We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



19

Human Apurinic/Apyrimidinic Endonuclease is a Novel Drug Target in Cancer

Rachel M Abbotts, Christina Perry and Srinivasan Madhusudan
Academic Unit of Oncology, University of Nottingham
United Kingdom

1. Introduction

Genomic DNA possesses an inherent instability, at risk from damage by spontaneous base lesions, metabolic by-products, and exogenous sources such as ultraviolet light, ionising radiation and chemical agents. Unrepaired, this damage could result in non-canonical base pairing during replication, leading to the propagation of potentially mutagenic lesions. A number of DNA repair mechanisms have evolved to ensure genomic integrity can be preserved. So critical are these repair pathways that mutations within constituent genes are associated with several cancer predisposition syndromes such as hereditary non-polyposis carcinoma coli (HNPCC) or BRCA-deficient breast and ovarian cancer syndromes (Sweasy, Lang, and DiMaio 2006).

Cancer therapies commonly rely upon the induction of DNA damage to exert their effects. Upregulation of DNA repair pathways in cancer is common and may impact upon response to therapy and contribute to development of treatment resistance. Inhibition of DNA repair offers exciting possibilities for the future treatment of cancer. DNA repair constituents may also be used as biomarkers to predict tumour response to treatment and improve outcome prognostication. Pharmacological inhibition of DNA repair might potentiate the effects of anticancer agents, improving response rates, overcoming resistance, and improving outcomes. Furthermore, there may be scope to specifically target tumour cells using DNA repair inhibitors by exploiting genetic differences with normal tissue.

Base excision repair (BER) is critical for the repair of damage induced by alkylating chemotherapy agents such as temozolomide and dacarbazine. Targeting BER has shown considerable promise in the form of poly (ADP-ribose) polymerase (PARP) inhibitors, and a number of groups are now focusing on other BER targets. This chapter will provide an overview of the BER pathway, with specific consideration of the compelling evidence base for targeting the critical enzyme apurinic/apyrimidinic endonuclease I (APE1) for cancer therapy.

2. Base excision repair

Base excision repair (BER) is responsible for detection and repair of damage caused by a number of mechanisms, including alkylation, oxidation, ring saturation, single strand breaks and base deamination. Although complex, with at least two sub-pathways (see figure 1), BER generally proceeds via: a) recognition and removal of a damaged base by a DNA

glycosylase to form an abasic site intermediate; b) cleavage of the phosphodiester backbone 5′ to the abasic site by apurinic/apyrimidinic endonuclease 1 (APE1); c) removal of the 5′ sugar fragment; d) incorporation of the correct base by a DNA polymerase; and e) sealing of the strand break by a DNA ligase (Figure 1) (Fortini et al. 2003; Nilsen and Krokan 2001; Izumi et al. 2003; Dianov et al. 2003; Sancar et al. 2004; Barnes and Lindahl 2004; Robertson et al. 2009; Abbotts and Madhusudan 2010).

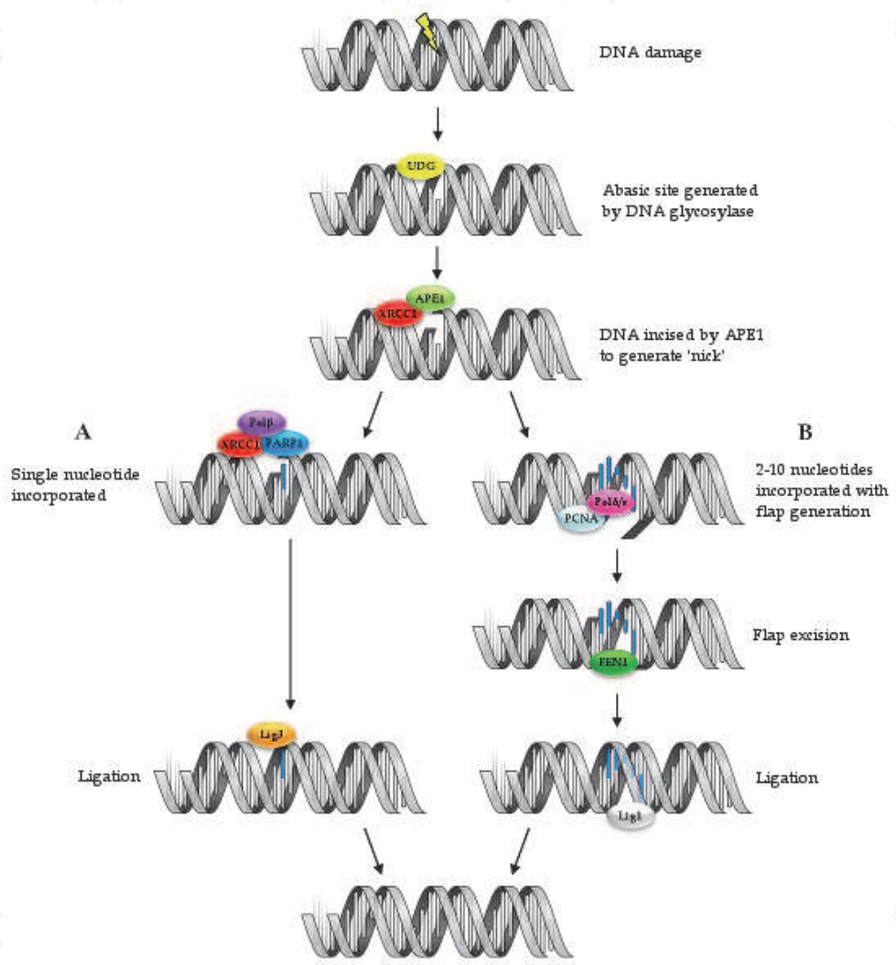


Fig. 1. Short-patch (A) and long-patch (B) base excision repair [1]

DNA glycosylases are a family of damage-specific enzymes which excise the damaged base via cleavage of the *N*-glycosidic bond linking it to the deoxyribose moiety. They induce localised DNA distortion to 'flip out' the damaged base into the binding site for processing. Some have dual functionality, also possessing the ability to cleave the DNA phosphodiester backbone to create a single strand break 3′ to the abasic site. More commonly, APE1 incises

1 UDG = uracil DNA glycosylase, APE1 = apurinic/apyrimidinic endonuclease 1, XRCC1 = X-ray repair cross-complementing group 1, PARP1 = poly(ADP-ribose) polymerase 1, dRP = deoxyribose phosphate, Polβ/δ/ε = DNA polymerase β/δ/ε, PCNA = proliferating cell nuclear antigen, Lig3 = DNA ligase III, FEN1 = flap endonuclease I, Lig1 = DNA ligase I

the DNA backbone 5′ to the abasic site, creating a nick bordered by 5'-deoxyribose phosphate (dRP) and 3′-hydroxyl groups. These groups act as blocking moieties, requiring further processing for BER to proceed. A number of enzymes possess this ability, including APE1, DNA polymerases β, λ and ι, and PNKP (polynucleotide kinase 3'-phosphatase).

Repair synthesis proceeds via a DNA polymerase. In the short-patch pathway, DNA Polβ incorporates a single nucleotide 'patch' into the processed abasic site. This pathway requires high concentrations of ATP for completion. When ATP concentrations are low or the oxidative state of the abasic lesion is altered, repair proceeds via the long-patch pathway. This involves the incorporation of 2-10 nucleotides by DNA polymerases δ and ε in conjunction with the sliding clamp protein PCNA (proliferating cell nuclear antigen), or alternatively, a Polβ/Rad9-Rad1-Hus1 complex, which bears structural similarity to PCNA. Long-patch nucleotide incorporation displaces the existing 5′ DNA in a flap intermediate which is removed by flap endonuclease I (FEN1) (Pascucci et al. 1999; Balakrishnan et al. 2009). The repair is then completed by sealing of the DNA strand break by a DNA ligase. In the short-patch pathway, this primarily occurs via the DNA ligase III-XRCC1 (X-ray cross-complementation group I) scaffold protein heterodimer, whereas the long-patch pathway is completed by DNA ligase I.

Coordination of the BER pathway relies upon members of the poly (ADP-ribose) polymerase (PARP) family, which bind to DNA strand breaks and stabilise the DNA strand until repair can be effected. Once bound, PARPs also catalyse the addition of poly (ADP-ribose) polymers to target proteins, affecting protein-protein interactions and catalytic activities (D'Amours et al. 1999). 90% of PARP poly(ADP-ribosyl)ation is automodification, leading to recruitment of other BER constituents such as XRCC1, DNA Polβ and DNA LigIII (Megnin-Chanet, Bollet, and Hall 2010). This automodification also stimulates the release of PARP from DNA, allowing access to BER proteins to proceed with repair. Inhibition of PARP leads to persistence of single strand breaks, causing stalling of replication forks and formation of lethal double strand breaks (Durkacz et al. 1980). PARP inhibitors are currently showing promise in clinical trials (Helleday et al. 2008; Jones and Plummer 2008; Chalmers 2009; O'Shaughnessy et al. 2009) (see 6. Targeting APE1 for therapy).

3. Apurinic/apyrimidinic endonuclease (APE1)

3.1 Abasic site formation

Abasic site formation occurs at a rate of ~50000 sites per cell per day, through the action of DNA glycosylases in the BER pathway and by spontaneous depurination (Lindahl 1993; Nakamura and Swenberg 1999; Atamna, Cheung, and Ames 2000). Abasic sites can also be induced by exogenous agents such as ionising radiation or alkylating and oxidizing drugs including temozolomide or bleomycin. Without repair, abasic sites cause stalling of replication forks, leading to strand breaks that are cytotoxic in high number (Wilson 2003).

3.2 Apurinic/apyrimidinic endonucleases

Apurinic/apyrimidinic (AP) endonucleases are critical for the recognition and processing of abasic sites during base excision repair. Two classes of AP endonucleases exist: Class I AP lyases, and Class II AP endonucleases. Class II AP endonucleases can be classified further into two families which are structurally distinct but catalyse reactions with identical products. These families are defined by their structural homology to the two endonucleases

expressed in *E. coli*, exonuclease III (exoIII, encoded by *xth* gene) and endonuclease IV (endoIV, encoded by *nfo*) (Figure 2).

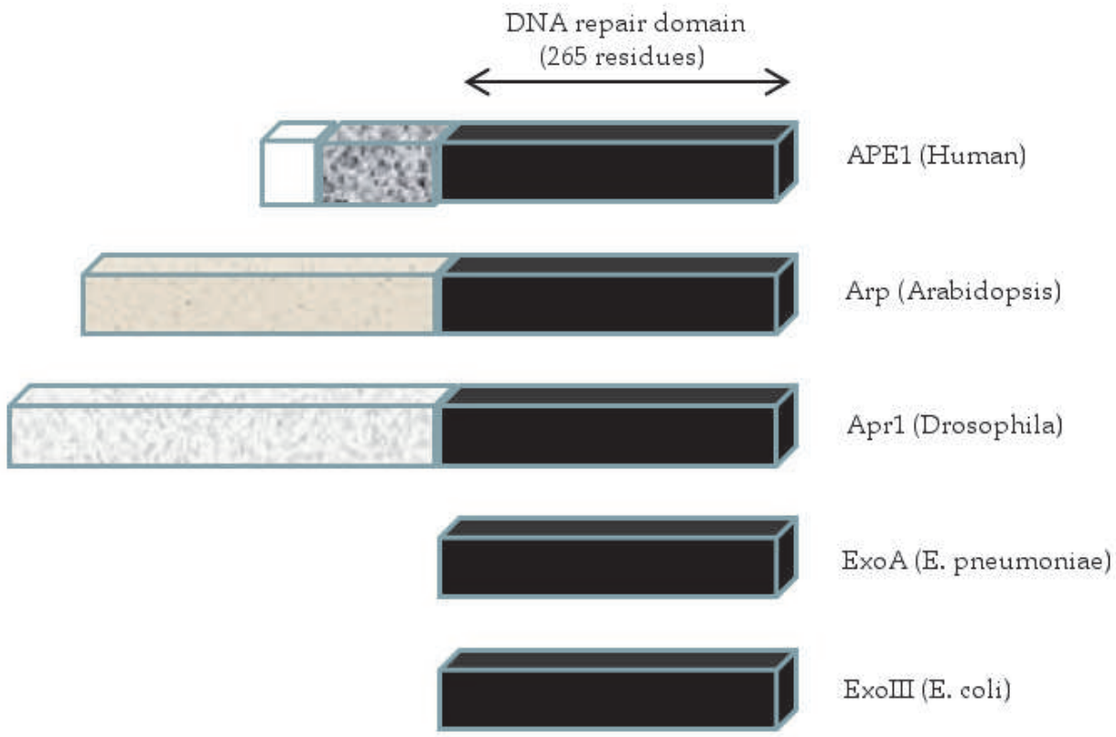


Fig. 2. The Exonuclease III family of AP Endonucleases in various species

The exoIII human homologue, APE1, accounts for 95% of AP endonuclease activity in human cells (Robson and Hickson 1991; Demple, Herman, and Chen 1991; Chen, Herman, and Demple 1991; Robson et al. 1992). A second exonuclease III-like protein, APE2, has recently been identified but is not yet fully characterised (Hadi and Wilson 2000; Hadi et al. 2002; Burkovics et al. 2006). Also known as HAP1 or Ref-1, APE1 is a ubiquitous multifunctional protein, with 350,000 – 7,000,000 units per cell (Chen, Herman, and Demple 1991). The 2.6kb APE1 gene is localised to 14q11.2-12. It consists of four introns and five exons that encompass a 954 nucleotide coding region, encoding a 318-amino acid protein of 35kDa. The C-terminal domain is essential for DNA repair activity, while the N-terminal domain possesses redox regulatory activity and also contains a nuclear localisation sequence. Preservation of APE1 function requires at least 10 evolutionarily conserved amino acids (Asp70, Asp90, Glu96, Tyr171, Asp210, Asn212, Asp219, Asp283, Asp308 and His309) (Figure 3).

APE1 is a globular protein arranged in a four-layered α/β sandwich, sharing significant structural homology with exoIII despite limited sequence homology (Gorman et al. 1997) (Figure 3B). The DNA repair active site is situated within a hydrophobic pocket on top of the α/β sandwich (Figure 3C). During DNA binding, the active site undergoes little conformation change, instead significantly distorting the DNA substrate, probably to displace the bound DNA glycosylase (Mol et al. 2000). Within the active site, highly conserved His309 and Thr283 are vital for catalytic activity. His309 is believed to act as a

general base to abstract a proton from water, forming a hydroxide which attacks the scissile bond of the phosphate group 5′ to the abasic site. Also essential is a Glu96-bound magnesium ion which, along with Thr283, may help stabilise the reaction intermediate (Gorman et al. 1997; Lipton et al. 2008).

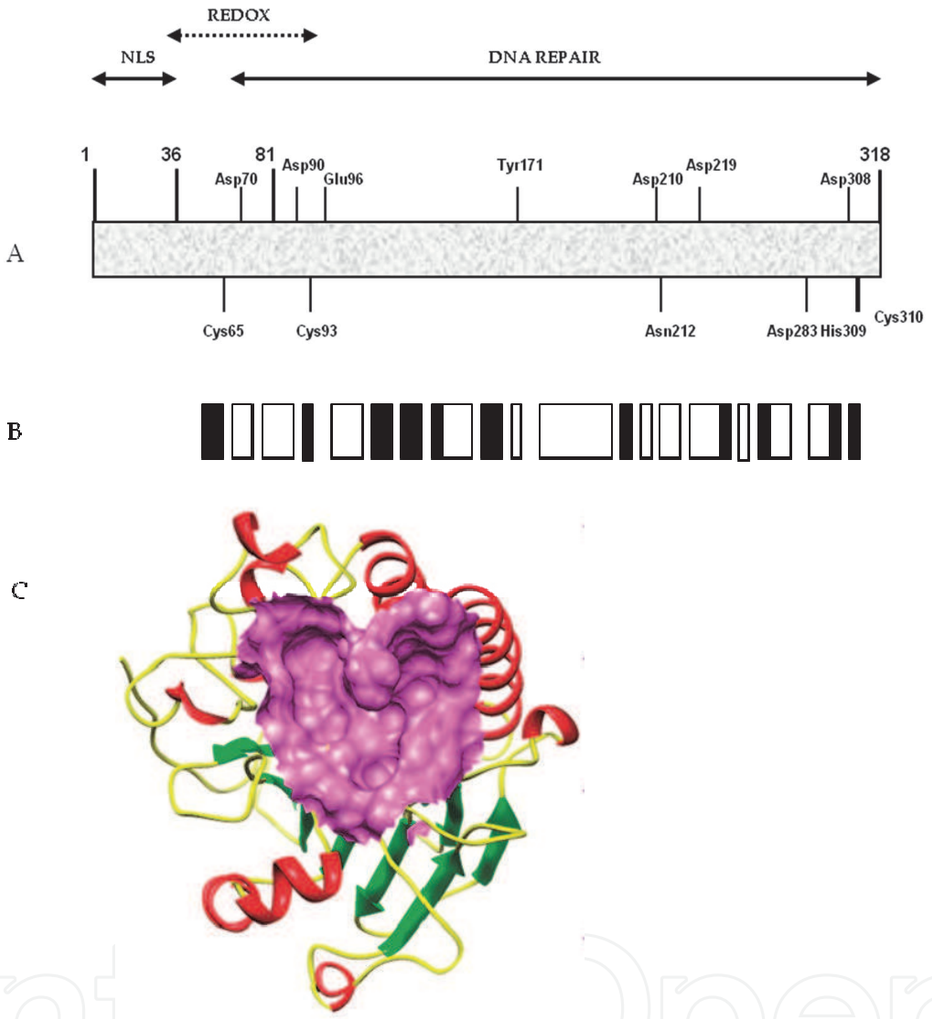


Fig. 3. A. Schematic representation of APE1 protein with critical residues (NLS = nuclear localization sequence). B. APE1 protein structure. White rectangles represent α-helical regions and shaded rectangles represent β-strands. C. Ribbon diagram of APE1 protein structure including DNA repair active site.

3.3 Roles of APE1 in DNA repair

APE1 endonuclease activity catalyses Mg^{2+}-dependent hydrolytic cleavage of the phosphodiester bond of the DNA backbone 5' to an abasic site, producing a nick flanked by a 3'-hydroxyl and a 5'-deoxyribose phosphate group. Like exonuclease III, APE1 has a number of other DNA repair roles mediated through the same highly-conserved active site. APE1 possesses 3′-phosphodiesterase activity, catalysing removal of fragmented sugar moieties 3′ to single strand breaks induced by bleomycin or ionising radiation (Parsons,

Dianova, and Dianov 2004). It has exonuclease activity, which may facilitate the removal of mis-paired nucleotides (or nucleoside analogues such as troxacitabine), including those incorrectly inserted by Polβ, thus preserving BER fidelity (Chou, Kukhanova, and Cheng 2000; Chou and Cheng 2002). It has weak 3′-phosphatase activity that removes 3′-phosphate blocking groups left after bifunctional DNA glycosylase base excision (Wiederhold et al. 2004). APE1 also appears to have a role in the nucleotide incision repair pathway, where an endonuclease recognises and processes oxidatively-damaged DNA in a glycosylase-independent manner (Gros et al. 2004; Ishchenko et al. 2006). A mitochondrial targeting signal in the C-terminal has been identified (Li et al. 2010), supporting evidence that APE1 has a role in the repair of oxidatively-damaged mitochondrial DNA (Frossi et al. 2002; Shokolenko et al. 2009).

3.4 Other functions of APE1

APE1 redox regulatory activity includes modulation of the activity of a number of transcription factors, including those involved in proliferation, downregulation of apoptosis and angiogenesis. These findings suggest a role for APE1 redox function in tumourigenesis, cancer progression and treatment resistance (Bapat, Fishel, and Kelley 2008; Luo et al. 2008; Luo et al. 2010). A number of other roles have also been ascribed to APE1, including acetylation-mediated gene regulation, RNA quality control, and involvement in NK-cell-mediated killing. Further discussion is beyond the scope of this chapter, and is reviewed at length elsewhere (Kelley, Georgiadis, and Fishel 2011).

4. Functional preclinical studies of APE1

4.1 APE1 DNA repair activity is critical for cell viability

Complete absence of APE1 is associated with embryonic lethality in mice (Xanthoudakis et al. 1996; Ludwig et al. 1998; Meira et al. 2001). Expression of floxed human APE1 transgene in APE1$^{-/-}$ mouse models by Izumi *et al.* was unable to counter early embryonic loss, but did allow culture of viable nullizygous mouse embryonic fibroblasts (MEFs). Inactivation of transgenic APE1 rapidly induced apoptosis, which could be overcome by transient transfection with wild-type APE1, but not by mutants lacking either DNA repair or acetylation-mediated gene regulatory functions, suggesting the essentiality of both functions. Conversely, transfection with a Cys65Ser mutant reported to be deficient in redox activity was able to prevent apoptosis, suggesting nonessentiality of APE1 redox activity (Izumi et al. 2005). Similarly, knock-in of a cysteine-to-alanine point mutation at Cys64 (Cys65 in hAPE1) is non-lethal in murine models – although the mutation was found to be associated with normal Fos- and Jun-reducing activity, raising doubts regarding the redox role of Cys64 in mice (Ordway, Eberhart, and Curran 2003). Elsewhere, siRNA downregulation of APE1 has been demonstrated to be associated with sequelae of BER inhibition such as AP site accumulation and apoptosis, and can be reversed by yeast Apn1 expression, which lacks redox activity (Fung and Demple 2005). Taken together, these results demonstrate the essentiality of the APE1 DNA repair function, but not redox activity, in cell viability.

4.2 APE1 depletion hypersensitises cells to DNA base damage

Induction of apoptosis in response to APE1 downregulation has been confirmed in numerous cell types and *in vivo* in rats and mice (Robertson et al. 1997; Evans, Limp-Foster,

and Kelley 2000). However, response to knockdown may vary between cell types. In ovarian cancer cells, APE1 knockdown causes S phase prolongation rather than apoptosis, reflected in xenografts as a reduced tumour growth rate that is associated with impaired glucose metabolism suggestive of reduced cellular proliferation (Fishel et al. 2008). Heterozygosity for APE1 in mice is associated with hypersensitivity to oxidative stress (Meira et al. 2001). Antisense depletion of APE1 hypersensitises HeLa cells to the alkylating agent methyl methanesulphonate (MMS), H_2O_2, menadione and paraquat (Walker et al. 1994). Antisense APE1 downregulation also increases sensitivity of lung cancer cells to ionising radiation (Chen and Olkowski 1994), pancreatic cancer cells to gemcitabine (Lau et al. 2004), and glioma cells to MMS, temozolomide and nitrosurea (Ono et al. 1994; Silber et al. 2002). SiRNA-mediated APE1 downregulation enhances cytotoxicity to alkylating agents and hydrogen peroxide in osteosarcoma cells (Wang, Luo, and Kelley 2004), cisplatin in non-small cell lung cancer cells (Wang et al. 2009), and ionising radiation in glioma cells (Naidu et al. 2010). Double negative APE1 mutation expression is associated with enhanced cytotoxicity to antimetabolites and alkylating agents (McNeill et al. 2009). Downregulation of APE1 using an adenoviral vector in a colon cancer mouse model successfully reduced APE1 expression levels and was associated with an increased response to ionising radiation (Xiang et al. 2008). This evidence highlights the therapeutic potential of targeting APE1 with small molecular inhibitors to improve radio- and chemotherapeutic efficiency.

4.3 APE1 overexpression protects cells from DNA damage and is implicated in treatment resistance

Upregulation of APE1 has a protective effect against agents causing DNA damage. Transfection of hAPE1 into AP endonuclease-mutant *E. coli* and Apn1-deficient yeast restored resistance to the effects of DNA damaging agents (Robson and Hickson 1991; Demple, Herman, and Chen 1991; Wilson et al. 1995). Co-expression of hAPE1 as a chimeric protein with MGMT conferred resistance to hydrogen peroxide and MMS in AP endonuclease-deficient *E. coli*. Overexpression of the chimeric protein in HeLa cells had a similar protective effect (Hansen et al. 1998). In human teratocarcinoma cells (Robertson et al. 2001) and melanocytes (Yang et al. 2005), overexpression of APE1 conferred resistance of radiation and chemotherapy, although this effect was not replicated in cells from other mammalian species (Herring et al. 1999; Tomicic, Eschbach, and Kaina 1997). Modulation of APE1 activity may offer a strategy to improve treatment response in tumours with high levels of APE1 expression.

Chemotherapy agents can induce APE1 upregulation, contributing to treatment resistance. In non small cell lung cancer cells, cisplatin treatment induces a dose-dependent increase in APE1 expression. When APE1 is downregulated using antisense methods, cisplatin cytotoxicity is significantly increased (Wang et al. 2009), suggesting that combining inhibitors of APE1 with chemotherapeutic agents may overcome treatment resistance.

5. APE1 and human cancer

5.1 APE1 overexpression in human cancers

APE1 expression is cell cycle dependent, with highest levels not surprisingly seen during early and middle S-phase (Fung, Bennett, and Demple 2001). Immunohistochemical analysis of many human cancers has demonstrated elevated levels of APE1 (see table). For example, APE1 protein expression is increased in human gliomas, and is positively correlated with

AP endonuclease activity. AP endonuclease activity was also found to be positively correlated with tumour grade, and with the fraction of S-phase cells, suggesting that APE1 activity is related to level of proliferation (Bobola et al. 2001). APE1 is also elevated in prostate cancer, with immunohistochemical staining levels increasing from low in benign prostatic hypertrophy to intense in prostatic carcinoma (Kelley et al. 2001).

Tumour site	APE1 expression	Preclinical findings	Clinical findings
Breast [2]	Nuclear in normal Mixed localisation in ductal carcinoma *in situ*		Nuclear expression associated with negative lymph node status, low angiogenesis Asp148Glu associated with reduced rate of early radiotherapy toxicity
Cervical [3]	Overexpression with nuclear localisation		Increased expression associated with radioresistance
Colon [4]	Predominantly cytoplasmic	siRNA inhibition sensitises LOVO cells and xenografts to ionising radiation (IR)	
Head & neck [5]	Overexpression with nuclear, cytoplasmic, or mixed localisation		Overexpression associated with earlier relapse, reduced survival Nuclear localisation associated with nodal positivity, treatment resistance
Gastro-oesophageal[6]	Mixed or nuclear expression		Nuclear expression associated with poor survival Cytoplasmic expression associated with differentiation
Germ cell [7]	Overexpression with nuclear localisation	Overexpression confers bleomycin resistance	
Glio-blastoma [8]	APE1 overexpression	Upregulation by oxidative stress associated with resistance to MMS, temozolomide (TMZ), IR Antisense downregulation sensitises cells to TMZ siRNA, CRT0044876 and lucanthone sensitise cells to IR	

Table 1. Summary of preclinical and clinical evidence for APE1 as a predictive and prognostic biomarker

2 (Kakolyris et al. 1998; Chang-Claude, Poponda, et al. 2005; Andreassen et al. 2005; Andreassen et al. 2006)
3 (Xu et al. 1997; Herring et al. 1998)
4 (Kakolyris et al. 1997; Xiang et al. 2008)
5 (Koukourakis et al. 2001)
6 (Al-Attar et al. 2010)
7 (Robertson et al. 2001)
8 (Bobola et al. 2001; Silber et al. 2002; Naidu et al. 2010)

Tumour site	APE1 expression	Experimental findings	Clinical findings
Lung [9]	Overexpression with mixed localisation (nuclear in normal tissue)	APE1 upregulated by cisplatin treatment siRNA inhibition reduces cell growth and induces apoptosis	Asp148Glu associated with sensitivity to IR, improved response to chemo-radiotherapy Low expression associated with cisplatin sensitivity, improved survival Overexpression associated with chemoresistance
Medullo-blastoma [10]	Predominantly nuclear Increased in expression in women, younger patients	siRNA inhibition sensitises cells to carmustine and TMZ	Overexpression associated with early relapse
Melanoma[11]	Predominantly nuclear	Potential APE1 inhibitor resveratrol sensitises cells to dacarbazine	
Osteo-sarcoma [12]	Overexpression	Reduced HO5 cell viability following antisense depletion Antisense downregulation sensitises cells to MMS, H_2O_2, thiotepa, etoposide, IR	Overexpression associated with poor survival
Ovarian [13]	Nuclear/cytoplasmic	siRNA inhibition reduces SKOV-3x growth	Nuclear expression associated with poor survival
Pancreatico-biliary [14]	Nuclear localisation	APE1 upregulated by gemcitabine treatment Antisense downregulation sensitises cell to gemcitabine	Absence of cytoplasmic staining associated with high risk features
Prostate [15]	Increasing overexpression from benign prostatic hypertrophy to prostatic intraepithelial neoplasia to cancer Predominantly cytoplasmic		

Table 1. (cont.). Summary of preclinical and clinical evidence for APE1 as a predictive and prognostic biomarker5.4. APE1 polymorphisms and cancer susceptibility

9 (Hu et al. 2001; Su et al. 2007; Wang et al. 2009)
10 (Bobola et al. 2005)
11 (Yang et al. 2005)
12 (Wang, Luo, and Kelley 2004)
13 (Moore et al. 2000; Fishel et al. 2008; Al-Attar et al. 2010)
14 (Lau et al. 2004; Al-Attar et al. 2010)
15 (Kelley et al. 2001)

5.2 APE1 subcellular localisation in cancer

APE1 expression demonstrates complex and heterogenous localisation patterns that vary between tissue types. Nuclear localisation is common, and is thought to reflect functions in DNA repair. Cytoplasmic localisation is commonly seen in cell types exhibiting rapid metabolic or proliferative rates, particularly when under high oxidative stress. Cytoplasmic localisation is predominantly within the mitochondria and endoplasmic reticulum, in keeping with the role of mitochondria in cellular response to oxidative stress, and may relate to APE1's role in mitochondrial DNA repair and redox regulation of transcription factors (Tell et al. 2005). In non-small cell lung cancer, APE1 dysregulation is common, with upregulation in the cytoplasm contributing to global overexpression and associated with increased superoxide production and lipid peroxidation (Yoo et al. 2008).

Alterations in subcellular distribution of APE1 compared to normal tissue have been seen in a number of human tumours. Normal colorectal mucosa features nuclear staining in the less differentiated cells in the lower parts of the crypts, with cytoplasmic staining in the superficial epithelium. In both adenomas and carcinomas, subcellular restriction is lost and a mixed localisation pattern develops, with a predominance of cytoplasmic staining (Kakolyris et al. 1997). Increased cytoplasmic staining is also seen in thyroid (Tell et al. 2000), hepatocellular (Di Maso et al. 2007), epithelial ovarian (Moore et al. 2000) and prostate carcinomas (Kelley et al. 2001). In contrast, melanomas display an increased level of APE1 expression which is predominantly localised to the nucleus, compared to cytoplasmic staining in normal skin (Yang et al. 2005). Increased levels of APE1 expression with nuclear-specific localisation are also seen in cervical carcinomas (Xu et al. 1997), bladder cancers (Sak et al. 2005), rhabdomyosarcomas (Thomson et al. 2001), and squamous cell head and neck cancers (Koukourakis et al. 2001). Some tumour types have shown variance of APE1 localisation between studies. There is consensus regarding elevated levels of APE1 in non-small cell lung cancer, but different groups have found predominantly cytoplasmic (Wang et al. 2009) or nuclear (Puglisi et al. 2001; Kakolyris et al. 1999) localisation.

5.3 APE1 expression and localisation as a marker

Alterations in APE1 expression may be of prognostic significance. In non-small cell lung cancer, elevated APE1 expression is an independent poor prognostic factor, associated with reduced disease-free and overall survival (Puglisi et al. 2001). Similarly, elevated APE1 is suggestive of poor prognosis in medulloblastoma (Bobola et al. 2005), ovarian, gastro-oesophageal and pancreatico-biliary cancers (Al-Attar et al. 2010). Alterations in APE1 localisation may also be of prognostic significance. Breast cancers display heterogenous localisation, compared to predominantly nuclear distribution in normal breast tissue. Localisation appears to be correlated to patient outcomes, with nuclear localisation being associated with better prognostic features such as differentiation, reduced angiogenesis and negative lymph node status (Kakolyris et al. 1998; Puglisi et al. 2002). Similar prognostic correlations are also seen in osteosarcoma (Wang, Luo, and Kelley 2004), where cytoplasmic staining is associated with poor survival outcomes. Conversely, in ovarian and pancreatico-biliary cancers, nuclear APE1 expression is associated with aggressive tumour biology and poor overall survival (Al-Attar et al. 2010).

Preclinical evidence suggests that increased APE1 expression may be associated with chemo-and radio-resistance due to efficient repair of therapeutically-induced DNA damage. In tumour samples, APE1 expression levels and subcellular localisation patterns may therefore have potential as a predictive marker for response to treatment. In non-small cell

lung cancers, increased APE1 expression is associated with resistance to cisplatin (Wang et al. 2009), and in cervical cancers elevated expression correlates to radio-resistance (Herring et al. 1998). In germ cell tumours (Robertson et al. 2001) and medulloblastoma (Bobola et al. 2005), increased APE1 levels are associated with both chemo- and radio-resistance. Similarly, increased nuclear localisation of APE1 in head and neck cancers is associated with chemo-and radio-resistance (Koukourakis et al. 2001). In contrast, however, high levels of APE1 expression in bladder tumours are associated with radiosensitivity and improved survival rates (Sak et al. 2005). The authors hypothesise that this may be because repair of irradiation-induced base damage requires phosphodiester backbone cleavage as an intermediary step, leading to the increased acquisition of potentially lethal double strand breaks – hence, efficient BER may actually increase radiotherapy-induced lethality. Alternatively, increased APE1 redox activity might lead to an increased stress response and hence a greater response to radiotherapy. While further study is required to clearly elucidate the prognostic significance of APE1 expression in different tumour types, the current body of evidence suggests the potential of APE1 as a prognostic biomarker.

5.4 APE1 polymorphisms and cancer susceptibility

Polymorphic APE1 variants have been reported and correlated to cancer susceptibility. In an analysis of seven APE1 polymorphisms, reduced repair activity was noted in four (Hadi et al. 2000). In a Chinese study, a Thr141Gly promoter polymorphism was associated with reduced levels of APE1 mRNA in blood and lung tissue, possibly due to reduced affinity for Oct-1 transcription factor, thought to be activated by DNA damage. Homozygosity for the Gly allele was associated with a 40% reduction in lung cancer risk (Lu et al. 2009). Asp148Glu, a variant which exhibits normal repair activity, is associated with an increased risk of cancer development (Gu et al. 2009), including melanoma (Li et al. 2006), pancreatic (Li et al. 2007), cervical (Farkasova et al. 2008) and lung cancer susceptibility (Agachan et al. 2009). The Asp148Glu variant may also be associated with hypersensitivity to ionising radiation (Hu et al. 2001), although it has also been demonstrated to have a protective effect against acute radiation toxicity reactions in normal skin (Chang-Claude, Popanda, et al. 2005). Further study is required to further elucidate how APE1 polymorphisms might impact response to treatment.

5.5 APE1 as a predictive and prognostic biomarker

A growing body of evidence suggests that alterations in APE1 expression levels and subcellular localisation may have predictive or prognostic significance in many human cancers. Similarly, a number of APE1 single-nucleotide polymorphisms (SNPs) have been identified and correlated to APE1 activity and tumour risk. Recent patent applications have been filed to utilise tissue APE1 as a biomarker in lung, breast and ovarian cancers (Deutsch 2003; Hagmann et al. 2008). Incorporating biomarker studies into future clinical trials offers the opportunity to corroborate and expand upon current knowledge to develop APE1 as a clinically relevant biomarker.

6. Targeting APE1 for therapy

The early promise of PARP inhibitors highlights the potential of BER proteins as therapeutic targets (Lord and Ashworth 2008; Fong et al. 2009). PARP inhibitors have shown particular promise in the setting of BRCA-deficient breast cancers, highlighting an important

therapeutic concept that may be applicable to inhibitors of APE1. Synthetic lethality exploits inter-gene relationships where the loss of function of either of two related genes is non-lethal, but loss of both causes cell death. This offers the potential to specifically target cancer cells through inhibition of a gene known to be in a synthetic lethal relationship with a mutated tumour suppressor gene (Rehman, Lord, and Ashworth 2010). BRCA-1 and -2 have long been identified as tumour suppressors, being mutated in an inherited cancer predisposition that increases susceptibility to breast and ovarian tumours (Miki et al. 1994). Both gene products have a role in the homologous recombination (HR) DNA repair pathway, which repairs double strand DNA breaks (DSBs) (Venkitaraman 2002). A degree of redundancy exists between the BER and HR pathways, allowing cells to compensate for the loss of one pathway. The BER enzyme PARP1, which binds to single strand DNA breaks and recruits other repair proteins, can be successfully targeted for inhibition, leading to failure of the BER pathway, replication fork stalling, and acquisition of double strand breaks. In normal cells, these double strand breaks are repaired via HR. In BRCA-deficient cells, however, loss of effective HR leads to DSB persistence and cell death. As heterozygosity at a BRCA allele is associated with effective HR, PARP inhibition specifically targets only tumour cells with acquired BRCA$^{-/-}$ homozygosity (Bryant et al. 2005; Farmer et al. 2005). Phase I and II trials of PARP inhibitors have demonstrated favourable efficacy and limited toxicity in BRCA-related breast and ovarian cancers (reviewed in (Rehman, Lord, and Ashworth 2010)) and phase III trials are underway.

Other potential synthetic lethal relationships in PARP inhibition are currently being explored. 'BRCAness' refers to a subset of breast cancers, including 'triple negative' (oestrogen-, progesterone- and HER2-negative) and 'basal phenotype' cancers, that possess molecular and histopathological similarity to BRCA-deficient tumours, that may successfully be targeted by PARP inhibition (Turner, Tutt, and Ashworth 2004; Giorgetti et al. 2007). There is also developing interest in PTEN (phosphatase and tensin homolog), which is mutated in many sporadic cancers and, like BRCA mutations, causes a defect in homologous recombination (Shen et al. 2007; Mendes-Pereira et al. 2009).

Recent evidence suggests that other BER factors may also be targeted by a synthetic lethality approach. Mismatch repair (MMR) is responsible for the repair of DNA damage occurring during replication, and shares a degree of overlap with BER function. For example, 8-oxoguanine base lesions, which are induced by metabolic ROS and can cause mutagenic GC→TA transversions if unrepaired, may be processed by both BER and MMR. Mutations in the mismatch repair (MMR) genes *MLH1* or *MSH2* are implicated in human non-polyposis carcinoma coli (HNPCC) and some sporadic colorectal cancers. SiRNA inhibition of the BER constituent DNA polymerase β/γ is selectively lethal in MLH1/MSH2 mutant cell lines, suggesting a synthetic lethality relationship. Given the potential for BER inhibitors as a synthetic lethality target, it remains to be established if additional factors such as APE1 may have a role in this capacity.

7. APE1 inhibitors: Progress to date

7.1 APE1 DNA repair domain inhibitors

The first reported inhibitor of the APE1 repair domain, CRT0044876, was identified following high-throughput fluorescence-based screening of a small molecular chemical library. Applied alone, this compound increased the rate of AP site accumulation in tumour cell lines without evidence of intrinsic cytotoxicity. In combination with various base

damaging agents, including the alkylators MMS and temozolomide (TMZ), a synergistic increase in AP site accumulation was noted, associated with essentially complete (>99%) cell death. This effect was not replicated when the DNA damaging agents used induced damage repaired by mechanisms other than BER, suggesting BER-specific inhibition (Madhusudan et al. 2005). CRT0044876-induced BER inhibition has been reproduced elsewhere (Guikema et al. 2007; Seo and Kinsella 2009), including cytotoxicity potentiation with ionising radiation (Koll et al. 2008), although another group was not able to replicate potentiation (Fishel and Kelley 2007).

CRT0044876 contains an indole ring which is thought to interact with the APE1 active site, while the compound's carboxylate group coordinates towards the active site catalytic magnesium atom. Utilising knowledge gained from the identification and development of CRT0044876, molecular modelling techniques were utilised to design inhibitor templates to screen a computer database of 2.6m chemical compounds. Promising hits were chosen for their active site 'fit' and drug-like properties, then screened in the laboratory for specific inhibitory activity. A number of highly-potent, highly-specific non-competitive inhibitors of APE1 DNA repair were identified. Like CRT0044876, these compounds had low intrinsic toxicity, but are able to potentiate the cytotoxicity of alkylating agents in various cancer cell lines. Interestingly, the inhibitory effect was significantly increased in the Asp148Glu APE1 polymorph, previously implicated in cancer predisposition (see Section 5.4. APE1 polymorphisms and cancer susceptibility) (Mohammed et al. 2011).

A number of other groups have been working on the development of APE1 DNA repair inhibitors. Seiple et al. have identified the potential of arylstibonic acids, which possess inherent inhibitory activity on an initial fluorescence-based high-throughput screen (Seiple et al. 2008). Simeonov et al. utilised a similar fluorescence screening assay to identify three compounds (6-hydroxy-DL-DOPA, Reactive Blue 2 and myricetin) which potentiate MMS cytotoxicity in HeLa cells associated with a quantifiable increase in AP site accumulation. Modelling studies of 6-hydroxy-DL-DOPA suggest that it docks to the APE1 active site in a similar manner to CRT0044876 (Simeonov et al. 2009). Bapat *et al.* modified the previously-described fluorescence assay to identify the novel inhibitor AR02, which is able to selectively block APE1 DNA repair function in glioma cells and potentiate cytotoxicity of alkylating agents (Bapat et al. 2010). Zawahir et al. performed an *in silico* pharmacophore model-based screen to identify 21 potent and specific inhibitors. The most potent of the inhibitors identified to date share common features of two carboxylate groups arranged around a hydrophobic core, bearing structural similarity to the 3'- and 5'- deoxyribosephosphate groups on abasic DNA (Seiple et al. 2008; Zawahir et al. 2009).

The topoisomerase II inhibitor lucanthone has also been identified as a potential inhibitor of APE1 DNA repair activity, without impact on redox function (Bases and Mendez 1997; Luo and Kelley 2004). Lucanthone treatment in cell culture induces an increase in abasic site accumulation (Mendez, Goldman, and Bases 2002), and potentiates the cytotoxic effects of MMS and temozolomide (Luo and Kelley 2004). Clinically, lucanthone treatment accelerates regression of brain metastases following whole brain radiotherapy (Del Rowe et al. 1999). However, it is unclear whether this effect is mediated via APE1 inhibition, or as a function of lucanthone's effect on topoisomerase (Fishel and Kelley 2007).

Methoxyamine is a small molecular inhibitor of BER which irreversibly binds to abasic DNA sites, preventing processing by APE1 (Liu and Gerson 2004). Methoxyamine potentiates temozolomide *in vitro* (Taverna et al. 2001; Fishel et al. 2007) and in tumour xenografts (Liu,

Nakatsuru, and Gerson 2002; Yan et al. 2007). It also potentiates radiotherapy cytotoxicity in combination with the potent radiosensitiser 5-iodo-2′-deoxyuridine (Taverna et al. 2003). Methoxyamine has undergone phase I clinical trials in combination with pemetrexed (Anthony et al. 2009) and temozolomide (Sawides et al. 2010) in patients with advanced refractory cancer.

7.2 APE1 redox domain inhibitors

Through redox-mediated transcription factor activation, APE1 has cytoprotective and angiogenic influence in response to cellular stresses. The APE1 redox domain has therefore also been evaluated as a possible target for small molecule inhibition.

The naturally-occurring compound resveratrol, found in grapes and red wine, has been suggested as an inhibitor of tumourigenesis (Bhat and Pezzuto 2002; Aziz, Kumar, and Ahmad 2003). Computer modelling suggests it may bind the APE1 redox domain (Yang et al. 2005). Resveratrol exposure has been shown to inhibit activation of the APE-1 dependent antiapoptotic transcription factors activator protein-1 (AP-1) and nuclear factor kappa B (NFκB), and is also able to sensitise melanoma cells *in vitro* to dacarbazine treatment (Yang et al. 2005). However, these results have not been substantiated elsewhere (Fishel and Kelley 2007; Luo et al. 2008).

Soy isoflavanes are under investigation for a possible role in the treatment of prostate cancer. Prostate cell survival is significantly decreased when co-treated with soy isoflavanes in combination with radiation, compared to radiation alone. This is associated with downregulation in APE1 levels, and therefore a reduced level of NFκB and the proangiogenic transcription factor hypoxia-inducible factor 1α (HIF-1α) binding that may mediate the increase in radiosensitivity (Raffoul et al. 2007; Singh-Gupta et al. 2008). However, it is unclear how APE1 downregulation is mediated by soy isoflavanes, and whether associated downregulation of BER also has an impact on treatment sensitivity (Kelley, Georgiadis, and Fishel 2011).

APX3330 (also known as E3330) is a small molecule inhibitor of APE1 redox function. It specifically and selectively blocks APE1-mediated reduction of various transcription factors to their activated state (Zou and Maitra 2008; Luo et al. 2008; Zou et al. 2009; Nyland et al. 2010). APX3330 exposure has been demonstrated to reduce tumour cell growth (Saitou et al. 2005), migration (Zou and Maitra 2008) and angiogenesis (Zou et al. 2009). A number of APX3330 analogues with improved potency are currently under evaluation (Kelley, Georgiadis, and Fishel 2011).

7.3 APE1 inhibition and toxicity

Inhibition of APE1 offers exciting therapeutic potential. Given that APE1 is ubiquitously expressed in normal and malignant cells, concerns exist regarding the risk of inhibitor toxicity in normal tissue, particularly when used in combination with systemic chemotherapy treatments. This risk could be reduced by targeting inhibitor use in cancers with high levels of APE1 overexpression, or combining inhibitor use with targeted treatment such as radiotherapy. Long term toxicity is also of concern, as inhibition of APE1 in normal cells may result in propagation of potentially mutagenic DNA damage, leading to secondary malignancies. However, it is likely that the target population for APE1 inhibition will be patients with advanced cancer, where risk of secondary malignancy will not be of clinical significance (Abbotts and Madhusudan 2010).

8. Conclusion

Genomic integrity is constantly challenged by damage inflicted from a variety of endogenous and exogenous sources, including spontaneous deamination, reactive oxygen species, ionising radiation, ultraviolet light and chemical agents. Highly conserved pathways of DNA repair have evolved to maintain stability within the genome. Base excision repair (BER) processes and repairs damage to individual bases induced by alkylation, oxidation or ring saturation. Human apurinic/apyrimidinic endonuclease 1 (APE1) is a critical BER enzyme that recognises and processes the site of excised base damage (an 'abasic' site). APE1 is of considerable interest as a potential predictive and prognostic biomarker in cancer. Polymorphisms causing variable APE1 activity may alter cancer susceptibility and treatment response. High levels of oxidative stress in the tumour microenvironment may induce an increased rate of DNA damage acquisition, leading to an upregulation of BER that contributes to the dysregulation of APE1 expression commonly observed in solid tumours. Furthermore, APE1 expression is upregulated in response to treatment with DNA damaging agents such as chemotherapy and ionising radiation, and is frequently associated with resistance to treatment and poor prognostic outcomes. Further characterisation of APE1 polymorphisms and expression levels in human cancer will allow development of APE1 as a predictive and prognostic biomarker.

Preclinical study has confirmed APE1 as an emerging therapeutic target in cancer. Overexpression of APE1 is induced by DNA damaging agents and is associated with treatment resistance. Constitutional or engineered downregulation of APE1 confers sensitivity to treatment, and can overcome chemoresistance. A number of inhibitors of the APE1 DNA repair domain are currently under development, showing promise *in vitro* in their ability to potentiate the actions of agents causing alkylating or oxidation damage and overcome treatment resistance. Further development of these inhibitors into clinically-relevant compounds is an important and expanding area of cancer therapeutics.

9. References

Abbotts, R., and S. Madhusudan. 2010. Human AP endonuclease 1 (APE1): from mechanistic insights to druggable target in cancer. *Cancer Treat Rev* 36 (5):425-35.

Agachan, B., O. Kucukhuseyin, P. Aksoy, A. Turna, I. Yaylim, U. Gormus, A. Ergen, U. Zeybek, B. Dalan, and T. Isbir. 2009. Apurinic/apyrimidinic endonuclease (APE1) gene polymorphisms and lung cancer risk in relation to tobacco smoking. *Anticancer Res* 29 (6):2417-20.

Al-Attar, A., L. Gossage, K. R. Fareed, M. Shehata, M. Mohammed, A. M. Zaitoun, I. Soomro, D. N. Lobo, R. Abbotts, S. Chan, and S. Madhusudan. 2010. Human apurinic/apyrimidinic endonuclease (APE1) is a prognostic factor in ovarian, gastro-oesophageal and pancreatico-biliary cancers. *Br J Cancer* 102 (4):704-9.

Andreassen, C. N., J. Alsner, J. Overgaard, C. Herskind, J. Haviland, R. Owen, J. Homewood, J. Bliss, and J. Yarnold. 2005. TGFB1 polymorphisms are associated with risk of late normal tissue complications in the breast after radiotherapy for early breast cancer. *Radiotherapy and Oncology* 75 (1):18-21.

Andreassen, C. N., J. Alsner, M. Overgaard, F. B. Sorensen, and J. Overgaard. 2006. Risk of radiation-induced subcutaneous fibrosis in relation to single nucleotide

polymorphisms in TGFB1, SOD2, XRCC1, XRCC3, APEX and ATM--a study based on DNA from formalin fixed paraffin embedded tissue samples. *Int J Radiat Biol* 82 (8):577-86.

Anthony, S. P., L. S. Rosen, G. J. Weiss, M. S. Gordon, B. J. Adams, S. L. Gerson, D. Alvarez, C. P. Theuer, and B. R. Leigh. 2009. A phase I study of daily oral TRC102 (methoxyamine) to enhance the therapeutic effects of pemetrexed in patients with advanced refractory cancer. *J Clin Oncol (Meeting Abstracts)* 27 (15S):2552.

Atamna, H., I. Cheung, and B. N. Ames. 2000. A method for detecting abasic sites in living cells: age-dependent changes in base excision repair. *Proc Natl Acad Sci U S A* 97 (2):686-91.

Aziz, M. H., R. Kumar, and N. Ahmad. 2003. Cancer chemoprevention by resveratrol: in vitro and in vivo studies and the underlying mechanisms (review). *Int J Oncol* 23 (1):17-28.

Balakrishnan, L., P. D. Brandt, L. A. Lindsey-Boltz, A. Sancar, and R. A. Bambara. 2009. Long patch base excision repair proceeds via coordinated stimulation of the multienzyme DNA repair complex. *J Biol Chem* 284 (22):15158-72.

Bapat, A., M. Fishel, and M. R. Kelley. 2008. Going Ape as an Approach to Cancer Therapeutics. *Antioxid Redox Signal*.

Bapat, A., L. S. Glass, M. H. Luo, M. L. Fishel, E. C. Long, M. M. Georgiadis, and M. R. Kelley. 2010. Novel Small-Molecule Inhibitor of Apurinic/Apyrimidinic Endonuclease 1 Blocks Proliferation and Reduces Viability of Glioblastoma Cells. *Journal of Pharmacology and Experimental Therapeutics* 334 (3):988-998.

Barnes, D. E., and T. Lindahl. 2004. Repair and genetic consequences of endogenous DNA base damage in mammalian cells. *Annu Rev Genet* 38:445-76.

Bases, R. E., and F. Mendez. 1997. Topoisomerase inhibition by lucanthone, an adjuvant in radiation therapy. *Int J Radiat Oncol Biol Phys* 37 (5):1133-7.

Bhat, K. P., and J. M. Pezzuto. 2002. Cancer chemopreventive activity of resveratrol. *Ann N Y Acad Sci* 957:210-29.

Bobola, M. S., A. Blank, M. S. Berger, B. A. Stevens, and J. R. Silber. 2001. Apurinic/Apyrimidinic endonuclease activity is elevated in human adult gliomas. *Clin Cancer Res* 7 (11):3510-8.

Bobola, M. S., L. S. Finn, R. G. Ellenbogen, J. R. Geyer, M. S. Berger, J. M. Braga, E. H. Meade, M. E. Gross, and J. R. Silber. 2005. Apurinic/apyrimidinic endonuclease activity is associated with response to radiation and chemotherapy in medulloblastoma and primitive neuroectodermal tumors. *Clin Cancer Res* 11 (20):7405-14.

Bryant, H. E., N. Schultz, H. D. Thomas, K. M. Parker, D. Flower, E. Lopez, S. Kyle, M. Meuth, N. J. Curtin, and T. Helleday. 2005. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. *Nature* 434 (7035):913-7.

Burkovics, P., V. Szukacsov, I. Unk, and L. Haracska. 2006. Human Ape2 protein has a 3 '-5 ' exonuclease activity that acts preferentially on mismatched base pairs. *Nucleic Acids Research* 34 (9):2508-2515.

Chalmers, A. J. 2009. The potential role and application of PARP inhibitors in cancer treatment. *Br Med Bull* 89:23-40.

Chang-Claude, J., O. Popanda, X. L. Tan, S. Kropp, I. Helmbold, D. von Fournier, W. Haase, M. L. Sautter-Bihl, F. Wenz, P. Schmezer, and C. B. Ambrosone. 2005. Association between polymorphisms in the DNA repair genes, XRCC1, APE1, and XPD and

acute side effects of radiotherapy in breast cancer patients. *Clinical Cancer Research* 11 (13):4802-4809.

Chang-Claude, J., O. Poponda, X. L. Tan, D. von Fournier, W. Haase, M. L. Sautter-Bihl, F. Wenz, P. Schmezer, and C. Ambrosone. 2005. Effect of polymorphisms in the DNA repair genes XRCC1, APE1 and XPD on acute side effects of radiotherapy (RT) in breast cancer patients. *Strahlentherapie Und Onkologie* 181:94-95.

Chen, D. S., T. Herman, and B. Demple. 1991. Two distinct human DNA diesterases that hydrolyze 3'-blocking deoxyribose fragments from oxidized DNA. *Nucleic Acids Res* 19 (21):5907-14.

Chen, D. S., and Z. L. Olkowski. 1994. Biological responses of human apurinic endonuclease to radiation-induced DNA damage. *Ann N Y Acad Sci* 726:306-8.

Chou, K. M., and Y. C. Cheng. 2002. An exonucleolytic activity of human apurinic/apyrimidinic endonuclease on 3' mispaired DNA. *Nature* 415 (6872):655-9.

Chou, K. M., M. Kukhanova, and Y. C. Cheng. 2000. A novel action of human apurinic/apyrimidinic endonuclease: excision of L-configuration deoxyribonucleoside analogs from the 3' termini of DNA. *J Biol Chem* 275 (40): 31009-15.

D'Amours, D., S. Desnoyers, I. D'Silva, and G. G. Poirier. 1999. Poly(ADP-ribosyl)ation reactions in the regulation of nuclear functions. *Biochem J* 342 (Pt 2):249-68.

Del Rowe, J. D., J. Bello, R. Mitnick, B. Sood, C. Filippi, J. Moran, K. Freeman, F. Mendez, and R. Bases. 1999. Accelerated regression of brain metastases in patients receiving whole brain radiation and the topoisomerase II inhibitor, lucanthone. *Int J Radiat Oncol Biol Phys* 43 (1):89-93.

Demple, B., T. Herman, and D. S. Chen. 1991. Cloning and expression of APE, the cDNA encoding the major human apurinic endonuclease: definition of a family of DNA repair enzymes. *Proc Natl Acad Sci U S A* 88 (24):11450-4.

Deutsch, W. A. 2003. Marker for diagnosing breast cancers and ovarian cancers. US Pat. 20030286338.

Di Maso, V., C. Avellini, L. S. Croce, N. Rosso, F. Quadrifoglio, L. Cesaratto, E. Codarin, G. Bedogni, C. A. Beltrami, G. Tell, and C. Tiribelli. 2007. Subcellular localization of APE1/Ref-1 in human hepatocellular carcinoma: possible prognostic significance. *Mol Med* 13 (1-2):89-96.

Dianov, G., S. L. Allinson, H. Budworth, and K. M. Sleeth. 2003. Mammalian Base Excision Repair. In *Eukaryotic DNA Damage Surveillance and Repair*, edited by K. W. Caldecott: Kluwer Academic/Plenium Publishers.

Durkacz, B. W., O. Omidiji, D. A. Gray, and S. Shall. 1980. (ADP-ribose)n participates in DNA excision repair. *Nature* 283 (5747):593-6.

Evans, A. R., M. Limp-Foster, and M. R. Kelley. 2000. Going APE over ref-1. *Mutat Res* 461 (2):83-108.

Farkasova, T., S. Gurska, V. Witkovsky, and A. Gabelova. 2008. Significance of amino acid substitution variants of DNA repair genes in radiosusceptibility of cervical cancer patients; a pilot study. *Neoplasma* 55 (4):330-7.

Farmer, H., N. McCabe, C. J. Lord, A. N. J. Tutt, D. A. Johnson, T. B. Richardson, M. Santarosa, K. J. Dillon, I. Hickson, C. Knights, N. M. B. Martin, S. P. Jackson, G. C. M. Smith, and A. Ashworth. 2005. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature* 434 (7035):917-921.

Fishel, M. L., Y. He, A. M. Reed, H. Chin-Sinex, G. D. Hutchins, M. S. Mendonca, and M. R. Kelley. 2008. Knockdown of the DNA repair and redox signaling protein Ape1/Ref-1 blocks ovarian cancer cell and tumor growth. *DNA Repair (Amst)* 7 (2):177-86.

Fishel, M. L., Y. He, M. L. Smith, and M. R. Kelley. 2007. Manipulation of base excision repair to sensitize ovarian cancer cells to alkylating agent temozolomide. *Clin Cancer Res* 13 (1):260-7.

Fishel, M. L., and M. R. Kelley. 2007. The DNA base excision repair protein Ape1/Ref-1 as a therapeutic and chemopreventive target. *Mol Aspects Med* 28 (3-4):375-95.

Fong, P. C., D. S. Boss, T. A. Yap, A. Tutt, P. J. Wu, M. Mergui-Roelvink, P. Mortimer, H. Swaisland, A. Lau, M. J. O'Connor, A. Ashworth, J. Carmichael, S. B. Kaye, J. H. M. Schellens, and J. S. de Bono. 2009. Inhibition of Poly(ADP-Ribose) Polymerase in Tumors from BRCA Mutation Carriers. *New England Journal of Medicine* 361 (2):123-134.

Fortini, P., B. Pascucci, E. Parlanti, M. D'Errico, V. Simonelli, and E. Dogliotti. 2003. The base excision repair: mechanisms and its relevance for cancer susceptibility. *Biochimie* 85 (11):1053-71.

Frossi, B., G. Tell, P. Spessotto, A. Colombatti, G. Vitale, and C. Pucillo. 2002. H(2)O(2) induces translocation of APE/Ref-1 to mitochondria in the Raji B-cell line. *J Cell Physiol* 193 (2):180-6.

Fung, H., R. A. O. Bennett, and B. Demple. 2001. Key role of a downstream specificity protein 1 site in cell cycle-regulated transcription of the AP endonuclease gene APE1/APEX in NIH3T3 cells. *Journal of Biological Chemistry* 276 (45):42011-42017.

Fung, H., and B. Demple. 2005. A vital role for Ape1/Ref1 protein in repairing spontaneous DNA damage in human cells. *Mol Cell* 17 (3):463-70.

Giorgetti, G., E. Galizia, F. Bianchi, G. Piccinini, C. Loretelli, L. Belvederesi, R. Catalani, D. Gargliardini, C. Ferretti, F. Corradini, R. Bracci, A. Santinelli, and R. Cellerino. 2007. Brcaness phenotype and methylation of BRCA1 promoter in sporadic breast cancers. *Annals of Oncology* 18:52-52.

Gorman, M. A., S. Morera, D. G. Rothwell, E. de La Fortelle, C. D. Mol, J. A. Tainer, I. D. Hickson, and P. S. Freemont. 1997. The crystal structure of the human DNA repair endonuclease HAP1 suggests the recognition of extra-helical deoxyribose at DNA abasic sites. *Embo J* 16 (21):6548-58.

Gros, L., A. A. Ishchenko, H. Ide, R. H. Elder, and M. K. Saparbaev. 2004. The major human AP endonuclease (Ape1) is involved in the nucleotide incision repair pathway. *Nucleic Acids Res* 32 (1):73-81.

Gu, D. Y., M. L. Wang, M. M. Wang, Z. D. Zhang, and J. F. Chen. 2009. The DNA repair gene APE1 T1349G polymorphism and cancer risk: a meta-analysis of 27 case-control studies. *Mutagenesis* 24 (6):507-512.

Guikema, J. E., E. K. Linehan, D. Tsuchimoto, Y. Nakabeppu, P. R. Strauss, J. Stavnezer, and C. E. Schrader. 2007. APE1- and APE2-dependent DNA breaks in immunoglobulin class switch recombination. *J Exp Med* 204 (12):3017-26.

Hadi, M. Z., M. A. Coleman, K. Fidelis, H. W. Mohrenweiser, and Iii Dm Wilson. 2000. Functional characterization of Ape1 variants identified in the human population. *Nucleic Acids Res* 28 (20):3871-9.

Hadi, M. Z., K. Ginalski, L. H. Nguyen, and D. M. Wilson, 3rd. 2002. Determinants in nuclease specificity of Ape1 and Ape2, human homologues of Escherichia coli exonuclease III. *J Mol Biol* 316 (3):853-66.

Hadi, M. Z., and D. M. Wilson, 3rd. 2000. Second human protein with homology to the Escherichia coli abasic endonuclease exonuclease III. *Environ Mol Mutagen* 36 (4):312-24.

Hagmann, M-L., J. Karl, J. Kloeckner, M. Roessler, M. Tacke, and M. Theirolf. 2008. APEX as a marker for lung cancer. WIPO WO/2008/116592: F. Hoffmann-La Roche Ltd.

Hansen, W. K., W. A. Deutsch, A. Yacoub, Y. Xu, D. A. Williams, and M. R. Kelley. 1998. Creation of a fully functional human chimeric DNA repair protein. Combining O6-methylguanine DNA methyltransferase (MGMT) and AP endonuclease (APE/redox effector factor 1 (Ref 1)) DNA repair proteins. *J Biol Chem* 273 (2):756-62.

Helleday, T., E. Petermann, C. Lundin, B. Hodgson, and R. A. Sharma. 2008. DNA repair pathways as targets for cancer therapy. *Nat Rev Cancer* 8 (3):193-204.

Herring, C. J., B. Deans, R. H. Elder, J. A. Rafferty, J. MacKinnon, G. Barzilay, I. D. Hickson, J. H. Hendry, and G. P. Margison. 1999. Expression levels of the DNA repair enzyme HAP1 do not correlate with the radiosensitivities of human or HAP1-transfected rat cell lines. *Br J Cancer* 80 (7):940-5.

Herring, C. J., C. M. West, D. P. Wilks, S. E. Davidson, R. D. Hunter, P. Berry, G. Forster, J. MacKinnon, J. A. Rafferty, R. H. Elder, J. H. Hendry, and G. P. Margison. 1998. Levels of the DNA repair enzyme human apurinic/apyrimidinic endonuclease (APE1, APEX, Ref-1) are associated with the intrinsic radiosensitivity of cervical cancers. *Br J Cancer* 78 (9):1128-33.

Hu, J. J., T. R. Smith, M. S. Miller, H. W. Mohrenweiser, A. Golden, and L. D. Case. 2001. Amino acid substitution variants of APE1 and XRCC1 genes associated with ionizing radiation sensitivity. *Carcinogenesis* 22 (6):917-22.

Ishchenko, A. A., E. Deprez, A. Maksimenko, J. C. Brochon, P. Tauc, and M. K. Saparbaev. 2006. Uncoupling of the base excision and nucleotide incision repair pathways reveals their respective biological roles. *Proc Natl Acad Sci U S A* 103 (8):2564-9.

Izumi, T., D. B. Brown, C. V. Naidu, K. K. Bhakat, M. A. Macinnes, H. Saito, D. J. Chen, and S. Mitra. 2005. Two essential but distinct functions of the mammalian abasic endonuclease. *Proc Natl Acad Sci U S A* 102 (16):5739-43.

Izumi, T., L. R. Wiederhold, G. Roy, R. Roy, A. Jaiswal, K. K. Bhakat, S. Mitra, and T. K. Hazra. 2003. Mammalian DNA base excision repair proteins: their interactions and role in repair of oxidative DNA damage. *Toxicology* 193 (1-2):43-65.

Jones, C., and E. R. Plummer. 2008. PARP inhibitors and cancer therapy - early results and potential applications. *Br J Radiol* 81 Spec No 1:S2-5.

Kakolyris, S., A. Giatromanolaki, M. Koukourakis, L. Kaklamanis, P. Kanavaros, I. D. Hickson, G. Barzilay, V. Georgoulias, K. C. Gatter, and A. L. Harris. 1999. Nuclear localization of human AP endonuclease 1 (HAP1/Ref-1) associates with prognosis in early operable non-small cell lung cancer (NSCLC). *J Pathol* 189 (3):351-7.

Kakolyris, S., L. Kaklamanis, K. Engels, S. B. Fox, M. Taylor, I. D. Hickson, K. C. Gatter, and A. L. Harris. 1998. Human AP endonuclease 1 (HAP1) protein expression in breast cancer correlates with lymph node status and angiogenesis. *Br J Cancer* 77 (7):1169-73.

Kakolyris, S., L. Kaklamanis, K. Engels, H. Turley, I. D. Hickson, K. C. Gatter, and A. L. Harris. 1997. Human apurinic endonuclease 1 expression in a colorectal adenoma-carcinoma sequence. *Cancer Res* 57 (9):1794-7.

Kelley, M. R., L. Cheng, R. Foster, R. Tritt, J. Jiang, J. Broshears, and M. Koch. 2001. Elevated and altered expression of the multifunctional DNA base excision repair and redox enzyme Ape1/ref-1 in prostate cancer. *Clin Cancer Res* 7 (4):824-30.

Kelley, M. R., M. M. Georgiadis, and M. L. Fishel. 2011. APE/Ref-1 Role in Redox Signaling: Translational Applications of Targeting the Redox Function of the DNA Repair/Redox Protein APE1/Ref-1. *Current Molecular Pharmacology (under submission)*.

Koll, T. T., S. S. Feis, M. H. Wright, M. M. Teniola, M. M. Richardson, A. I. Robles, J. Bradsher, J. Capala, and L. Varticovski. 2008. HSP90 inhibitor, DMAG, synergizes with radiation of lung cancer cells by interfering with base excision and ATM-mediated DNA repair. *Mol Cancer Ther* 7 (7):1985-92.

Koukourakis, M. I., A. Giatromanolaki, S. Kakolyris, E. Sivridis, V. Georgoulias, G. Funtzilas, I. D. Hickson, K. C. Gatter, and A. L. Harris. 2001. Nuclear expression of human apurinic/apyrimidinic endonuclease (HAP1/Ref-1) in head-and-neck cancer is associated with resistance to chemoradiotherapy and poor outcome. *Int J Radiat Oncol Biol Phys* 50 (1):27-36.

Lau, J. P., K. L. Weatherdon, V. Skalski, and D. W. Hedley. 2004. Effects of gemcitabine on APE/ref-1 endonuclease activity in pancreatic cancer cells, and the therapeutic potential of antisense oligonucleotides. *Br J Cancer* 91 (6):1166-73.

Li, C., Z. Liu, L. E. Wang, S. S. Strom, J. E. Lee, J. E. Gershenwald, M. I. Ross, P. F. Mansfield, J. N. Cormier, V. G. Prieto, M. Duvic, E. A. Grimm, and Q. Wei. 2006. Genetic variants of the ADPRT, XRCC1 and APE1 genes and risk of cutaneous melanoma. *Carcinogenesis* 27 (9):1894-901.

Li, D. H., Y. N. Li, L. Jiao, D. Z. Chang, G. Beinart, R. A. Wolff, D. B. Evans, M. M. Hassan, and J. L. Abbruzzese. 2007. Effects of base excision repair gene polymorphisms on pancreatic cancer survival. *International Journal of Cancer* 120 (8):1748-1754.

Li, M. X., Z. Y. Zhong, J. W. Zhu, D. B. Xiang, N. Dai, X. J. Cao, Y. Qing, Z. Z. Yang, J. Y. Xie, Z. P. Li, L. Baugh, G. Wang, and D. Wang. 2010. Identification and Characterization of Mitochondrial Targeting Sequence of Human Apurinic/Apyrimidinic Endonuclease 1. *Journal of Biological Chemistry* 285 (20):14871-14881.

Lindahl, T. 1993. Instability and decay of the primary structure of DNA. *Nature* 362 (6422):709-15.

Lipton, A. S., R. W. Heck, S. Primak, D. R. McNeill, D. M. Wilson, 3rd, and P. D. Ellis. 2008. Characterization of Mg(2+) Binding to the DNA Repair Protein Apurinic/Apyrimidic Endonuclease 1 via Solid-State (25)Mg NMR Spectroscopy. *J Am Chem Soc*.

Liu, L., and S. L. Gerson. 2004. Therapeutic impact of methoxyamine: blocking repair of abasic sites in the base excision repair pathway. *Curr Opin Investig Drugs* 5 (6):623-7.

Liu, L., Y. Nakatsuru, and S. L. Gerson. 2002. Base excision repair as a therapeutic target in colon cancer. *Clin Cancer Res* 8 (9):2985-91.

Lord, C. J., and A. Ashworth. 2008. Targeted therapy for cancer using PARP inhibitors. *Current Opinion in Pharmacology* 8 (4):363-369.

Lu, J., S. Zhang, D. Chen, H. Wang, W. Wu, X. Wang, Y. Lei, J. Wang, J. Qian, W. Fan, Z. Hu, L. Jin, H. Shen, W. Huang, Q. Wei, and D. Lu. 2009. Functional characterization of a promoter polymorphism in APE1/Ref-1 that contributes to reduced lung cancer susceptibility. *FASEB J.*

Ludwig, D. L., M. A. MacInnes, Y. Takiguchi, P. E. Purtymun, M. Henrie, M. Flannery, J. Meneses, R. A. Pedersen, and D. J. Chen. 1998. A murine AP-endonuclease gene-targeted deficiency with post-implantation embryonic progression and ionizing radiation sensitivity. *Mutat Res* 409 (1):17-29.

Luo, M., S. Delaplane, A. Jiang, A. Reed, Y. He, M. Fishel, R. L. Nyland Ii, R. F. Borch, X. Qiao, M. M. Georgiadis, and M. R. Kelley. 2008. Role of the Multifunctional DNA Repair and Redox Signaling Protein Ape1/Ref-1 in Cancer and Endothelial Cells: Small-Molecule Inhibition of the Redox Function of Ape1. *Antioxid Redox Signal*.

Luo, M., H. He, M. R. Kelley, and M. M. Georgiadis. 2010. Redox regulation of DNA repair: implications for human health and cancer therapeutic development. *Antioxid Redox Signal* 12 (11):1247-69.

Luo, M., and M. R. Kelley. 2004. Inhibition of the human apurinic/apyrimidinic endonuclease (APE1) repair activity and sensitization of breast cancer cells to DNA alkylating agents with lucanthone. *Anticancer Res* 24 (4):2127-34.

Madhusudan, S., F. Smart, P. Shrimpton, J. L. Parsons, L. Gardiner, S. Houlbrook, D. C. Talbot, T. Hammonds, P. A. Freemont, M. J. Sternberg, G. L. Dianov, and I. D. Hickson. 2005. Isolation of a small molecule inhibitor of DNA base excision repair. *Nucleic Acids Res* 33 (15):4711-24.

McNeill, D. R., W. Lam, T. L. DeWeese, Y. C. Cheng, and D. M. Wilson, 3rd. 2009. Impairment of APE1 function enhances cellular sensitivity to clinically relevant alkylators and antimetabolites. *Mol Cancer Res* 7 (6):897-906.

Megnin-Chanet, F., M. A. Bollet, and J. Hall. 2010. Targeting poly(ADP-ribose) polymerase activity for cancer therapy. *Cell Mol Life Sci* 67 (21):3649-62.

Meira, L. B., S. Devaraj, G. E. Kisby, D. K. Burns, R. L. Daniel, R. E. Hammer, S. Grundy, I. Jialal, and E. C. Friedberg. 2001. Heterozygosity for the mouse Apex gene results in phenotypes associated with oxidative stress. *Cancer Res* 61 (14):5552-7.

Mendes-Pereira, A. M., S. A. Martin, R. Brough, A. McCarthy, J. R. Taylor, J. S. Kim, T. Waldman, C. J. Lord, and A. Ashworth. 2009. Synthetic lethal targeting of PTEN mutant cells with PARP inhibitors. *Embo Molecular Medicine* 1 (6-7):315-322.

Mendez, F., J. D. Goldman, and R. E. Bases. 2002. Abasic sites in DNA of HeLa cells induced by lucanthone. *Cancer Invest* 20 (7-8):983-91.

Miki, Y., J. Swensen, D. Shattuckeidens, P. A. Futreal, K. Harshman, S. Tavtigian, Q. Y. Liu, C. Cochran, L. M. Bennett, W. Ding, R. Bell, J. Rosenthal, C. Hussey, T. Tran, M. Mcclure, C. Frye, T. Hattier, R. Phelps, A. Haugenstrano, H. Katcher, K. Yakumo, Z. Gholami, D. Shaffer, S. Stone, S. Bayer, C. Wray, R. Bogden, P. Dayananth, J. Ward, P. Tonin, S. Narod, P. K. Bristow, F. H. Norris, L. Helvering, P. Morrison, P. Rosteck, M. Lai, J. C. Barrett, C. Lewis, S. Neuhausen, L. Cannonalbright, D. Goldgar, R. Wiseman, A. Kamb, and M. H. Skolnick. 1994. A Strong Candidate for the Breast and Ovarian-Cancer Susceptibility Gene Brca1. *Science* 266 (5182):66-71.

Mohammed, M. Z., V. N. Vyjayanti, C. A. Laughton, L. V. Dekker, P. M. Fischer, D. M. Wilson, 3rd, R. Abbotts, S. Shah, P. M. Patel, I. D. Hickson, and S. Madhusudan. 2011. Development and evaluation of human AP endonuclease inhibitors in melanoma and glioma cell lines. *Br J Cancer*.

Mol, C. D., T. Izumi, S. Mitra, and J. A. Tainer. 2000. DNA-bound structures and mutants reveal abasic DNA binding by APE1 and DNA repair coordination [corrected]. *Nature* 403 (6768):451-6.

Moore, D. H., H. Michael, R. Tritt, S. H. Parsons, and M. R. Kelley. 2000. Alterations in the expression of the DNA repair/redox enzyme APE/ref-1 in epithelial ovarian cancers. *Clin Cancer Res* 6 (2):602-9.

Naidu, M. D., J. M. Mason, R. V. Pica, H. Fung, and L. A. Pena. 2010. Radiation Resistance in Glioma Cells Determined by DNA Damage Repair Activity of Ape1/Ref-1. *Journal of Radiation Research* 51 (4):393-404.

Nakamura, J., and J. A. Swenberg. 1999. Endogenous apurinic/apyrimidinic sites in genomic DNA of mammalian tissues. *Cancer Res* 59 (11):2522-6.

Nilsen, H., and H. E. Krokan. 2001. Base excision repair in a network of defence and tolerance. *Carcinogenesis* 22 (7):987-98.

Nyland, R. L., M. H. Luo, M. R. Kelley, and R. F. Borch. 2010. Design and Synthesis of Novel Quinone Inhibitors Targeted to the Redox Function of Apurinic/Apyrimidinic Endonuclease 1/Redox Enhancing Factor-1 (Ape1/Ref-1). *Journal of Medicinal Chemistry* 53 (3):1200-1210.

O'Shaughnessy, J., C. Osborne, J. Pippen, M. Yoffe, D. Patt, G. Monaghan, C. Rocha, V. Ossovskaya, B. Sherman, and C. Bradley. 2009. Efficacy of BSI-201, a poly (ADP-ribose) polymerase-1 (PARP1) inhibitor, in combination with gemcitabine/carboplatin (G/C) in patients with metastatic triple-negative breast cancer (TNBC): Results of a randomized phase II trial. *J Clin Oncol* 27 (18 suppl):abstr 3.

Ono, Y., T. Furuta, T. Ohmoto, K. Akiyama, and S. Seki. 1994. Stable expression in rat glioma cells of sense and antisense nucleic acids to a human multifunctional DNA repair enzyme, APEX nuclease. *Mutat Res* 315 (1):55-63.

Ordway, J. M., D. Eberhart, and T. Curran. 2003. Cysteine 64 of Ref-1 is not essential for redox regulation of AP-1 DNA binding. *Mol Cell Biol* 23 (12):4257-66.

Parsons, J. L., Dianova, II, and G. L. Dianov. 2004. APE1 is the major 3'-phosphoglycolate activity in human cell extracts. *Nucleic Acids Res* 32 (12):3531-6.

Pascucci, B., M. Stucki, Z. O. Jonsson, E. Dogliotti, and U. Hubscher. 1999. Long patch base excision repair with purified human proteins. DNA ligase I as patch size mediator for DNA polymerases delta and epsilon. *J Biol Chem* 274 (47):33696-702.

Puglisi, F., G. Aprile, A. M. Minisini, F. Barbone, P. Cataldi, G. Tell, M. R. Kelley, G. Damante, C. A. Beltrami, and C. Di Loreto. 2001. Prognostic significance of Ape1/ref-1 subcellular localization in non-small cell lung carcinomas. *Anticancer Res* 21 (6A):4041-9.

Puglisi, F., F. Barbone, G. Tell, G. Aprile, B. Pertoldi, C. Raiti, M. R. Kelley, G. Damante, A. Sobrero, C. A. Beltrami, and C. Di Loreto. 2002. Prognostic role of Ape/Ref-1 subcellular expression in stage I-III breast carcinomas. *Oncol Rep* 9 (1):11-7.

Raffoul, J. J., S. Banerjee, V. Singh-Gupta, Z. E. Knoll, A. Fite, H. Zhang, J. Abrams, F. H. Sarkar, and G. G. Hillman. 2007. Down-regulation of apurinic/apyrimidinic

endonuclease 1/redox factor-1 expression by soy isoflavones enhances prostate cancer radiotherapy in vitro and in vivo. *Cancer Res* 67 (5):2141-9.

Rehman, F. L., C. J. Lord, and A. Ashworth. 2010. Synthetic lethal approaches to breast cancer therapy. *Nature Reviews Clinical Oncology* 7 (12):718-724.

Robertson, A. B., A. Klungland, T. Rognes, and I. Leiros. 2009. Base excision repair: the long and short of it. *Cellular and Molecular Life Sciences* 66:981-993.

Robertson, K. A., H. A. Bullock, Y. Xu, R. Tritt, E. Zimmerman, T. M. Ulbright, R. S. Foster, L. H. Einhorn, and M. R. Kelley. 2001. Altered expression of Ape1/ref-1 in germ cell tumors and overexpression in NT2 cells confers resistance to bleomycin and radiation. *Cancer Res* 61 (5):2220-5.

Robertson, K. A., D. P. Hill, Y. Xu, L. Liu, S. Van Epps, D. M. Hockenbery, J. R. Park, T. M. Wilson, and M. R. Kelley. 1997. Down-regulation of apurinic/apyrimidinic endonuclease expression is associated with the induction of apoptosis in differentiating myeloid leukemia cells. *Cell Growth Differ* 8 (4):443-9.

Robson, C. N., and I. D. Hickson. 1991. Isolation of cDNA clones encoding a human apurinic/apyrimidinic endonuclease that corrects DNA repair and mutagenesis defects in E. coli xth (exonuclease III) mutants. *Nucleic Acids Res* 19 (20):5519-23.

Robson, C. N., D. Hochhauser, R. Craig, K. Rack, V. J. Buckle, and I. D. Hickson. 1992. Structure of the human DNA repair gene HAP1 and its localisation to chromosome 14q 11.2-12. *Nucleic Acids Res* 20 (17):4417-21.

Saitou, Y., K. Shiraki, T. Yamanaka, K. Miyashita, T. Inoue, Y. Yamanaka, Y. Yamaguchi, N. Enokimura, N. Yamamoto, K. Itou, K. Sugimoto, and T. Nakano. 2005. Augmentation of tumor necrosis factor family-induced apoptosis by E3330 in human hepatocellular carcinoma cell lines via inhibition of NF kappa B. *World J Gastroenterol* 11 (40):6258-61.

Sak, S. C., P. Harnden, C. F. Johnston, A. B. Paul, and A. E. Kiltie. 2005. APE1 and XRCC1 protein expression levels predict cancer-specific survival following radical radiotherapy in bladder cancer. *Clin Cancer Res* 11 (17):6205-11.

Sancar, A., L. A. Lindsey-Boltz, K. Unsal-Kacmaz, and S. Linn. 2004. Molecular mechanisms of mammalian DNA repair and the DNA damage checkpoints. *Annu Rev Biochem* 73:39-85.

Sawides, P., Y. Xu, L. Liu, J. A. Bokar, P. Silverman, A. Dowlati, and S. L. Gerson. 2010. Pharmacokinetic profile of the base-excision repair inhibitor methoxyamine-HCl (TRC102; MX) given as an one-hour intravenous infusion with temozolomide (TMZ) in the first-in-human phase I clinical trial. *J Clin Oncol (Meeting Abstracts)* 28 (15S):e13662.

Seiple, L. A., J. H. Cardellina, 2nd, R. Akee, and J. T. Stivers. 2008. Potent inhibition of human apurinic/apyrimidinic endonuclease 1 by arylstibonic acids. *Mol Pharmacol* 73 (3):669-77.

Seo, Y. J., and T. J. Kinsella. 2009. Essential Role of DNA Base Excision Repair on Survival in an Acidic Tumor Microenvironment. *Cancer Research* 69 (18):7285-7293.

Shen, W. H., A. S. Balajee, J. L. Wang, H. Wu, C. Eng, P. P. Pandolfi, and Y. X. Yin. 2007. Essential role for nuclear PTEN in maintaining chromosomal integrity. *Cell* 128 (1):157-170.

Shokolenko, I., N. Venediktova, A. Bochkareva, G. L. Wilson, and M. F. Alexeyev. 2009. Oxidative stress induces degradation of mitochondrial DNA. *Nucleic Acids Research* 37 (8):2539-2548.

Silber, J. R., M. S. Bobola, A. Blank, K. D. Schoeler, P. D. Haroldson, M. B. Huynh, and D. D. Kolstoe. 2002. The apurinic/apyrimidinic endonuclease activity of Ape1/Ref-1 contributes to human glioma cell resistance to alkylating agents and is elevated by oxidative stress. *Clin Cancer Res* 8 (9):3008-18.

Simeonov, A., A. Kulkarni, D. Dorjsuren, A. Jadhav, M. Shen, D. R. McNeill, C. P. Austin, and D. M. Wilson, 3rd. 2009. Identification and characterization of inhibitors of human apurinic/apyrimidinic endonuclease APE1. *PLoS One* 4 (6):e5740.

Singh-Gupta, V., H. Zhang, S. Banerjee, D. Kong, J. J. Raffoul, F. H. Sarkar, and G. G. Hillman. 2008. Radiation-induced HIF-1alpha cell survival pathway is inhibited by soy isoflavones in prostate cancer cells. *Int J Cancer*.

Su, D., S. Ma, P. Liu, Z. Jiang, W. Lv, Y. Zhang, Q. Deng, S. Smith, and H. Yu. 2007. Genetic polymorphisms and treatment response in advanced non-small cell lung cancer. *Lung Cancer* 56 (2):281-8.

Sweasy, J. B., T. Lang, and D. DiMaio. 2006. Is base excision repair a tumor suppressor mechanism? *Cell Cycle* 5 (3):250-9.

Taverna, P., H. S. Hwang, J. E. Schupp, T. Radivoyevitch, N. N. Session, G. Reddy, D. A. Zarling, and T. J. Kinsella. 2003. Inhibition of base excision repair potentiates iododeoxyuridine-induced cytotoxicity and radiosensitization. *Cancer Res* 63 (4):838-46.

Taverna, P., L. Liu, H. S. Hwang, A. J. Hanson, T. J. Kinsella, and S. L. Gerson. 2001. Methoxyamine potentiates DNA single strand breaks and double strand breaks induced by temozolomide in colon cancer cells. *Mutat Res* 485 (4):269-81.

Tell, G., G. Damante, D. Caldwell, and M. R. Kelley. 2005. The Intracellular Localization of APE1/Ref-1: More than a Passive Phenomenon? *Antioxid Redox Signal* 7 (3-4):367-84.

Tell, G., L. Pellizzari, C. Pucillo, F. Puglisi, D. Cesselli, M. R. Kelley, C. Di Loreto, and G. Damante. 2000. TSH controls Ref-1 nuclear translocation in thyroid cells. *J Mol Endocrinol* 24 (3):383-90.

Thomson, B., R. Tritt, M. Davis, and M. R. Kelley. 2001. Histology-specific expression of a DNA repair protein in pediatric rhabdomyosarcomas. *J Pediatr Hematol Oncol* 23 (4):234-9.

Tomicic, M., E. Eschbach, and B. Kaina. 1997. Expression of yeast but not human apurinic/apyrimidinic endonuclease renders Chinese hamster cells more resistant to DNA damaging agents. *Mutat Res* 383 (2):155-65.

Turner, N., A. Tutt, and A. Ashworth. 2004. Hallmarks of 'BRCAness' in sporadic cancers. *Nature Reviews Cancer* 4 (10):814-819.

Venkitaraman, A. R. 2002. Cancer susceptibility and the functions of BRCA1 and BRCA2. *Cell* 108 (2):171-82.

Walker, L. J., R. B. Craig, A. L. Harris, and I. D. Hickson. 1994. A role for the human DNA repair enzyme HAP1 in cellular protection against DNA damaging agents and hypoxic stress. *Nucleic Acids Res* 22 (23):4884-9.

Wang, D., M. Luo, and M. R. Kelley. 2004. Human apurinic endonuclease 1 (APE1) expression and prognostic significance in osteosarcoma: enhanced sensitivity of

osteosarcoma to DNA damaging agents using silencing RNA APE1 expression inhibition. *Mol Cancer Ther* 3 (6):679-86.

Wang, D., D. B. Xiang, X. Q. Yang, L. S. Chen, M. X. Li, Z. Y. Zhong, and Y. S. Zhang. 2009. APE1 overexpression is associated with cisplatin resistance in non-small cell lung cancer and targeted inhibition of APE1 enhances the activity of cisplatin in A549 cells. *Lung Cancer*.

Wiederhold, L., J. B. Leppard, P. Kedar, F. Karimi-Busheri, A. Rasouli-Nia, M. Weinfeld, A. E. Tomkinson, T. Izumi, R. Prasad, S. H. Wilson, S. Mitra, and T. K. Hazra. 2004. AP Endonuclease-Independent DNA Base Excision Repair in Human Cells. *Mol Cell* 15 (2):209-20.

Wilson, D. M., 3rd. 2003. Properties of and substrate determinants for the exonuclease activity of human apurinic endonuclease Ape1. *J Mol Biol* 330 (5):1027-37.

Wilson, D. M., 3rd, R. A. Bennett, J. C. Marquis, P. Ansari, and B. Demple. 1995. Trans-complementation by human apurinic endonuclease (Ape) of hypersensitivity to DNA damage and spontaneous mutator phenotype in apn1-yeast. *Nucleic Acids Res* 23 (24):5027-33.

Xanthoudakis, S., R. J. Smeyne, J. D. Wallace, and T. Curran. 1996. The redox/DNA repair protein, Ref-1, is essential for early embryonic development in mice. *Proc Natl Acad Sci U S A* 93 (17):8919-23.

Xiang, D. B., Z. T. Chen, D. Wang, M. X. Li, J. Y. Xie, Y. S. Zhang, Y. Qing, Z. P. Li, and J. Xie. 2008. Chimeric adenoviral vector Ad5/F35-mediated APE1 siRNA enhances sensitivity of human colorectal cancer cells to radiotherapy in vitro and in vivo. *Cancer Gene Ther*.

Xu, Y., D. H. Moore, J. Broshears, L. Liu, T. M. Wilson, and M. R. Kelley. 1997. The apurinic/apyrimidinic endonuclease (APE/ref-1) DNA repair enzyme is elevated in premalignant and malignant cervical cancer. *Anticancer Res* 17 (5B):3713-19.

Yan, L., A. Bulgar, Y. L. Miao, V. Mahajan, J. R. Donze, S. L. Gerson, and L. L. Liu. 2007. Combined treatment with temozolomide and methoxyamine: Blocking apurininc/pyrimidinic site repair coupled with targeting topoisomerase II alpha. *Clinical Cancer Research* 13 (5):1532-1539.

Yang, S., K. Irani, S. E. Heffron, F. Jurnak, and F. L. Meyskens, Jr. 2005. Alterations in the expression of the apurinic/apyrimidinic endonuclease-1/redox factor-1 (APE/Ref-1) in human melanoma and identification of the therapeutic potential of resveratrol as an APE/Ref-1 inhibitor. *Mol Cancer Ther* 4 (12):1923-35.

Yoo, D. G., Y. J. Song, E. J. Cho, S. K. Lee, J. B. Park, J. H. Yu, S. P. Lim, J. M. Kim, and B. H. Jeon. 2008. Alteration of APEI/ref-1 expression in non-small cell lung cancer: The implications of impaired extracellular superoxide dismutase and catalase antioxidant systems. *Lung Cancer* 60 (2):277-284.

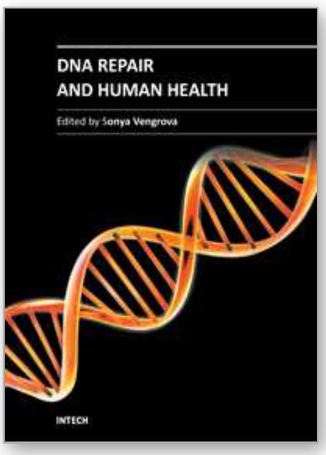
Zawahir, Z., R. Dayam, J. Deng, C. Pereira, and N. Neamati. 2009. Pharmacophore guided discovery of small-molecule human apurinic/apyrimidinic endonuclease 1 inhibitors. *J Med Chem* 52 (1):20-32.

Zou, G. M., C. Karikari, Y. Kabe, H. Handa, R. A. Anders, and A. Maitra. 2009. The Ape-1/Ref-1 redox antagonist E3330 inhibits the growth of tumor endothelium and endothelial progenitor cells: therapeutic implications in tumor angiogenesis. *J Cell Physiol* 219 (1):209-18.

Zou, G. M., and A. Maitra. 2008. Small-molecule inhibitor of the AP endonuclease 1/REF-1 E3330 inhibits pancreatic cancer cell growth and migration. *Mol Cancer Ther* 7 (7):2012-21.

IntechOpen

IntechOpen



DNA Repair and Human Health

Edited by Dr. Sonya Vengrova

ISBN 978-953-307-612-6
Hard cover, 792 pages
Publisher InTech
Published online 26, October, 2011
Published in print edition October, 2011

Over the past decades, great advances have been made in understanding the cellular DNA repair pathways. At the same time, a wealth of descriptive knowledge of human diseases has been accumulated. Now, the basic research of the mechanisms of DNA repair is merging with clinical research, placing the action of the DNA repair pathways in the context of the whole organism. Such integrative approach enables understanding of the disease mechanisms and is invaluable in improving diagnostics and prevention, as well as designing better therapies. This book highlights the central role of DNA repair in human health and well-being. The reviews presented here, contain detailed descriptions of DNA repair pathways, as well as analysis of a large body of evidence addressing links between DNA damage repair and human health. They will be of interest to a broad audience, from molecular biologists working on DNA repair in any model system, to medical researchers.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Rachel M. Abbotts, Christina Perry and Srinivasan Madhusudan (2011). Human Apurinic/Apyrimidinic Endonuclease is a Novel Drug Target in Cancer, DNA Repair and Human Health, Dr. Sonya Vengrova (Ed.), ISBN: 978-953-307-612-6, InTech, Available from: http://www.intechopen.com/books/dna-repair-and-human-health/human-apurinic-apyrimidinic-endonuclease-is-a-novel-drug-target-in-cancer

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2011 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the Creative Commons Attribution 3.0 License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen