study of six hundred and twelve renal cell carcinoma (RCC) patients and six hundred and thirty two age and sex matched healthy controls, APE1 polymorphisms (-656 T>G, rs1760944 and 1349 T>G, rs1130409) were assessed. Compared with 1349 TT/TG genotypes, the variant genotype 1349 GG had a significantly increased risk of RCC (adjusted odds ratio 1.47; 95% CI 1.10-1.95), suggesting a role for APE1 polymorphism as a biomarker in RCC [60]. In a case-control study of seven hundred and sixty six glioma patients and eight hundred and twenty four cancer-free controls APE1/Ref-1 promoter -141T/G variant (rs1760944) was evaluated. Allele G was associated with significant decreased glioblastoma risk (OR 0.80; 95% CI 0.65-0.98; P 0.032) [61].In conclusion emerging studies of APE1 in tumours suggest that APE1 is a promising biomarker in cancer. However, large prospective studies are required to confirm these observations.

2.3. XRCC1

X-ray repair cross-complementing group 1 (XRCC1) is a scaffolding protein and coordinates BER [62]. Cells deficient in XRCC1 are hypersensitive to DNA damaging agents such as ionizing radiation and alkylating agents. Pre-clinically XRCC1 deficiency can induce mutagenesis [63]. Embryonic knock out of XRCC1 is lethal. The most extensively studied polymorphisms of XRCC1 are Arg194Trp, Arg280His, Arg399Gln, Arg399Gln, Pro161Leu and Tyr576S. Ensembl data base records ten somatic mutations and six genetic variations of human XRCC1gene. Table 3 summarizes the current knowledge regarding the association between APE1 and its role as a biomarker. XRCC1 SNPs rs1799782 and rs25487 were investigated using the TaqMan assay in one hundred and eighty five pancreatic cancer cases and one thousand four hundred and sixty five controls. The minor allele, rs25487 was significantly associated with pancreatic cancer risk in the per-allele model (OR 1.29; CI 1.01-1.65; P 0.043). Haplotype analysis of XRCC1 also showed a statistically significant association with pancreatic cancer risk [64]. Endometrial biopsy samples in a case control study assessed the polymorphisms Arg399Gln. Gln/Gln genotype of XRCC1was more prevalent in patients than in controls suggesting XRCC1 polymorphisms as a biomarker in endometrial cancer [54]. In a case control study, polymorphisms of XRCC1 Arg399Gln allele increased the risk of colon cancer (OR 1.5-2.1)[57]. In a cohort of ninety nine advanced colorectal cancer patients treated with oxaliplatin based chemotherapy, polymorphisms of XRCC1 Arg399Gln (G-->A) genotypes were detected by TaqMan-MGB probe allelic discrimination method. Cox proportional hazards model, adjusted for stage, performance status, and chemotherapy regimen, showed that XRCC1 G/G genotype increased the OR significantly (OR 3.555; 95 % CI, 2.119 - 5.963; P < 0.01). The result suggests that XRCC1 Arg399Gln polymorphism is associated with response to chemotherapy and time to

progression in advanced colorectal cancer patients. This study pointed XRCC1 polymorphism as a predictive biomarker in advanced CRC patients treated with oxaliplatin based chemotherapy [65].

	BER factor	Key findings	Year of publication	Ref
1	XRCC1	XRCC1 polymorphisms affect pancreatic cancer risk in Japanese.	2012	[64]
2	XRCC1	Elevated cancer risk associated with XRCC1 polymorphism.	2012	[66]
3	XRCC1	XRCC1 polymorphism might influence the risk of developing glioma	2012	[68]
4	XRCC1, XRCC3	Polymorphisms in DNA repair genes have roles in the susceptibility and survival of ovarian cancer patients.	2012	[69]
5	XRCC1	XRCC1 polymorphism is associated with significantly increased risk of gastric cancer	2012	[70]
6	XRCC1	High XRCC1 and low ATM were independently associated with poor survival in gastric cancer	2012	[76]
7	XRCC1	XRCC1 polymorphisms affect pancreatic cancer risk in Japanese.	2012	[64]
8	XRCC1	Genetic variations in XRCC1 exhibit variation in the sensitivity to platinum based chemotherapy in NSCLC	2012	[71]
9	XRCC1	Polymorphisms of XRCC1 gene might have contributed to individual susceptibility to lung cancer.	2012	[72]
10	XRCC1	Arg194Trp polymorphism could be associated with nonmelanoma skincancer and extramammary Paget's disease risk in a Japanese population.	2012	[Chiyomaru, 2012 #1047] [122]
11	XRCC1	Polymorphism of XRCC1 Arg399Gln may be a candidate for contributing to the difference in the OS of gemcitabine/platinum-treated advanced NSCLC patients.	2012	[73]
12	XRCC1	XRCC1 Arg399Gln polymorphisms is associated with a response to oxaliplantin-based chemotherapy and time to progression in advanced colorectal cancer in Chinese population.	2012	[65]

	BER factor	Key findings	Year of publication	Ref
13	XRCC1	The 751 Lys/Gln polymorphism of the ERCC2 gene may be linked to endometrial cancer	2012	[Sobczuk, 2012 #1050][123]
14	XRCC1, XRCC3	XRCC1 and XRCC3 gene polymorphisms for risk of colorectal cancer in the Chinese population.	2012	[124]
15	XRCC1	XRCC1 399Gln is an independent unfavourable prognostic factor in unresected NSCLC treated with radiotherapy and chemoradiotherapy	2012	[125]
16	XRCC1	XRCC1-Arg399Cln polymorphism is associated with susceptibility to HCC, and XRCC1 Gln allele genotype showed significant prognostic associations.	2012	[126]
17	XRCC1	XRCC1 -77T"/>C polymorphism is associated with cancer risk, and individuals with XRCC1-77C variant have a significantly higher cancer risk, particularly in the Asian population	2012	[67]
18	XRCC1	XRCC1 protein expressions in tumor is novel candidate prognostic markers and predictive factor for benefit from adjuvant platinum-based chemotherapy in resectable gastric carcinoma.	2012	[75]
19	XRCC1	Genetic polymorphisms in XRCC1 gene might be associated with overall survival and response to platinum-based chemotherapy in lung cancer patients.	2012	[127]
20	XRCC1	XRCC1 T-77C and eNOS G874T may confer an increased risk of acute skin reactions to radiotherapy in breast cancer patients	2012	[128]
21	XRCC1	XRCC1 399Gln/Gln genotype have an increased risk of colorectal cancer	2012	[129]
22	XRCC1	XRCC1 Arg399Gln allele is a risk factor for the development breast cancer, especially among Asian and African populations.	2011	[130]
23	XRCC1	genetic polymorphisms in XRCC1 may affect survival post radiotherapy for localized prostate cancer.	2010	[131]
24	XRCC1	Combined polymorphisms of ERCC1 and XRCC1 may predict OS and response to palliative chemotherapy with FOLFOX / XELOX in metastatic CRC patients	2010	[132]

	BER factor	Key findings	Year of publication	Ref
25	XRCC1	XRCC1 194 CT genotype associated with inferior overall survival in advanced gastric cancer patients treated with Cisplatin-Taxane combined chemotherapy.	2010	[133]
26	XRCC1	XRCC1 codon 194 and codon 399 polymorphisms may predict the sensitivity of advanced NSCLC to palliative chemotherapy treatment with vinorelbine and Cisplatin.	2009	[134]
27	XRCC1	XRCC 1 polymorphism may predict higher response rate to palliative Cisplatin based chemotherapy in NSCLC patients	2009	[135]
28	XRCC1	XRCC1 polymorphism in clinical stage III may be a prognostic survival marker in HNSCC.	2009	[136]
29	XRCC1	SNP of XRCC1 gene at codon 399 influences the response to platinum based neo-adjuvant chemotherapy treatment in patients with cervical cancer.	2009	[137]
30	XRCC1, APE1	Polymorphism in APE1 and XRCC1 may represent prognostic factors in metastatic melanoma.	2009	[138]
31	XRCC1	A rarely occurring XRCC1 variant may predict response to Neoadjuvant chemo-radiotherapy for the treatment of oesophageal cancer.	2009	[139]
32	XRCC1	XRCC1 variant alleles may be associated with shorter overall survival in lung cancer patients	2008	[140]
33	XRCC1	Genotypes of XRCC1 Arginine194Tryptophan and GGH-401Cytosine/Thymine associated with the response to platinum based neo-adjuvant chemotherapy treatment in patients with cervical cancer	2008	[141]
34	XRCC1	XRCC1 variant may predict the risk of recurrence of bladder TCC post BCG treatment.	2008	[142]
35	XRCC1	XRCC1 gene polymorphism may predict survival in good PS advanced Gastric cancer patients treated with Oxalipaltin based palliative chemotherapy.	2007	[143]
36	XRCC1	Polymorphism in XRCC1 gene is a potential prognostic and predictive marker in breast cancer patients treated with adjuvant CMF chemotherapy	2007	[144]

	BER factor	Key findings	Year of publication	Ref
37	XRCC1	XRCC1 polymorphism may predict survival advantage for SCLC and NSCLC patients after platinum based treatment	2007	[145]
38	XRCC1	XRCC1 polymorphism may predict response to palliative FOLFOX and can also be a prognostic survival factor in metastatic colorectal cancer.	2006	[146]
39	XRCC1	Variant alleles of XRCC1 associated with the absence of pathologic complete response and poor survival in oesophageal cancer	2006	[147]
40	XRCC1	XRCC1 polpmorphism may represent a prognostic factor in advanced NSCLC patients treated with palliative Cisplatin and Gemcitabine.	2006	[148]
41	OGG1, LIG3, APE1, POLB, XRCC1, PCNA	XRCC1 polymorphism may be a prognostic factor in patients with CRC	2006	[95]
42	XRCC1	XRCC1-01may predict survival outcome in patients with MBC treated with high dose chemotherapy.	2006	[74]
43	XRCC1	Combined XPD and XRCC1 genotypes might be prognostic factors in muscle-invasive bladder cancer patients treated with CRT.	2006	[149]
44	XRCC1	Polymorphism of XRCC1 R399Q is associated with response to platinum-based NAC in bulky cervical cancer	2006	[150]
45	XRCC1	Polymorphisms in the XRCC1 gene may impact the response rate to platinum based palliative chemotherapy in NSCLC patients.	2004	[151]
46	XRCC1	Polymorphism of XRCC1 gene may be associated with resistance to oxaliplatin/5-FU chemotherapy in advanced colorectal cancer.	2001	[152]

Abbreviations:ATM: ataxia telangiectasia mutated protein, FOLFOX: oxaliplatin and 5FU based chemotherapy, XELOX: oxliplatin and Capecitabine based chemotherapy, TCC: transitional cell carcinoma, BCG: Bacillus Calmette–Guérin, CRT: chemoradiotherapy, MBC: metastatic breast cancer.

Table 3. XRCC1

Meta-analysis of fifty three case-control studies with twenty one thousand three hundred and forty nine cases and twenty three thousand six hundred forty nine controls for XRCC1 Arg280His polymorphism and its cancer risk were estimated using fixed or random effect

models. Minor variant His allele and Arg-His/His-His genotypes showed a statistical association with the risk of cancer (OR 1.16; 95% CI 1.08-1.25) [66]. Meta-analysis of thirteen studies involving a total of eleven thousand six hundred and seventy eight individuals showed that there was significant association between the C variant of XRCC1-77T>C polymorphism and cancer risk in all four genetic comparison models (OR C vs. T 1.19; 95% CI 1.07-1.31; P 0.001; OR homozygote model 1.28; 95% CI 1.07-1.52; P 0.007; OR recessive genetic model 1.22; 95% CI 1.04-1.44; P 0.015; OR dominant model 1.21; 95% CI 1.07-1.35, P 0.001). XRCC1 -77T>C polymorphism is associated with cancer risk, and individuals with XRCC1 -77C variant have a significantly higher cancer risk, particularly in the Asian population [67]. Using a PCR-RFLP method, XRCC1 Arg194Trp, Arg280His and Arg399Gln were genotyped in six hundred and twenty four glioma patients and five hundred and eighty healthy controls. Significant differences in the distribution of the Arg399Gln allele were detected between glioma patients and healthy controls by a logistic regression analysis (OR 1.35; 95% CI 1.17-1.68; P 0.001). Arg399Gln variant (allele A) carriers had an increased glioma risk compared to the wild-type (allele G) homozygous carriers (OR 1.40, 95%CI 1.12-1.76, P 0.003)[68]. In a prospective follow-up study, a cohort of three hundred and ten ovarian cancer patients treated with platinum-based chemotherapy between January 2005 to January 2007 were followed up to 2010. Genotyping of XRCC1 and XRCC3 polymorphisms was conducted by TaqMan Gene Expression assays. Lower survival rate in XRCC1 399 Arg/Arg genotype than in Gln/ Gln, with a significant increased risk of death (HR 1.69; 95% CI 1.07-2.78) were observed. However no significant association between XRCC1 Arg194Trp and XRCC1 Arg280His gene polymorphisms and ovarian cancer death was observed. [69]. A multicenter 1:1 matched case- control study of three hundred and seven pairs of gastric cancers patients and controls between October 2010 and August 2011 was undertaken. XRCC1 Arg194Trp and ADPRT Val762Ala were sequenced. Demographic data collected using a self-designed questionnaire. Individuals carrying XRCC1 Trp/Trp or Arg/Trp variant genotype had a significantly increased risk of gastric cancer (OR 1.718; 95% CI, 1.190-2.479). [70]. In a cohort of advanced NSCLC patients treated with platinum based chemotherapy, XRCC1 polymorphism was evaluated. XRCC1 Arg194Arg, FAS-1377GG, and FASL-844T allele displayed no response to platinum, whereas patients with XRCC1 194Trp allele and XPC PAT +/+ had 68.8% response rate to platinum. In Logistic Regression analysis, a significant gene-dosage effect was detected along with the increasing number of favourable genotypes of these four polymorphisms (P 0.00002). Multi-loci analysis showed the importance of genetic variations involved in BER repair and apoptotic pathways in sensitivity of platinum-based chemotherapy in NSCLC [71]. In a meta-analysis of forty four published case-control studies demonstrated that codon 194, codon 399 and -77 T > C polymorphisms of XRCC1 gene might have contributed to individual susceptibility to lung cancer [72]. In a another study, sixty two advanced NSCLC patients in a training set and forty five patients in a validation set treated with gemcitabine/platinum were genotyped for XRCC1 polymorphism. Wild-type genotype of XRCC1 Arg399Gln (G/G) was associated with decreased median overall survival than those carrying variant genotypes (G/A+A/A). In addition, there was a statistically significant longer median OS in patients carrying wild-type ERCC2 Asp312Asn genotype (G/G) (51 months, 95% CI, 19-82 months versus 10 months, log-rank test, P < 0.001) than those carrying heterozygous variant genotypes (G/A). This points out the predictive biomarker status of XRCC1 in platinum treated NSCLC patients[73]. XRCC1 polymorphism is a potential predictive marker of platinum based treatment response in non-small cell lung carcinoma, col-

orectal carcinoma, advanced gastric, advanced cervical, advanced operable oesophageal cancer. It may also predict response to adjuvant CMF chemotherapy and high dose chemotherapy in breast cancer [74].

In a training and validating cohort of Gastric cancer patients, XRCC1 protein levels were significantly downregulated in gastric cancers compared to adjacent non-cancerous tissues. Low tumour XRCC1 expression significantly correlated with shorter overall survival as well as with clinic-pathologic characteristics in patients without adjuvant treatment. Multivariate regression analysis showed that low XRCC1 expressions, separately and together, were independent negative markers of OS. Adjuvant fluorouracil-leucovorin-oxaliplatin (FLO) significantly improved OS compared with surgery alone (log-rank test, P 0.01). However, this effect was evident only in the XRCC1 low expression group (HR 0.44, 95% CI 0.26-0.75; P 0.002); Adjuvant fluorouracil-leucovorin-platinum (FLP) did not improve OS, except in the patients with low XRCC1 expressions (P 0.024). XRCC1 protein expressions in tumour are novel candidate prognostic markers and predictive factors for benefit from adjuvant platinum-based chemotherapy (FLO or FLP) in patients with resectable gastric carcinoma [75]. SMUG1, FEN1, XRCC1 and ATM are involved in ROS induced oxidative DNA damage repair in gastric cancer patients. High expression of SMUG1, FEN1 and XRCC1 correlated to high T-stage (T3/T4) (P 0.001, 0.005 & 0.02 respectively). High expression of XRCC1 and FEN1 also correlated to lymph node positive disease (P 0.009 and 0.02 respectively). High expression of XRCC1, FEN1 & SMUG1 correlated with poor disease specific survival (P 0.001, 0.006 and 0.05 respectively) and poor disease free survival (P 0.001, 0.001 & 0.02 respectively) [76]. Muscle-invasive transitional cell carcinoma tumour samples from ninety patients treated with radical radiotherapy was evaluated for XRCC1 protein expression. Nuclear staining of XRCC1 was 96.5% (range, 0.6-99.6%). High expression levels of XRCC1 (> or = 95% positivity) were associated with improved patient cancer-specific survival (log-rank, P 0.006) [77].

XRCC1 has shown to be a promising prognostic biomarker in a majority of cancer groups including HNSCC, breast, ovarian, endometrial, cervical, lung, gastric, oesophageal, pancreatic, glial, colorectal, hepatocellular, bladder transitional cell carcinoma, metastatic melanoma and non melanomatous skin cancer.

2.4. FEN1

FEN1 is a structure-specific 5′ endo/exonuclease with a range of functions during DNA repair and replication. It is a BER long patch protein. FEN1 also has a role in the processing of the okazaki lagging DNA strand synthesis. As an endonuclease, FEN1 recognizes double-stranded DNA with a 5′-unannealed flap and makes an endonucleolytic cleavage at the base of the flap. As a 5′ exonuclease, it degrades nucleotides from a nick or a gap. It may also be involved in maintaining stability of telomeres, inhibiting repeat sequence expansion and involved in creation of double-stranded DNA breaks when mammalian cells are subjected to X-ray irradiation[78]. Human flap endonuclease 1 gene has been shown to have 4 somatic mutations, one polymorphism, and two transcripts in the Ensembl data base. In the following section we will review the potential of FEN1 as a prognostic, predictive biomarker and its feasibility as a drug target in cancer treatment (See Table 4).

	BER factor	Key findings	Year of publication	Ref
1	FEN1	Polymorphisms in FEN1 confer susceptibility to gastrointestinal cancers	2012	[79]
2	FEN1	High expression of XRCC1, FEN1 & SMUG1 correlated with poor disease free survival	2012	[76]
3	FEN1	FEN1 protein expression was also associated with poor prognosis in prostatectomy-treated patients. Knock-down of FEN1 with small interfering RNA inhibited the growth of LNCaP cells.	2012	[83]
4	FEN1	Genetic polymorphisms in FEN1 confer susceptibility to lung cancer.	2009	[153]
5	FEN1	FEN1 overexpression is common in testis, lung and brain tumors. Down-regulation of FEN1 by siRNA increased sensitivity to methylating agents (temozolomide, MMS) and cisplatin in LN308 glioma cells	2009	[81]
6	FEN1	RAD54B-deficient human colorectal cancer cells are sensitive to SL killing by reduced FEN1 expression	2009	[85]
7	FEN1	FEN1 is significantly up-regulated in multiple cancers. The overexpression and promoter hypomethylation of FEN1 may serve as biomarkers for monitoring the progression of cancers	2008	[82]
8	FEN1	FEN-1 is overexpressed in prostate cancer and is associated with higher Gleason score.	2006	[84]

Abbreviations: SMUG1: Single-strand selective monofunctional uracil-DNA glycosylase

Table 4. FEN1

Human germ line variants (-69G >A and 4150G > T) in the FEN1 gene have been associated with DNA damage in coke oven workers and lung cancer risk in general populations. This was studied in one thousand eight hundred and fifty gastrointestinal cancer (hepatocellular carcinoma, esophageal cancer, gastric cancer and colorectal cancer) patients and two thousand two hundred and twenty two healthy controls. It was found that the FEN1 -69GG genotypes were significantly correlated to increased risk for developing gastrointestinal cancer compared with the -69AA genotype highlighting FEN1 as an important gene in human gastrointestinal oncogenesis and a potential biomarker [79]. We recently investigated this relationship in a cohort of gastric cancer patients and found high expression of FEN1 correlated to lymph node positive disease with poor disease specific survival and poor disease free survival [76]. In pro-myelocytic leukemia cell line HL-60, gene expression of FEN-1 has been shown to be higher

in cells during mitotic phase as compared to cells in the resting phase. FEN1 expression markedly decreases when these cells reach maturity upon induction of terminal differentiation [80]. This study pointed out the relationship between increased FEN1 expression and proliferating cancer cells. Subsequent studies showed increased FEN 1 expression in testis, lung and brain cancer specimens as studied by Western blot analysis and compared with the normal tissue from the same patient. FEN1 over expression was observed in nineteen samples from testicular tumours (mostly seminomas), four samples from NSCLC, nine samples from glioblastoma multiforme and in five samples from astrocytomas. Down regulation of FEN1 expression in LN308 glioblastoma cell line by siRNA resulted in hypersensitivity to cisplatin, temozolomide, nimustine and methyl methanesulfonate (MMS)[81]. Statistically significant increased amount of FEN1 expression has been demonstrated in breast tumor tissue (~2.4 fold, $P< 0.0001$, $n = 50$), uterine tumor tissue (~2.3 fold, $P = 0.0006$, $n = 42$), colon tumor tissue (~1.5 fold, $P < 0.0001$, $n = 35$), stomach tumor tissue (~1.5 fold, $P= 0.0005$, $n = 28$), lung tumor tissue (~1.9 fold, $P = 0.0066$, $n=21$) and kidney tumor tissue (~2.3 fold, $P = 0.0063$, $n = 20$), compared to matched normal tissues[82]. FEN1 also found to be increased in castration refractory prostate cancer (CRPC) cells. The knock-down of FEN1 with si RNA inhibited the growth of these LNCaP cells [83] pointing it as a potential drug target in prostate cancer. In primary prostate cancer from two hundred and forty six patients who had had a radical prostatectomy, FEN-1 nuclear expression correlated with Gleason score. These results suggest that FEN-1 might be a potential marker for selecting patients at high risk and therapy [84]. Interestingly, synthetic lethality (SL) has been observed in RAD54B-deficient human colorectal cancer cell line by iatrogenic reduction of FEN1 expression thus demonstrating it to be a potential novel therapeutic biological target [85].

2.5. Polymerase beta, PCNA

Polymerase beta (pol β) is essential for short patch BER. It is present in all tissues at a lower level [86] and has no cell-cycle dependence. Majority of BER proceeds through the short-patch whereby a single nucleotide is removed and replaced. Unlike other DNA polymerases, pol β has no proof reading capability[87] hence its over expression has the potential for mutagenesis[88, 89]. Proliferating cell nuclear antigen(PCNA) is an accessory protein required for replication by DNA polymerase δ, and as a consequence, PCNA is required during the long patch BER [90]. Lesions left unrepaired by the short patch BER is facilitated by PCNA to switch to the long patch BER. PCNA then helps polymerase δ to excise and replace 2-8 nucleotide patch in the long path of BER. Table 5 summarizes recent insight into the prognostic and predictive significance of pol β and PCNA.

Twenty somatic pol β mutations in prostate tumors are already known. The somatic missense pol β mutations (p.K27N, p.E123K, p.E232K, p.P242R, p.E216K, p.M236L, and the triple mutant p.P261L/T292A/I298T) were assessed *in vitro* for the biochemical properties of the polymerase. Experiments suggest that interfering with normal polymerase beta function may be a frequent mechanism of prostate tumour progression [91].Three non-synonymous single nucleotide substitutions, Gln8Arg, Arg137Gln and Pro242Arg have been identified as polymorphisms in DNA Pol β. The Arg137Gln variant demonstrates significantly reduced polymerase activity

and impaired interaction with PCNA, and reduced BER efficiency when assayed in a reconstitution assay or with cellular extracts. Other polymorphisms within DNA Pol β include *A165G* and *T2133C*, which were associated with overall survival in a study of patients with pancreatic cancer [92, 93]. One hundred and fifty two ovarian cancer samples subjected to RT-PCR and sequencing, a variant of polymerase beta (deletion of exon 4-6 and 11-13, comprising of amino acid 63-123, and 208- 304) was detected in heterozygous condition. Statistical analysis showed this variant to be associated with risk of stage IV, endometrioid type ovarian carcinoma[94]. In a case-control study (three hundred and seventy seven cases along with three hundred and twenty nine controls) designed to assess gene-environment interactions, samples were genotyped by use of an oligonucleotide microarray and the arrayed primer extension technique. Twenty-eight single nucleotide polymorphisms in 15 DNA repair genes including pol β P242R were evaluated. It was demonstrated that pol β polymorphism is associated with a decreased risk of colorectal cancer [95]. Pol β over expression reduces the efficacy of anticancer drug therapies including ionizing radiation, bleomycin, monofunctional alkylating agents and cisplatin. Small-scale studies in different cancers showed that pol β is mutated in approximately 30% of tumours. These mutations further lower pol β fidelity in DNA synthesis exposing the genome to serious mutations. These findings suggested pol β to be a promising therapeutic target in cancer treatment [96].

	BER factor	Key findings	Year of publication	Ref
1	Pol beta	variant form of Pol β cDNA is associated with edometrioid type, stage IV ovarian carcinoma	2012	[94]
2	Pol beta	A proportion of prostate cancer patients express functionally important somatic mutations of pol β.	2011	[91]
3	Pol Beta	Over expression of pol β reduces the efficacy of anticancer drug therapies including, Cisplatin, bleomycin, monofunctional alkylating agents and ionizing radiation.	2011	[96]
4	Pol beta, PCNA	More than 30% of human tumors characterized to date express DNA pol β variants, a polymorphism encoding an arginine to glutamine substitution, R137Q, has lower polymerase activity	2009	[92]
4	Pol beta, PCNA	Pancreatic cancer patients carrying at least 1 of the 2 homozygous variant pol β GG or CC genotypes have a significantly better overall survival	2007	[93]
5	OGG1, LIG3, APE1, POLB, XRCC1, PCNA	pol β P242R was also associated with decreased risk of colorectal cancer	2006	[95]

Table 5. Other BER factors

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3. Summary and the future developments

Numerous DNA base excision repair proteins are currently under development as potential biomarkers and therapeutic targets. Studies presented above provide compelling evidence that BER factors are promising prognostic and predictive biomarkers in cancer. More recent evidence also suggests that BER is an attractive target for drug discovery. APE1 inhibitors, for example, are currently in development and may have therapeutic application in the near future. [34, 97, 98]. Moreover, DNA polymerase beta inhibitor is also currently under developmental stage and early reports reveal the ability of DNA pol β inhibitors to potentiate the cytotoxicity of alkylating agents [99]. In contrast, several other studies demonstrate that pol β-null cells, although sensitive to temozolomide, are not sensitive to other chemotherapeutic agents such as melphalan, mitozolomide, BCNU, and IR [34, 100, 101]. Therefore further research is warranted to confirm pol β as a drug target in cancer.The principles of synthetic lethality has been transferred from the bench to the bedside with PARP-1 inhibitors in BRCA-deficient (HR-defective) cancer cells [102, 103]. Recent evidence suggests that other factors in BER are also important synthetic lethality targets for personalized cancer therapy.

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