·Review·

Anticancer clinical utility of the apurinic/apyrimidinic endonuclease/redox factor-1 (APE/Ref-1)

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[**Abstract**] Apurinic/apyrimidinic endonuclease/redox factor-1 (APE/Ref-1), as a type of multifunctional protein, plays an essential role in the base excision repair (BER) pathway, which is responsible for the repair of DNA caused by oxidative and alkylation damage. As importantly, APE/Ref-1 also functions as a redox factor maintaining transcription factors in an active reduced state. APE/Ref-1 stimulates the DNA-binding activity of numerous transcription factors that are involved in cancer promotion and progression, such as AP-1 (Fos/Jun), NF-κB, HIF-1α, p53, and others. Based on the structures and functions of APE1/Ref-1, we will provide an overview of its activities and explore the budding clinical use of this protein as a target in cancer treatment, and propose that APE/Ref-1 has a great potential for application in clinical research.

Key words: Apurinic/apyrimidinic endonuclease; neoplasm; gene therapy

Apurinic/apyrimidinic endonuclease (APE), also known as redox factor 1 (Ref-1), is a good example of a macromolecular multifunctional protein, with most of the characteristic structures and functions that have been identified so far. It is involved in numerous critical cell responses, including tumor occurrence and development, oxidative stress, cell cycle regulation, and apoptosis. An increasing number of studies suggest that, not only is APE/Ref-1 related to the occurrence, development, and prognosis of various tumors, but it is also linked to the sensitivity to radiotherapy and chemotherapy in a good number of tumors. Herein we summarize the research progress regarding APE/Ref-1 in the treatment and diagnosis of patients with cancer.

General features of APE/Ref-1

Structures of APE/Ref-1

The APE/Ref-1 gene is localized on chromosome 14 (14q11.2–12), with a full length of 216 kb for the transcriptional region. It consists of five extrons, four introns, and one open reading frame. Human APE/Ref-1 cDNA is about 1441 nucleotides and encompasses 205 nucleotides in the 5' translated region, 954 in the encoding region, 216 in the 3' non-translated region and a poly (A) tail. The encoding region encodes the APE/Ref-1 protein that contains 318 amino acids[1]. Based on its homogeneity to the endonuclease in E. coli, APE/Ref-1 can be classified into two families: exonuclease III (xth) family and endonuclease IV (nfo) family. The exonuclease III family includes exonuclease III (E. coli), APEX (mouse), rAPE (rat), BAP1 (bovine), and APE1/Ref-1 or hAPE (human). The endonuclease IV family includes endonuclease III (E. coli) and CeApn1 (gongylonema pulchrum). The human APE gene is highly homogeneous to that in mammals, with similar structures.

The APE/Ref-1 protein consists of 318 amino acid residues, resulting in a molecular weight of 36.5 ku (human APE). It has a spatial configuration of a 4-layer α /β sandwich, which is mainly constituted by two overlapping functional domains at the N- and C-terminals[1]. The domain in the N-terminal, which is a flexible region with irregular structures containing 43–93 amino acid residues, is mainly responsible for the regulation of oxidation and reduction. Whereas the domain on the C-terminal, as a tightly packed globular nuclease domain that includes 61-80 amino acid residues, is mainly responsible for DNA repair as endonuclease. The nuclease domain is homogeneous not only to the ExoIII but also to DNase I, which acts as an endonuclease[2]. Also within the N-terminal is a nuclear localization signal or sequence (NLS). The N-terminal domain of APE/Ref-1 is responsible for the redox function, while the terminal provides DNA-repair functions.

Functions of APE/Ref-1

APE/Ref-1: DNA repair activity The apurinic/apyrimidinic (AP) site is one of the most common kinds of DNA damage, which is caused by the hydrolyzation of the N-glycosidic bond that ligases DNA base to deoxyribose as a result of spontaneous hydrolysis

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and oxidative stress. The AP site hinders DNA replication and gives rise to gene mutation and genetic instability, and is thus highly cytotoxic and mutagenic to the cells[3]. The AP site is mainly repaired by base excision repair pathway, which is initiated by APE/Ref-1. APE/Ref-1 is the only bifunctional enzyme with DNA AP site repair activity in human cells. Its repairing activity protects cells from the cytotoxicity caused by the continuously accumulating exogenous and endogenous AP site mutation.

This is how APE/Ref-1 is involved in base excision repair (BER): first, DNA glycosidase recognizes the damaged base, hydrolyzes the N-glycosidic bond, and excising a specific modified base. At this time, the DNA backbone is intact, but one base of the single strand is missing, resulting in a 'void', that is, the AP site. Then, a specific AP endonuclease (APE) recognizes the AP site and exerts its endonuclease activity by excising the 5'-phosphodiester bond, or allows exonuclease to catalyze to 5'→ 3' degeneration on the residue. In this process, DNA polymerase-beta (Pol β) is involved in the excision reaction. Finally, DNA polymerase, ligase, and XRCC1 (X-ray repair complementing repair 1) fill in the void and constitute an intact DNA strand[4]. In addition, studies have also shown that APE/Ref-1 is coordinates BER pathway by interacting with downstream BER proteins, such as accompanying the initial damaged base excision as catalyzed by DNA transglycosylase and the repair and synthesis catalyzed by Pol β, and is possibly involved in subsequent steps of the repair process[2].

Besides AP endonuclease activity, APE/Ref-1 also shows 3'-diesterase or phosphodiesterase activity, which, however, is 200 times lower than its AP endonuclease activity[5]. The diesterase activity of APE/Ref-1 has important role in repairing the DNA damage resulting from radiation;alternatively,by acting as a 3'-phosphoesterase, APE/Ref-1 initiates repair of DNA strand breaks with 3'-blocking damage, which are produced by reactive oxygen species (ROS)[6]. Moreover, APE/Ref-1 also provides 3'-5' exonuclease activity which plays important roles in the excision of deoxyribonucleoside analogues from DNA[7]. The inhibition of this activity may be helpful in treating tumors with nucleoside analogues, such as gemcitabine. Other studies have also found that APE/Ref-1 is involved in nucleotide excision repair (NER). The mechanism underlying NER may be that APE/Ref-1 excises the 5'-terminal of the damaged ribose sugar-phosphate backbone and causes a break that generates 3'-OH and 5'-phosphate bonds, and thus provides substrates for FEN-1 [8]. Other studies also suggest that APE may be the endonuclease that exerts a proofreading mechanism in NER and therefore improves the accuracy of NER repair and synthesis[7].

APE/Ref-1: redox activity As a protein with reduction activities, APE/Ref-1 keeps numerous transcription factors in an active reductive state. Studies have shown that APE/Ref-1 is involved in regulating gene expression and facilitating their DNA binding activity by maintaining the reductive state of a highly conservative cysteine residue in the DNA binding domain of transcriptional factors[9]. Besides regulating phosphorylation, many transcriptional factors are also subject to the regulation of oxidation and reduction. Some transcriptional factors have to maintain their activity by keeping the reductive state of the amino acid residues in some critical sites. A large number of studies have demonstrated that APE1/Ref-1 acts as a genetic on-off switch by altering the oxidation-reduction state of cysteine in these sites. Transcriptional factors that are subject to reductive regulation by APE/Ref-1 include members of c-Fos and c-Jun families, such as AP-1 (activator protein 1), NF-κB, c-Myb, ATF/CREB, Egr-1 (early growth response-1), Pax5, p53, and PEBP2[10]. The binding capacity of these transcriptional factors to DNA is dependent on their DNA-binding domains or the oxidation-reduction state of the specific cysteine residues around the regulating domains. APE/Ref-1 modifies the DNA-binding capacity of transcriptional factors by regulating the oxidation-reduction state of their cysteine residues and is therefore indirectly involved in regulating gene expression. Transcriptional factors that are subject to APE/Ref-1 regulation are related to many important processes, including cell growth and proliferation, differentiation, cell cycle, and apoptosis. Recently, Georgiadis *et al.*[11] performed an overall analysis on seven cysteine residues in APE/Ref-1 and found that Cys 65 was a cysteine residue seen only in mammals and was critical in its oxidation-reduction activity. Luo *et al.*[12] reported that the oxidation-reduction activity was completely gone when Cys 65 mutates to alanine.

APE/Ref-1 in relation to cell apoptosis Many studies have suggested that APE/Ref-1 is closely related to cell apoptosis. It was found that APE-Ref-1 transcriptional activity and nuclear immunoreactivity gradually decreased before a DNA fragmentation. In mouse brain-injury models established by transient focal cerelbral ischemia, decreased immunoreactivity of APE/Ref-1 was seen at a few hours before TUNEL positive stained cells appeared. When decreased immunoreactivity of APE/Ref-1 expands from the central region to the surrounding area in a much similar manner to apoptosis, the scope of the damage expands as well[13]. Hall *et al.*[14] have demonstrated that upregulation of APE/Ref-1 promotes endothelial cell survival in response to hypoxia and TNF through NF-κB-independent and NF-κB-dependent signaling cascades, respectively. Demple *et al.*[15] used an RNA-interference technology to knock-down the APE expression in mammalian cells and found that the suppression for APE/Ref-1 causes arrest of cell proliferation arrest and activation of apoptosis in various tumor cell types. When cells were transfected with a homogeneous yeast protein Apn1, which has similar repair activities to APE, such effect could be reversed. This further illustrates that the repair activity of APE has a critical effect on cell proliferation and apoptosis.

Regulation of APE/Ref-1 expression

APE/Ref-1 expression is regulated at both the transcriptional level and post-transcriptional level. APE/Ref-1 contains a number of potential sites for phosphorylation sites including consensus sequences for casein kinase I and II and protein kinase C. On the post-translational level, APE/Ref-1 is mainly regulated by phosphorylation and redox modification.

In vivo and in vitro studies reveal that many genotoxic exposures, such as ionizing radiation, UV radiation, chemotherapeutic agents, and oxidative agents produced ROS in

intracellular environments, initiate DNA base oxidation and hydrolyzation and DNA strand breakage, resulting in increase of APE/Ref-1 expression [16,17]. Further investigations have found that induced APE/Ref-1 expression in cells can increase their resistance to H_2O_2, bleomycin, and radiation. On the other hand, cell vitality decreased when such expression is inhibited. ROS induces APE/Ref-1 protein expression by two steps: first, it induces the transfer of cytoplasm into the nucleus, which can take different amounts of time in different tissues; the second step is to initiate protein resynthesis by transcriptional activation of the promoter[18].

Some evidence suggests that the oxidation-reduction activity of APE/Ref-1 is regulated by the phosphorylation of specific sites as catalyzed by protein kinase C (PKC). When treated by oxidizing agents (hypochlorite) and methyl methanesulfanate, human leukemic cells responded with an increase in redox activity by APE/Ref-1 that also involved an increased PKC activity and a corresponding increase in the phosphorylation of APE, but DNA repair activity of APE/Ref-1 was not impacted. This finding indicates that the redox function of APE/Ref-1 is dependent on PKC phosphorylation when treated by DNA damaging agents. It is assumed that APE/Ref-1 phosphorylation level determines whether APE/Ref-1 exerts either repair activity or oxidation-reduction activity. Furthermore, APE/Ref-1 phosphorylation may have played a certain role in the APE1 transfer into the cell nucleus[19].

APE/Ref-1is down-regulated by its own product, thus constituting an autoregulatory functional loop. So far, it is the only known repair enzyme with self-regulation. There are some negative regulating elements in the upstream of the APE-Ref-1 promoter, including one negative calcium-responsive element A (nCaRE) and two negative calcium-responsive element B sequences (nCaRE-B1 and B2). As a negative transcription regulating factor, APE/Ref-1 interacts with negative calcium-responsive element binding protein (nCaREP) and binds to its own nCaRE, thereby inhibiting and regulating its gene expression[20].

Current understandings on APE/Ref-1 in the field of oncology

APE/Ref-1 expression in precancerous lesions and cancer tissue and its implication

First, increased hAPE1 (human apurinic/apyrimidinic endonuclease 1) expression and altered subcellular localization can be seen in various tumor tissue, including colorectal, non-small cell lung, hepatic, glioma and head-and-neck squamous cell cancers, and are related to tumor occurrence and development[21-27]. Take colorectal cancer as an example. In normal colonic mucosa, the predominant staining of hAPE1 nuclear in the less differentiated cells located at the lower part of the cryst, but it was cytoplasmic in the more differentiated superficial colonic epithelium. In adenoma and cancer, the intranuclear limited distribution disappears and is replaced by co-distribution in the nucleus and the cytoplasm, more prominently in the cytoplasm[27]. In addition, large amounts of clinical data have show n that the level of expression and subcellular localization of hAPE1 are related to the clinical staging, pathologic classification, lymph node metastasis, and poor prognosis in various tumors including breast, cervical, colorectal, and hepatic cancers and osteosarcoma[21,23,25,28-31]. In breast cancer and head-and-neck tumors, hAPE1 expression can be distributed in the nucleus, the cytoplasm, or both, while it is only localized in the nucleus in normal tissue. Such particular distribution patterns are closely related to the invasiveness and prognosis of the tumors. Nuclear distribution is always associated with better prognosis, such as higher levels of differentiation, less vascularization, and absent lymph node metastasis. Cytoplasmic and intranuclear/cytoplasmic staining, on the other hand, is linked to poor prognosis, such as tumor angiogenesis with concomitant positive lymph nodes and p53. Some data also suggest that high levels of hAPE1 expression are associated with shortened times to recurrence and tumor vascularization[26,30,31].

APE/Ref-1 polymorphism in relation to tumors

The investigation into the relationship between APE/Ref-1 SNP and tumors has just gotten started. Japanese scientists Shinmura *et al*[32]. have identified two mutants I64V and D148E in primary lung cancer. Pieretti *et al.*[33] detected two mutants Q51H and D148E in both ovarian and endometrial cancers. The distribution of the APE1 gene SNP seen in Chinese patients with colorectal cancer is similar to that in the study by Shinmura *et al*. D148E can be found in different populations and different types of tumors. As a commonly seen polymorphism, D148E is located in the DNA repair region of the APE1 gene. 148Glu occurs with high frequency in different populations, therefore the investigation into the function of this mutant is of great significance. In vitro studies have found no difference in terms of the activity between 148Glu and its wild-type counterpart. Whereas Hu *et al.*[34] used in-vitro cultured peripheral leukocytes and found that the 148Glu homozygote has significantly elevated sensitivity to ionic irradiation as compared to its wild-type and heterozygotic counterparts.

In recent years, increasing evidence suggests that the APE/Ref-1 polymorphic changes and some genotypes signal the genetic changes in its DNA repair function and are related to tumor occurrence and development and the response to radiotherapy and chemotherapy. Narter et al. reported that the AA genotype and A allele of hAPE1 are more frequent in bladder transitional epithelial cancer group than in bladder adenocarcinoma group. The distribution of hAPE genotypes is clearly different between local and invasive cases, with significantly more GG allele of hAPE in invasive cancer types[35]. Some evidence has suggested marked association between smoking status and the hAPE Asp148Glu polymorphism. The occurrence of one or two hAPE Glu alleles significantly increases the risk for lung cancer. Moreover, some particular polymorphic changes of hAPE (Asp148Glu) are correlated to the response to radiotherapy and chemotherapy in non-small cell lung cancer[36,37]. Genetic polymorphisms of XRCC1 (399Arg/Glu+Glu/Glu) and hAPE (148Asp/Asp) are risk factors for prostate cancer[38]. The 399Glu allele of XRCC1 and the 148Glu allele of hAPE are

related to the incidence of acute skin side effects after radiotherapy in patients with breast cancer; presumably they may be protective against the development of acute side effect after radiotherapy[39]. The association between APE/Ref-1 polymorphic changes and tumors has yet to be further investigated in larger-scale case control studies. Its particular genotype can be used as candidate site for genetic epidemiologic study and may be somehow predictive for the clinical efficacy of radiotherapy and chemotherapy.

APE/Ref-1 in relation to tumor treatments

APE/Ref-1 protein expression is related to the sensitivity to irradiation in the tumors. Herring *et al.*[40] studies the relationship between a radiotherapy sensitivity index SF2 (surviving fraction at 2 Gy) and hAPE1 in cervical cancer cells and found elevated sensitivity to radiotherapy in the cells when hAPE1 expression was decreased, suggesting that hAPE1 expression could be used as a marker to determine whether tumors are sensitive to radiotherapy. Sak *et al.*[41] reported the expression of hAPE1 and XRCC1 proteins were strongly associated with bladder cancer patient outcome following radiotherapy. In glioma and germ cell tumors, high levels of hAPE1 expression are confers resistance to radiotherapy[42,43].

At present, study reports regarding hAPE1, tumor resistance, and tumor cell apoptosis are increasing[44]. Clinical data suggest that increased hAPE1 expression and altered subcellular localization are related to the resistance to platinum compounds in various tumors including non-small cell lung, hepatic, and head-and-neck squamous cell carcinomas[23,31,45]. Wang *et al.*[45] reported that hAPE1 overexpression is associated with cisplatin resistance in non-small cell lung cancer. Patients with lower hAPE1 expression have significantly better prognosis than those with higher hAPE1 expression. When hAPE1 expression is inhibited by APE small interfering RNA (siRNA), A549 cells showed increased sensitivity to cisplatin. Currently, it is generally considered that hAPE1 level and its disordered intracellular distribution may be used as markers to predict the sensitivity to radiotherapy and chemotherapy in the tumors.

APE/Ref-1 as an effective target for antitumor treatments

Studies have shown that the DNA repair function of APE/Ref-1 is essential in maintaining an intact genome and cell vitality. Even without endogenous DNA damage, strong downregulation of APE by APE1 siRNA can stop cell proliferation, and significantly activated apoptosis which is correlated with accumulation of basic DNA damage[46]. Since both radiotherapy and chemotherapy can cause DNA damage, it is theoretically logical and also clinically feasible that cytotoxicity to tumor cells can be enhanced by interrupting DNA damage repair pathways. APE/Ref-1 is endowed with 3'-5' endonuclease activity and has a certain role in the excision of mispaired deoxyribonucleotide analogues[7]. The inhibition of such functions may be helpful in treating tumors with gemcitabine and its analogues. With regard to whether APE/Ref-1 can be an effective target for antitumor treatments, more and more investigations have been conducted as well. Lab studies have found that yeast without the AP endonuclease Apn1 sh ows significantly stronger response to 5-FU treatment[47]. Available studies suggest that decreased hAPE1 expression can induce better sensitivity to chemotherapeutic agents, including bleomycin, carmustine, TMZ, and gemcitabine, in tumor cells[48,49].

Studies on promoting tumor cell apoptosis and inhibiting proliferation by suppressing the redox activity of APE/Ref-1 are still under way. Some scientists have proposed that conventional antitumor treatments produce large amounts of ROS via multiple pathways and keep tumor cells in oxidative stress besides producing direct cytotoxicity to the tumor cells. They activate cell apoptosis and exert their cytotoxicity in tumor cells by causing oxidative DNA damage and regulating the expression of relevant genes. The oxidation-reduction activity of APE has important role during this process[15]. The transcriptional factors regulated by APE/Ref-1 include HIF-1α, p53, NF-κB, CREB, AP-1, and so forth, whereas all these transcriptional factors are important in tumor initiation, development, and angiogenesion[14]. Therefore, some scientists have presumed that inhibiting the redox activity of APE/Ref-1 may deprive these transcriptional factors of their DNA binding capacity, and thereby interrupt the angiogenesis signal and the immortalization of tumor cells. Such presumptions have been primarily confirmed. Available studies have demonstrated that the DNA binding capacity of NF-κB is decreased by inhibiting the redox activity of APE/Ref-1[50]. In a recent study, APE/Ref-1 was shown to enhance the binding capacity of YB-1 to the Y-box element via acetylated form of APE/Ref-1 and thus induce the activation of the multi-drug resistance gene (MDR1). In tumor cells with overexpression of MDR1, APE/Ref-1 can reduce the sensitivity to cisplatin or adriamycin in tumor cells[51].

Currently, many studies have used the antisense oligonucleotide technique and RNA interference (RNAi) to inhibit APE expression to explore the feasibility of using APE as a target for antitumor treatment. These studies have yielded encouraging progress. At first, scientists use the antisense oligodeoxynucleotide technique to inhibit APE/Ref-1 selectively and found the cells more sensitive to alkylating agents and oxidative agents[52,53]. More recently, with the progress in RNAi, scientists used specific hAPE siRNA to knock down APE expression and also increase the cytotoxicity of radiotherapy and chemotherapy in tumor cells. Fishel *et al.*[54] used the siRNA technique to knock down hAPE1 protein in ovarian cancer cells SKOV-3x and revealed that cell growth was inhibited and the S phase was prolonged in the cells. When the hAPE1 protein was decreased in the human ovarian tumor xenografts, tumor volume was significantly reduced. It has been reported that Ad5/F35-APE1 siRNA can effectively inhibit the increased expression of APE and the activation of NF-κB induced by radiotherapy and markedly enhance the inhibition on the growth of the tumor xenografts by radiotherapy[55]. Research on the combination of the specific APE/Ref-1 inhibitor and available antitumor gene therapies also further confirmed that APE/Ref-1 was very promising as an antitumor gene therapy. Wang *et al.*[56] found that pSilenceApe1 can remarkably decrease the expression of hAPE1 and VEGF proteins in osteosarcoma OS-9901

xenografts. Endostatin in combination with pSilenceApe1 showed significantly higher inhibition rates on the tumor as compared to controls or either monotherapies. In the combination group, it was also seen that microvascular density reduced and cell apoptosis increased.

The latest study by McNeill *et al.*[57] suggested that, when treated with a dominant negative protein of hAPE1 (ED) that has been inactivated by catalyzation, the sensitivity of tumor cells to streptozotocin and temozolomide increased by 2.0 times and 5.3 times, respectively. More inspiringly, with ED treatment, the cell killing effect of fluorouracil and fluorodeoxyuridine increased by 5 times and 25 times respectively. They proposed that the increased cytotoxicity by ED may be related to the deprivation of the ability to induce N(7)-guanine and N(3)-adenine modifications and inability to generate O (6)-guanine adducts and DNA crosslinks.

In addition, based on the chemical structure of APE/Ref-1 and using new techniques including computer-based model analysis and high throughput screening, some small-molecule specific APE/Ref-1 inhibitors have been identified. These molecules pioneer a new way for clinical applications of APE/Ref-1. Inhibitors of the redox activity of APE/Ref-1 that have been identified so far include natural molecules such as soy isoflavone[49], resveratrol[58], and the benzoquinone derivative E3330[59]. Inhibitors of the DNA repair activity of APE/Ref-1 include methoxyamine[60] and lucanthone[61,62]. In in-vitro studies, these compounds can increase the cytotoxicity to tumor cells to a certain degree when used in combination with radiotherapy and chemotherapy. For example, when the DNA-repair function of APE/Ref-1 is inhibited by lucanthone, the cytotoxicity on breast and ovarian cancer cells by alkylating agents is markedly enhanced[61,62]. When the redox activity of APE1 is inhibited by MX, a significant enhancement of the antitumor of TMZ was observed in xenograft models of colorectal, ovarian, and breast cancers[60-64]. But the effect of these compounds on tumor cells in in-vitro studies is uncertain and is still under investigation.

Prospects of APE/Ref-1 in the field of oncology

On a fundamental level

APE/Ref-1 is a key rate-limiting enzyme in the BER pathway of DNA repair, which is mainly responsible for repairing DNA damage caused by oxidative agents and alkylating agents. More importantly, as a redox factor, APE/Ref-1 regulates the DNA binding capacity of numerous transcriptional factors, the expression of their downstream target genes via the redox mechanisms, and is thereby involved in various critical cellular activities, including oxidative stress, cell cycle regulation, and apoptosis. Regulated transcriptional factors include many important factors that are involved in cell proliferation, differentiation, transformation, and apoptosis, such as NF-κ B, AP-1, Egr-1, p53, PEBP2, Myb, HIF-1α, and Pax5, Pax8. These transcriptional factors are linked with the sensitivity to chemotherapy[12]. APE/Ref-1 is the pivotal molecule that connects some cellular critical biologic processes including DNA damage, oxidative stress, and gene transcriptional regulation, and has an important role in the promotion and development of tumor cells and their sensitivity to radiotherapy and chemotherapy. Studies have found that its level of expression and subcellular distribution are highly and precisely regulated processes, which therefore diverts investigators' attention from APE/Ref-1 as an individual molecule to the extra coordination between APE/Ref-1 and other genes. The investigation into the post-transcriptional modifications and the coordination mechanisms between the various functions of APE/Ref-1 has opened vast perspectives of further exploration of the biologic significance of APE/Ref-1, further understanding of the promotion and development of tumors, and the underlying mechanisms of resistance to radiotherapy and chemotherapy.

On a clinical level

On the clinical study level, APE/Ref-1 generally shows increased expression levels and altered subcellular localization in various tumors, and is related to tumor invasiveness and metastasis, prognosis, and resistance to radiotherapy and chemotherapy. Hence, the expression status of APE can be used as a predictive marker for the sensitivity to radiotherapy and chemotherapy in the tumors. Furthermore, a good number of studies have shown that, by reducing APE expression in tumor cells with the antisense oligonucleotide technique, RNAi, and specific APE inhibitors, tumor cell apoptosis and sensitivity to radiotherapy and chemotherapy can be increased, endothelial migration induced, and tumor angiogenesis retained. Based on the currently available foreign and domestic literature, it has many reasons to believe that APE can become an excellent target to increase the chemo-sensitivity in tumor cells. However, as a bifunctional enzyme, what are the respective roles for the endonuclease activity and the redox activity of APE in the promotion and development of tumor cells and their sensitivity to radiotherapy and chemotherapy? How to coordinate these functions in tumor cell? These questions remain to be explored in future studies.

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