Role of APE1 in hepatocellular carcinoma and its prospects as a target in clinical settings (Review)

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Received June 18, 2024; Accepted August 21, 2024

DOI: 10.3892/mco.2024.2780

Abstract. In recent years, the incidence of liver cancer has increased annually. However, current medical treatments for liver cancer are limited, and most patients have a high risk of recurrence after surgery. Therefore, the discovery and development of novel treatment targets for liver cancer is urgently needed. Apurinic/apyrimidinic endonuclease 1 (APE1) is a protein that has a DNA repair function and serves an important role in various physiological processes, including reduction-oxidation, cell proliferation and differentiation. The expression levels of APE1 are abnormally elevated in liver cancer cells, as ectopic expression of the APE1 gene has been reported, in addition to other abnormal signs, such as cell proliferation and migration. Therefore, it could be suggested that APE1 is an important indicator of hepatocellular carcinogenesis. APE1 may be used as a therapeutic target for tumors and proposed targeted therapy against abnormal APE1 expression could potentially inhibit the progression of tumors. The present review aimed to introduce the important role of APE1 in the physiological processes of tumor cells and the feasibility of using APE1 as a potential therapeutic target, providing a novel direction for the clinical treatment of liver cancer.

Contents

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Key words: hepatocellular carcinoma, apurinic/apyrimidinic endonuclease 1, targeted therapy

1. Introduction

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related mortality measured in a total of 185 countries in 2020, following only colorectal cancer among digestive system tumors, and its fatality rate is increasing (1,2). A global review suggested that there are hundreds of thousands of new HCC cases annually, which demonstrates a progressive rise in the prevalence of this disease (3,4). Numerous factors can contribute to the development of HCC. Viral hepatitis B and C infection, alcohol abuse, non-alcoholic fatty liver disease and other metabolic liver disorders may induce mutations in hepatocytes, thereby precipitating the onset of liver cancer (5). Due to the asymptomatic or insidious onset of HCC, detection is often challenging, with the majority of patients being diagnosed at advanced stages of the disease (6). Currently, the treatment options for HCC are relatively limited, mainly including surgical resection, liver transplantation, radiofrequency ablation and arterial embolization (7-9). However, these treatment modalities each come with their own set of limitations, and due to the varying physical conditions of patients, there are also constraints on the selection of appropriate therapies (10). Therefore, targeted biological therapies for HCC have increasingly garnered attention from researchers (11). As a multi-kinase inhibitor, sorafenib is the first oral medication approved for the treatment of unresectable HCC (12,13). Previous studies have reported that sorafenib exerts inhibitory effects on the proliferation and migration of tumor cells (14,15). Additionally, it regulates vascular endothelial growth factors, suppresses tumor angiogenesis and promotes apoptosis in cancer cells by inhibiting related signaling pathways (16-18). However, sorafenib is associated with serious side effects and comes with a high cost, which limits its scope of application (19,20). Lenvatinib exerts its therapeutic effects on HCC by targeting multiple kinase receptors, such as VEGFR1-3, fibroblast growth factor receptor 1-4 and c-KIT, albeit with the limitation of potential resistance development due to various mechanisms, which include tumor microenvironment alterations and drug transport activation (21,22). Combination therapy with atezolizumab and bevacizumab is associated with limited improvements in survival and may lead to adverse reactions, including hypertension, cardiac dysfunction and thyroid function changes (23,24). Therefore,

it is necessary to develop a more efficacious and targeted drug for the treatment of HCC.

The protein encoded by the human apurinic/apyrimidinic endonuclease 1 (APE1) gene is also referred to as APEX1, APE, APE1, APEX, APX, HAP1 and REF1. The APE1 protein possesses two distinct domains [DNA repair and reduction-oxidation (redox)], serving a crucial role in the DNA base excision repair (BER) pathway, which is closely associated with tumor cell proliferation (25). Additionally, APE1 is critically involved in the repair of DNA damage induced by a wide array of carcinogens, encompassing both those generated internally through cellular metabolism and externally through environmental exposure, thereby safeguarding the integrity of the genetic material and mitigating the risk of carcinogenesis (25,26). In the tumor microenvironment, APE1 may serve a role in inflammation and stromal cells, affecting tumor development and therapy efficacy due to its key role in regulating oxidative stress responses and inflammatory processes (27,28). Furthermore, APE1 is involved in the regulation of multiple transcription factors associated with cancer-related signaling pathways, including p53, NF-κB, activator protein 1 (AP-1), paired box (Pax)-5, Pax-8, hypoxia-inducible factor 1 (HIF-1), cAMP response element binding protein, activating transcription factor and HIF-1α. Previous studies have reported that, following the malignant transformation of tissues, the expression levels of APE1 are elevated in lung cancer (29), prostate cancer (30), breast cancer (31), HCC (32) and pancreatic cancer (33), which suggests that APE1 is a tumor-associated factor.

In normal hepatocytes, APE1 is expressed at lower levels and is primarily localized in the nuclei (34). However, in liver cancer cells, the expression level of APE1 is increased, is ectopically localized and can also be detected in the cytoplasm (35,36). Therefore, APE1 has been considered to be an important diagnostic indicator for hepatocellular carcinogenesis.

2. Functions of APE1

APE1 and DNA damage repair. When cells are exposed to ionizing radiation, assault from oxygen free radicals or improper cleavage by DNA endonucleases, apurinic/apyrimidinic sites (AP sites) can be readily formed (37). AP sites, a common form of DNA damage, can result from exposure to X-ray and ultraviolet radiation. The absence of a nucleotide base at an AP site can disrupt the action of DNA/RNA polymerases during transcription and synthesis, which leads to interruptions in nucleotide substitution and insertion. Furthermore, the chemical reactivity of AP sites can cause the breakage of cross-links between DNA molecules, as well as DNA-protein and DNA-DNA cross-links (38,39). These factors contribute to the high mutagenicity and cytotoxicity within radiation exposed cells. Consequently, the repair of AP sites is a crucial mechanism for maintaining genomic stability. The BER pathway is the primary pathway for repairing DNA damage, including AP sites, and APE1 is a key rate-limiting enzyme in this pathway (40,41). During the DNA repair process, APE1 interacts with proteins involved in the BER pathway, such as poly(ADP-ribose) polymerase 1 (42), X-ray repair cross complementing 1 (43), DNA polymerase β (44), DNA ligase III, proliferating cell nuclear antigen and flap structure-specific endonuclease 1, and exerts certain stimulatory effects on these proteins, allowing it to participate in and regulate BER (37) (Fig. 1).

APE1 and RNA damage repair. APE1 is also capable of cleaving AP sites present in single-stranded RNA molecules (45). Previous studies have reported that numerous non-coding RNAs and a number of specific microRNAs (miRNAs) directly bind to APE1 in cancer cells in specific ways (46,47). Early *in vitro* evidence and indirect observations have demonstrated the ability of APE1 to bind to and cleave RNA, as well as the relationship between the downregulation of APE1 and miRNA expression (25,47). Malfatti *et al* (48) demonstrated that APE1 can bind to the drosha ribonuclease III (DROSHA)-processing complex, which is associated with the regulation of primary miRNAs (pri-miRs) in cervical cancer in response to oxidative stress. The deletion of APE1 leads to increased oxidation of pri-miR-221/222 and enhances its interaction with DROSHA. The endoribonuclease activity of APE1 towards pri-miR-221/222 affects PTEN expression and is directly related to cancer progression (48).

APE1 and redox regulation. APE1 can also act as a redox factor, stimulating the binding of multiple redox factors, including AP-1, NF-κB, HIF-1α and p53, to DNA, thereby participating in processes such as cell proliferation, migration and inflammatory reactions (49,50). For instance, APE1 reduces the binding of the transcription factor Oct1 to the lectin-like oxidized low-density lipoprotein receptor-1 (LOX1) promoter, which leads to the downregulation of LOX1. Consequently, this suppression inhibits the activation of macrophages and the formation of foam cells induced by oxidized low-density lipoprotein in THP-1 cells (51). Of the seven cysteine residues present in the APE1 protein (Cys65, Cys93, Cys99, Cys138, Cys208, Cys296 and Cys310), Cys65, Cys93 and Cys99 are associated with the redox activity of APE1 (52,53) (Fig. 2). Furthermore, since only Cys65 is present in mammalian cells, mutations in the structure of Cys65 may affect the redox activity of APE1, whereas its DNA repair function remains unaffected.

3. Involvement of APE1 in signaling pathways

Research into the functions of APE1 initially focused on its repair activity as an endonuclease for DNA damage (38,48,54). However, as research progresses, an increasing number of studies have indicated that APE1 not only functions as a DNA repair enzyme but also acts as a redox protein to regulate the activation of various transcription factors, and it is increasingly recognized as a key factor in multiple signaling pathways (25,55) (Fig. 3). The APE1 pathway is a signaling pathway that is highly conserved from prokaryotes to humans, whereas its redox regulation of other signaling pathways is unique to mammals (56). APE1 inhibits adipocyte differentiation by suppressing the expression of transcription factors such as CCAAT-enhancer binding protein α, peroxisome proliferator-activated receptor γ and adaptor protein complex 2 in 3T3-L1 cells (57). APE1 has been reported to be associated with a large number of signaling pathways, including the

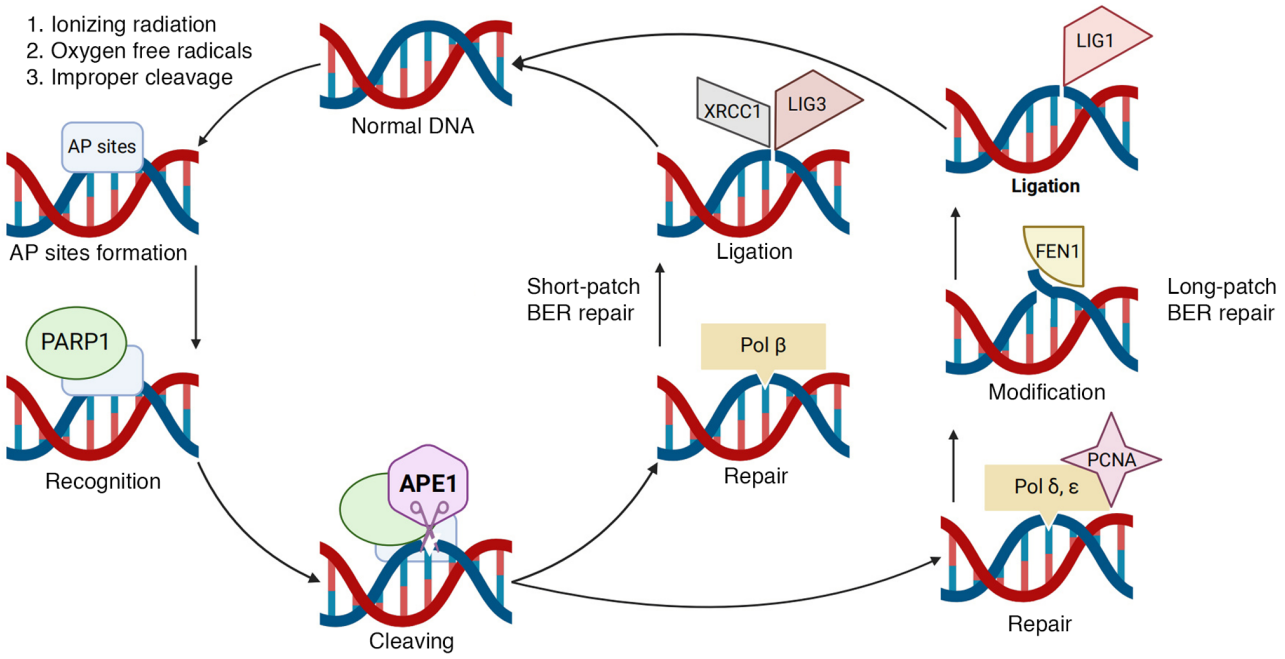

Figure 1. APE1-related base excision repair pathways, including short-patch repair and long-patch repair. AP, apurinic/apyrimidinic; PARP1, poly(ADP-ribose) polymerase 1; LIG, DNA ligase; XRCC1, X-ray repair cross complementing 1; FEN1, flap structure-specific endonuclease 1; pol, polymerase; PCNA, proliferating cell nuclear antigen; APE1, apurinic/apyrimidinic endonuclease 1; BER, base excision repair.

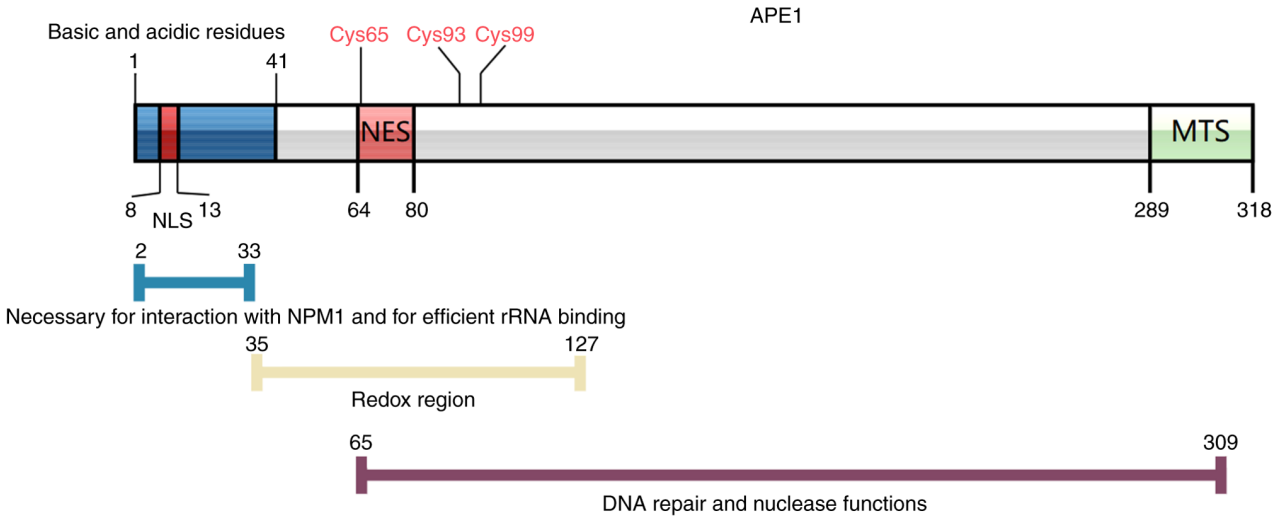

Figure 2. Structural representation of the apurinic/apyrimidinic endonuclease 1 protein. NLS, nuclear localization signal; NES, nuclear export signal; MTS, mitochondrial targeting sequence.

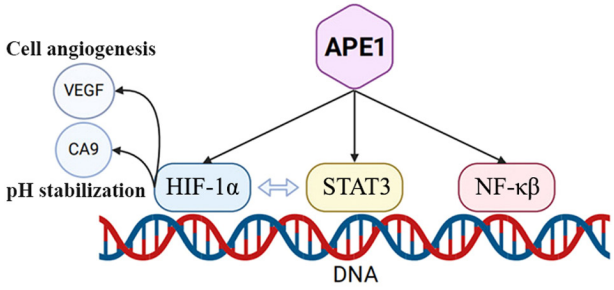

Figure 3. APE1-related signaling pathways. By acting on STAT3, hypoxia-inducible factors and NF-κB, APE1 is involved in regulating these signaling pathways, regulating cell proliferation and differentiation. APE1, apurinic/apyrimidinic endonuclease 1. HIF-1α, hypoxia-inducible factor 1α.

STAT3, HIF-1α, NF-κB, AP-1 and P53 signaling pathways, which are typically closely related to the occurrence and development of tumor cells (26,33,58,59). APE1 has increased activity levels in pediatric acute lymphoblastic leukemia when compared with normal cells, and testing on patient samples has shown that signaling pathways associated with APE1, such as the NF-κB signaling pathway, are activated under conditions of oxidative and DNA damage (60,61). E3330 is an inhibitor that specifically targets the redox activity of APE1 and has been demonstrated in cell experiments to suppress the survival of lymphoma cells by interfering with the redox activity of APE1, downregulating the expression levels of the downstream target genes of APE1 and promoting lymphoma cell

apoptosis (60,61). However, *in vivo* experiments using xenogeneic cell transplantation in nude mice have shown that the growth rate of tumor cells in E3330-treated mice is decreased, the expression of APE1-associated downstream target genes is downregulated (62) and E3330 has an inhibitory effect on tumors (63,64).

STAT3. STAT3 serves a vital role in both normal and cancerous cells. During the processes of cell proliferation and survival, STAT3 can be phosphorylated by Janus kinase to form dimers, which are then translocated into the nucleus to regulate gene transcription (65-67). In tumor cells, the STAT3 signaling pathway is often activated, and APE1 is also active, regulating gene transcription by affecting the sensitivity of STAT3 to DNA binding sites (68). Studies have shown that inhibition of the redox activity of APE1 by inhibitors against REF1/APE1 can reduce the expression levels of downstream target genes of STAT3 and suppress cancer cell proliferation (68,69). Therefore, the combined use of the STAT3 signaling pathway and APE1 inhibitors to inhibit tumor cell proliferation may represent a novel direction for clinical cancer treatment.

HIF-1. HIFs are a class of cellular factors produced by cells in a specific hypoxic environment, serving an essential role in various tissues and organs, and are abnormally expressed during the process of cellular carcinogenesis. Research has shown that HIF-1 is closely associated with the APE1 signaling pathway (33,70). The redox function of APE1 can promote the activation of HIF-1. Under hypoxic conditions, inhibiting the activity of APE1 can reduce the expression levels of downstream genes of HIF-1 and decrease the survival of tumor cells (33). HIF-1 and STAT3 also exhibit a synergistic effect against cell carcinogenesis (70-72). Furthermore, inhibitors of APE1 can be used to simultaneously suppress the transcription of genes downstream of both signaling pathways (73).

NF-κB. NF-κB is an intracellular transcription factor generated in response to both intracellular and extracellular signals, serving a vital role in various physiological processes of cells, including proliferation, migration, regeneration and the immune response (74). Research has demonstrated that the NF-κB signaling pathway also serves an important role in tumor formation (74). Once activated, it can lead to carcinogenesis through a series of changes, including inhibiting apoptosis or altering the tumor cell microenvironment. During the cell repair process following DNA damage, the NF-κB signaling pathway is also activated, promoting the generation of reactive oxygen species (ROS). Subsequently, ROS cause DNA damage in cells (75), which further activates the NF-κB signaling pathway and increases the expression levels of related anti-apoptotic and pro-proliferation genes, promoting the malignant transformation of cells (76).

APE1 is essential for the activation of the NF-κB signaling pathway, and the DNA binding of NF-κB depends on the redox activity of APE1. Research has demonstrated that inhibition of APE1 leads to decreased transcription of downstream genes regulated by NF-κB (62,77), and that APE1 can reduce the proliferative capacity of tumor cells and promote tumor cell apoptosis (34,69).

4. Impact of APE1 on cell carcinogenesis

During cell carcinogenesis, APE1 expression in the nuclei and cytoplasm is elevated, and there are changes to the DNA repair and redox functions involving APE1 (78). Furthermore, high intracellular APE1 expression levels have been associated with poor outcomes of anticancer treatment, poor response to chemotherapy, low survival rates and shorter relapse-free intervals (79,80). Plasma APE1 levels are elevated in patients with colorectal, kidney, liver and pancreatic cancers and cutaneous squamous cell carcinoma (cSCC). APE1 is upregulated in human pancreatic cancer cells, and modulating its redox activity using APE1 inhibitors blocks the proliferation and migration of cancer cells (62), indicating that the redox activity of APE1 is closely related to cell proliferation and migration. A similar phenomenon has been observed in ovarian tumors, where ovarian tumor cells exhibited increased APE1 expression, and its knockdown inhibited tumor cell proliferation (81). Additionally, APE1 promotes the proliferation of cSCC cells. The deletion of APE1 can inhibit the viability of cSCC cells, while the upregulation of APE1 promotes cell proliferation (82). This has also been reported in HCC (62). Conventionally, the notion persists that APE1 is exclusively located within the nucleus, but emerging research has demonstrated that APE1 is expressed in the cytoplasm of both lung tumor and HCC cells (36,74). In HCC, all signaling pathways involving APE1 can stimulate cells to enhance their proliferation, metastasis and anti-apoptotic capabilities (83). Therefore, the downregulation of APE1 expression in tumor cells is likely to become a treatment for tumors in the future, and it may be ideal for patients who cannot tolerate chemotherapy or radiotherapy.

The development and progression of tumors involves the abnormal expression of multiple related genes (84). APE1 is a transcription factor that serves a vital role in DNA repair and redox functions, regulating cancer-related pathways (78,85), and is closely associated with carcinogenesis and proliferation of tumor cells. Research has shown that APE1 expression is associated with the staging and classification, degree of invasion and recurrence of tumors. Therefore, plasma APE1 expression levels can be used as biomarkers for the detection of bladder cancer (34). However, to date, there have been few reports on the relationship between APE1 and HCC. Current research suggests that, compared with that in non-cancerous tissues, APE1 expression in HCC tissues is increased, and it serves a crucial role in the carcinogenesis and progression of HCC (35). The downregulation of APE1 expression can effectively reduce the proliferation of Hep3B cells and promote tumor cell apoptosis (34). This suggests that APE1 may be able to promote tumor growth by inhibiting cell apoptosis. Tumor cells exhibit an enhanced proliferative capacity and a low apoptosis rate compared with non-tumor cells. The cytoplasmic localization of APE1 has been implicated in the carcinogenesis of various cancer types, including ovarian, lung and colorectal cancer, suggesting its potential as a prognostic marker and therapeutic target (86,87). Enhanced cytoplasmic APE1 expression, often associated with p53 aberrations, may predict survival and relapse in patients with cancer, highlighting the importance of the subcellular distribution of APE1 in tumor progression and aggression (74,88,89). Therefore, for

Table I. Comparison of APE1 blockers. Resveratrol, isoflavones, tanshinone and E3330 are clinical drugs that inhibit tumor growth by blocking APE1 expression and inhibiting the redox function of APE1.

Drug name	Mechanism of action	Role	Clinical application
Resveratrol	Inhibiting APE1 activities, such as its redox-regulating functions and reducing the activity of activator protein 1 and NF-κB	Sensitizing tumor cells to radiotherapy and chemotherapy	Melanoma, medulloblastoma, pancreaticobiliary cancer, ovarian cancer, non-small cell lung cancer, hepatocellular carcinoma
Isoflavones	Inhibiting APE1 expression and downregulating the expression levels of NF-κB and hypoxia-inducible factors	Inhibiting tumor cell growth and promoting apoptosis	Non-small cell lung cancer and prostate hyperplasia
Tanshinone	Inhibiting APE1 functions by binding to rAPE1 protein	Inhibiting tumor cell growth and sensitizing tumor cells to radiotherapy and chemotherapy	Cervical carcinoma and colonic cancer
E3330	Inhibiting the redox function of APE1 and blocking NF-κB activation	Inhibiting tumor cell growth, invasion and migration and suppressing angiogenesis	Pancreatic, ovarian, prostatic, colon and breast tumors

APE1, apurinic/apyrimidinic endonuclease 1; rAPE1, recombinant APE1.

cancer treatment, inhibiting cell proliferation and differentiation by promoting tumor cell apoptosis can be an effective method for tumor suppression.

5. Prospects of APE1-targeted drugs in clinical settings

APE1 serves an important role in the development and progression of cancer, and its expression is closely associated with the prognosis of patients (90). In HCC, APE1 expression is higher in cancerous tissue cells compared with that in para-neoplastic tissues (32). Elevated APE1 levels dysregulate homologous recombination and the cell cycle, contributing to chemoresistance (91). Research has indicated that APE1 inhibitors can enhance the efficacy of cisplatin chemotherapy, photodynamic therapy and radiotherapy (69,92-94). High APE1 expression is inversely associated with $CD4^+$ naive T cell infiltration, which is a predictor of recurrence-free survival in patients with non-small cell lung cancer, with improved survival in patients with high APE1 expression levels (95). High APE1 expression in breast cancer nuclei is associated with poor disease-free survival, and is associated with the luminal A subtype and estrogen receptor positivity, while low APE1 expression in patients with low Ki-67 cases predicts worse overall survival rates (96). Combining APE1/REF1 redox inhibitors with the standard-of-care chemotherapy drug cisplatin *in vitro* more effectively inhibits bladder cancer cell proliferation when compared with cisplatin alone (69). Therefore a number of studies have proposed methods to treat HCC by inhibiting the action of APE1. By administering APE1 inhibitors, the functions of APE1 are inhibited, which further suppresses tumor cell proliferation and promotes tumor cell apoptosis (97-100) (Table I).

Resveratrol is also known as 3,4',5-trihydroxy-trans-stilbene and is a type of natural polyphenol compound. Experiments have shown that resveratrol pretreatment enhances human melanoma cell sensitivity to the chemotherapeutic drug dacarbazine (97,101). However, it has been shown *in vitro* that resveratrol effectively reduces the activities of AP-1 and NF-κB by inhibiting the redox function of APE1, and such an effect has been observed in a wide range of cancer types (102). Furthermore, resveratrol can be used as a selective inhibitor of APE1, laying the foundation for its clinical application.

Isoflavones are a class of natural compounds that have an important protective effect against cancer (98,103). It has been reported *in vitro* that isoflavones can effectively inhibit tumor cell proliferation and potentiate cell death by radiation (104). In non-small cell lung cancer, isoflavones sensitize tumor cells to radiation by inhibiting the DNA repair function of APE1 (105). In addition, in prostate cancer, soy isoflavones can downregulate NF-κB and HIF-1 simultaneously by inhibiting APE1, potentiating tumor cell apoptosis, inhibiting tumor tissue angiogenesis and sensitizing tumor cells to radiation (102). From this perspective, isoflavones, as inhibitors of APE1, have an inhibitory effect on tumor progression. This also suggests that inhibiting APE1 activity could be a potential effective treatment strategy for cancer.

Tanshinone is a Traditional Chinese Medicine that can inhibit the redox activity of APE1 (99). It can effectively inhibit the proliferation of human cervical and colon cancer cells. Furthermore, tanshinone pre-treatment can enhance the sensitivity of certain tumor cell lines, such as HeLa and HCT116 cells, to ionizing radiation and chemotherapy drugs. As an inhibitor of APE1, tanshinone may have a promising future in cancer treatment.

E3330 is also known as (2E)-3-[5-(2,3-dimethoxy-6-methyl-1,4-benzoquinoyl)]-2-nonyl-2-propenoic acid and is a compound that can selectively inhibit the redox activity of APE1 without having any impact on its DNA repair function (100). Therefore, E3330 has no inhibitory effect on the BER pathway. By increasing disulfide bond formation

involving Cys65 and/or Cys93, E3330 effectively decreases the redox-active population of APE1 molecules (100,106). A previous study reported that E3330 can effectively inhibit the proliferation of tumor cells in ovarian, colon, lung, breast, brain, pancreatic and prostate cancers and multiple myeloma but does not significantly inhibit the proliferation of normal cells (107). By inhibiting the activity of APE1, the activities of some transcriptional regulators, including NF-κB, activator protein and HIF-1, are blocked, which have marked effects on the proliferation, invasion and metabolism of tumor cells, thereby inhibiting tumor progression (62). In addition, E3330 can effectively inhibit tumor cell proliferation and migration in pancreatic cancer (64).

A number of studies have reported that the redox domain of APE1 is indispensable for tumor-associated epithelial cell differentiation, function and angiogenesis following tumor cell migration (77,108). In liver cancer, APE1 can facilitate the development of HCC both *in vitro* and *in vivo* (35). APE1 overexpression and the increase in enzyme activity are related to the survival and drug resistance of cancer cells (109). Furthermore, the inhibition of APE1 leads to the accumulation of lipid peroxidation and enhanced ferroptosis in HCC (110). Western blotting analysis has demonstrated that diethylnitrosamine (DEN) treatment enhanced APE1 protein expression (111). The antioxidant effect of Licochalcone B and fullerene C60 may be the mechanism by which these compounds reduce the expression of APE1, which is predominantly activated by oxidative stress (111,112). This has a protective effect against DEN-induced HCC.

6. Conclusions

Inhibition of APE1 has the potential to be an effective treatment approach for tumors. It can be concluded from the aforementioned findings that APE1 serves a vital role in the development and progression of tumors. The inhibition of APE1 activity can effectively control tumor cell proliferation and spread, suggesting that targeting of APE1 may be a novel direction for the treatment of HCC, especially for patients with poor response to surgical therapy and chemotherapy.

Acknowledgements

Not applicable.

Funding

The present study was supported by the National Natural Science Foundation of China (grant nos. 81930119, 82090050 and 82090053) and the CAMS Innovation Fund for Medical Sciences (grant no. 2019-I2M-5-056).

Availability of data and materials

Not applicable.

Authors' contributions

LY and ZS equally contributed to the present manuscript, the conception and design of the study, literature review and analysis, and drafting, critical revision and editing of the manuscript. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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