

Role of Tumor Suppressor Protein p53 in Apoptosis and Cancer Therapy

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Abstract

TP53, encoding p53, is one of the most famous tumor suppressor genes. The majority of human cancers demonstrate the inactivation of the p53 pathway. Mutant p53 not only, no longer, functions as a tumor suppressor but can also exert tumor-promoting effects. The basic function of p53 is to respond to cellular stress. We here in this review article discusses about the recent advances in p53 research, mainly focusing on apoptosis and therapy for human cancer. Hence, this review aims to update the current related articles and provide a further understanding about such molecular changes relevant to trigger imbalances in the regulation of apoptosis in cancer.

Keywords: Docosahexaenoic acid (DHA); Tumor protein (TP53); Activating transcription factor 3 (ATF3); Choline Cytidylyltransferase (CCT); Methylguanine-DNA methyltransferase (MGMT)

Introduction

p53 (also known as protein 53 or tumor protein 53), is a tumor suppressor protein that in humans is encoded by the *TP53* gene. p53 is crucial in multi cellular organisms, where it regulates the cell cycle and, thus, functions as a tumor suppressor that is involved in preventing cancer. As such, p53 has been described as “the guardian of the genome”, the “guardian angel gene”, and the “master watchman”, referring to its role in conserving stability by preventing genome mutation.

In humans, p53 is encoded by the *TP53* gene located on the short arm of chromosome 17

The *TP53* gene, which encodes p53, is one of the most frequently mutated genes in human cancers. It is reported that approximately half of all cancers have inactivated p53

p53 has many mechanisms of anticancer function, and plays a role in apoptosis, genomic stability and inhibition of angiogenesis. In its anti-cancer role, p53 works through several mechanisms:

It can activate DNA repair proteins when DNA has sustained damage.

It can induce growth arrest by holding the cell cycle at the G₁/S regulation point on DNA damage recognition (if it holds the cell here for long enough, the DNA repair proteins will have time to fix the damage and the cell will be allowed to continue the cell cycle).

It can initiate apoptosis, the programmed cell death, if DNA damage proves to be irreparable.

P53 plays a specific role in cytoplasm and nucleus. In cytoplasm it shows cellular stress. While in nucleus it shows all cellular responses like Apoptosis, Cell- cycle arrest DNA repair, Differentiation and Senescence (Figure 1).

Docosahexaenoic acid (DHA) induces P53-dependent growth inhibition in transformed colon and lung cell lines expressing wildtype P53

DHA has anti-proliferative effects on tumor cells. In the current study, the role of p53 dependent growth inhibition by DHA has

been thoroughly studied. Previous work has established that DHA is capable of growth inhibitory effects independent of p53 mutational status in colon carcinomas, however, one of the same studies showed an increase in the number of apoptotic cells, only in the DHA treated cells of the colon carcinoma with wild type p53. Significant increases in the number of DHA-treated cells by p53 siRNA or pifithrin-a addition were observed only in the COLO-205 and A549 cell lines expressing wild type p53, and these correlated with a reduction in the percentage of apoptotic and necrotic cells. This data confirms a role for p53-dependent growth inhibition with DHA treatment [1]. A similar experiment has done to kill cancer cells using CCT α siRNA. Choline Cytidylyltransferase (CCT) is a rate limiting enzyme required for cell proliferation. The Cells conditionally lacking CCT α activity undergo death by apoptosis. Thus Inhibition of CCT α expression using CCT α

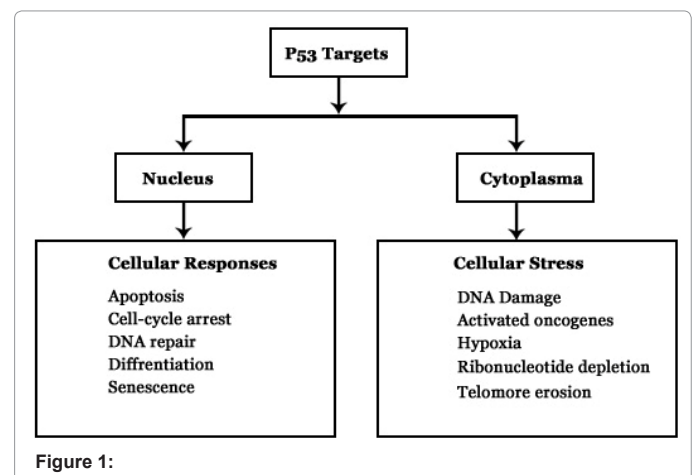


Figure 1:

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Received May 15, 2011; Accepted July 15, 2011; Published July 18, 2011

Citation: Naga Deepthi CH, VVL Pavan Kumar A, Rameshbabu, Indirapriyadarshini U (2011) Role of Tumor Suppressor Protein p53 in Apoptosis and Cancer Therapy. J Cancer Sci Ther S17:001. doi:10.4172/1948-5956.S17-001

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siRNA sequences as anticancer agents induce death of lung cancer cells [2].

Lack of Methylguanine-DNA methyltransferase (MGMT) makes a tumor susceptible to temozolomide provided mismatch repair system (MMR) is functional. A non-functional MMR renders the tumor resistant to alkylating agents [3]. Anti-Angiogenic studies have made hysteric escalations in the evolution of effectual anti-cancer drugs. This review, in an attempt to contribute to the contemporary therapies, talks about a novel therapeutic approach of targeting tumor cells by depriving oxygen from them through increased hypoxia which surpasses their minimum requirement for oxygen; the latter achieved by interfering at the interface of oxygen diffusion between the blood vessels and tumor cells [4].

p53 stimulated apoptosis in breast carcinoma cells

Resistance to apoptosis leads to the progression of many solid cancers [5]. Azurin, a potent anticancer redox protein secreted by *Pseudomonas aeruginosa* (*P. aeruginosa*) species has been reported to have activity against breast cancer cell lines; *P. aeruginosa* MTCC (Microbial Type culture collection) 2453 was the strain that secreted the most azurin and showed remarkable apoptosis in breast carcinoma cells like T-47D and ZR-75-1 [6]. Butyric acid (BA), an extracellular metabolite produced from periodontopathic bacteria result in progression of oral cancer such as oral squamous cell carcinoma (OSCC) [7]. Emerging prognostic factors such as Nottingham prognostic index (NPI) or triple-negative status might improve the models currently used by clinicians [8]. Intensity Modulated Radiation Therapy (IMRT) is widely accepted as an appropriate method to treat tumors at many different anatomic locations including lungs [9]. Chemokines and Chemokine receptors play a role in Prostate Cancer Development and Progression [10]. Bone marrow aspiration along with trephine biopsy is essential for the diagnosis and management of multiple myeloma [11].

Increasing apoptosis in human glioblastoma t98g xenograft

Glioblastoma is the most malignant brain tumor of astroglial origin. ATRA plus IFN- γ induced extrinsic pathway of apoptosis by activation of caspase-8 and cleavage of Bid to tBid and also promoted intrinsic pathway of apoptosis due to down regulation of hTERT, c-IAP2, and survivin and up regulation of Smac/Diablo. Mitochondrial release of apoptosis-inducing factor (AIF) induced caspase-independent pathway and also up regulation of calpain and caspase-dependent pathways ultimately activated caspase-3 for apoptosis. Increased activities of calpain and caspase-3 degraded 270 kDa α -spectrin at the specific sites to generate 145 kDa spectrin breakdown product (SBDP) and 120 kD SBDP, respectively. Results indicated that ATRA plus IFN- γ activated multiple molecular mechanisms for increasing apoptosis in human glioblastoma *in vivo* [12]. Interferon γ (IFN γ), a potent inhibitor of proliferation is an inducer of apoptosis [13]. Tissue microarrays (TMAs) have been commonly utilized in translational research to rapidly screen numerous biomarkers in large samples [14]. Lectin cytochemical studies in leukemia revealed its usefulness in differentiating lymphoid leukemias from myeloid leukemias. Hence used as biological markers in haematological malignancies [15]. Genes encoding enzymatic activities implicated in the eicosanoid cascade are expressed in meningiomas. lipoxygenase (LOX) and cyclooxygenase (COX) derived arachidonic acid metabolites might act on tumor growth not only by acting on cell growth but also by altering the local cytokine and/or angiogenic networks [16]. Endocan also called endothelial cell-specific-molecule-1

is a product of endothelial cells, could be a pertinent biomarker to select patients and/or to clinically monitor the efficacy of cancer drugs [17]. Y-90 SIR-Spheres therapy is useful in reducing or stabilizing multiple liver metastases from a variety of tumors [18]. Recent studies shows that there is the possibility of malignant transformation of benign fibrous histiocytoma [19]. Some recent studies suggest that many of these pro-inflammatory chemokines and their receptors are the products of protooncogenes or tumor suppressor pathways in many cancers including that of the prostate [10]. The individual's personality type has major impact on psychoneuroimmune mechanisms linking aggression stress through inflammation to cancer [20] MicroRNA Analysis in Human Papillomavirus (HPV)-Associated Cervical Neoplasia and Cancer [21]. Epidermal Growth Factor (EGF) and Platelet-Derived Growth Factor (PDGF) as Tissue Healing Agents: Clarifying Concerns about their Possible Role in Malignant Transformation and Tumor Progression [22].

p53 inhibition for cancer therapy

The inhibition of p53 can protect normal cells during genotoxic chemotherapy or radiation therapy. The side effects of genotoxic therapy for cancer are largely caused by p53-mediated apoptosis. The small molecule pifithrin- α can block p53-dependent transcriptional activity and protect mice from the lethal side effects associated with anticancer treatment [1]. If we can avoid dose-limiting genotoxic stress to normal cells during chemotherapy or radiotherapy for cancer, it will thus allow a higher dose to be used for patients who are not sufficiently responsive to conventional chemotherapy. It seems that radiotherapy or chemoradiation can be appropriate alternative to total laryngectomy in laryngeal cancers [23]. Treatment with IFN and doxorubicin has been demonstrated in osteosarcoma patients, but tumour resistance to IFN- α is common [24]. Lymphangiomas is also a type of cancer for this surgical resection still remains the best treatment for lymphangiomas; other treatment options, such as sclerotherapy have been proposed as an alternative to reduce the impact and complications of surgery [25].

Metastasis Associated 1 (MTA1) Aids the AKT Pathway by Inhibiting Expression of a Key Regulator, PTEN the phosphatase and tensin analogue mutated on chromosome 10. PTEN is a tumour suppressor gene known to be mutated in several cancers [12]. Endothelial antigens that stimulate immune-mediated damage of tumor vessels represent possible targets for the development of antiangiogenic vaccines aimed at preventing the progression of solid tumors [26]. S-1, an oral anticancer drug, caused only mild toxicity and had highly effective antitumor activity. Furthermore, the RR of S-1 NAC might predict regional lymph node metastasis [27]. FIR inhibited the proliferation of HepG2 at non-thermal circumstances (at 25 ± 0.5 , $37 \pm 0.5^\circ\text{C}$). FIR will serve as a tool against diseases induced by HepG2 [28]. Efficacy of transcatheter arterial infusion (TAI) alone or combined with transcatheter arterial chemoembolization (TACE) on advanced hepatocellular carcinoma (HCC) [29]. In current clinical practice, platinum-based chemotherapy is the major option for patients with LACC [30]. Dermatofibrosarcoma protuberans (DFSP) is a low-grade malignant tumor but has high local recurrence rate. Transformed DFSPs are more aggressive tumors which need more energetic treatments. Cysteine-Rich Secretory Protein-3 (CRISP3) Is Strongly Up-Regulated in Prostate Carcinomas with the TMPRSS2-ERG Fusion Gene [31]. Urothelial carcinoma is the most common histological type of bladder tumours [32]. Investigation is done on expression pattern of epidermal growth factor receptor (EGFR) in urinary bladder cancer and its association with human epidermal growth factor receptor 2

(HER2), epidermal growth factor (EGF), interleukin-6 (IL-6) and high risk human papilloma virus (HPV) types 16 and 18 [33]. Treatment precision of image-guided liver SBRT using implanted fiducial markers depends on marker-tumour distance [34]. Denosumab is superior to zoledronic acid, a potent bisphosphonate used as the standard therapy for bone metastases, for patients with prostate or breast cancers and is noninferior for patients with other solid tumors in terms of the median time to first on-study skeletal-related event. It will be an effective new treatment option for patients with bone metastases [35]. Knockdown of ornithine decarboxylase antizyme 1 causes loss of uptake regulation leading to increased N (1), N (11)-bis(ethyl)norspermine (BENSpm) accumulation and toxicity in NCI H157 lung cancer cells [36]. NUP98-HOXA9-transgenic zebrafish develop a myeloproliferative neoplasm and provide new insight into mechanisms of myeloid leukaemogenesis [37] p53 gene mutation incites the pathogenesis of human gastric adenocarcinomas [38].

Role of p53 in cancer therapy

Radiotherapy is a common treatment for prostate cancer, but failure is observed 30 to 40% of the time. It is more common in patients with abnormal p53. It is more common in patients with abnormal p53. The phytochemical diferuloylmethane (curcumin) a naturally occurring flavinoid derived from the rhizome of *Curcuma longa*, shows potential radiosensitizing effects. In the present study, the effect of curcumin and radiation on cell viability, apoptosis and clonogenic cell death was examined in LNCaP (wild type p53) and PC3 (mutant p53) prostate cancer cells [39]. The cell viability and cell proliferation decreased in presence of both curcumin and radiation as compared to curcumin or radiation alone in both the cell lines. Regardless of p53 status, combination treatment with curcumin (2.5 to 10 μ M) and radiation (2 Gy) had a synergistic effect on clonogenic cell death in both LNCaP and PC3 cells. Curcumin appears to radiosensitize prostate cancer cells and may be a possible adjuvant to radiotherapy in the treatment of cancer. Thus there is a Synergistic Effect Between Curcumin (diferuloylmethane) and Radiation on Clonogenic Cell Death Independent of p53 in Prostate Cancer Cells [39]. Ovarian cancer patients with extensive omental disease were possibly better treated with primary cytoreductive surgery, since they were more likely to have less responsive to NACT [40]. Breast cancer incidence and mortality rates decrease with environmental conditions that promote Vitamin D synthesis in human skin including lower latitude and higher personal exposure to sunlight [41]. Recent studies also showing that Osteopontin (OPN) is a secreted phosphoprotein which plays a critical role in metastasis of colon, liver, and breast cancers [42]. Forty patients receiving tamoxifen (hormone therapy) along with other chemo- drugs also showed good response. Tamoxifen induced substantial tumor regression and increased disease free survival [43]. Elevated Src kinase activity is linked to the progression of solid tumors, including head and neck squamous cell carcinoma (HNSCC) [44]. Proteolytically-cleaved fragments of cell-surface proteins from live tumor cells stimulate anti-tumor immune response *In vitro* [45].

Many viruses have been associated with human breast cancers, human papillomavirus (HPV) strains HPV16 and HPV18 in breast carcinoma shows different phenotypic changes. HPV16 and HPV18 significantly inhibited proliferation and adhesion of T-47D cells, although viability was not affected. Differential effects on proliferation were observed in MCF7 cells; HPV16 inhibited proliferation, while HPV18 stimulated proliferation. No measurable effects in adhesion or viability in MCF7 cells were observed. The phenotypic changes

in T-47D and MCF7 cells were associated with changes in mRNA expression of caspase-2,-3 and -8, but not p53 [46]. Chemotherapy play a critical role in the Treatment of Kaposi's Sarcoma [29]. also granulocyte-Macrophage Colony-Stimulating Factor, Interferon Alpha and Interleukin-2 as Adjuvant Treatment for High-Risk Renal Cell Carcinoma [47] similarly Pre-clinical Validation of Targeted Radionuclide Therapy Using a [¹³¹I] Labelled Iodoquinoline Derivative for an Effective Melanoma Treatment [48]. Baculovirus expressed tumstatin was used to evaluate its anti-angiogenic and anti-tumorigenic functions such as inhibition of endothelial cell proliferation, cell viability, migration, tube formation, cap dependent protein translation and the associated signaling mechanism including in-vivo tumor study [49]. Regrowth Concentration Zero (RC0) as complementary endpoint parameter evaluates compound candidates during preclinical drug development for cancer treatment [50]. It was concluded that early establishment of adequate preventive measures and proper management of both the EGFR inhibitor-related, acne-like rash and radiation dermatitis in SCCHN patients undergoing concomitant treatment will prevent treatment interruption, potentially allowing better locoregional control of the disease [50]. Multiple molecular alterations can be frequently detected in the pathogenesis and development of Hepatocellular carcinoma (HCC), such as members of Ras family, Bcl-2 family and tumor suppressors. Importantly, most of these alterations are responsible for disrupting the balance between cell proliferation and apoptosis, which has been generally voted as a key event closely associated with carcinogenesis. Hence, this review aims to update the current related articles and provide a further understanding about such molecular changes relevant to trigger imbalances in the regulation of apoptosis in HCC [51].

Chemotherapy and radiation therapy in cancer

A case report of severe metoclopramide-induced akathisia in a breast cancer patient being treated with chemotherapy is also presented and made a conclusion that movement disorders as an adverse effect of metoclopramide have been described on a regular basis over the past decades [52] an observational study state that outcome and medical costs of patients with invasive aspergillosis and acute myelogenous leukemia-myelodysplastic syndrome treated with intensive chemotherapy [53]. Invasive pulmonary aspergillosis (IPA) is a significant problem in patients with chemotherapy-induced prolonged neutropenia as pulmonary deposition of conidia is the first step in developing IPA [54]. CHOP compared with CHOP plus granulocyte colony-stimulating factor in elderly patients with aggressive non-Hodgkin's lymphoma. The relative dose-intensity of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy could be improved by prophylactic administration of granulocyte colony-stimulating factor (G-CSF) in elderly patients with aggressive non-Hodgkin's lymphoma (NHL) [55]. incorporation of PET-CT changes radiotherapy treatment in pediatric Hodgkin lymphoma [56].

Treatment with CHOP chemotherapy in elderly patients with aggressive non-Hodgkin's lymphoma (NHL) is less effective and accompanied by more adverse effects than in younger patients. The prophylactic use of granulocyte colony-stimulating factor (G-CSF) might improve the results, but increases the costs of treatment. Recent studies show that treatment with CHOP or CHOP+G-CSF for aggressive non-Hodgkin lymphoma (NHL) [57]. High-dose therapy improves progression-free survival and survival in relapsed follicular non-Hodgkin's lymphoma [58].

Lamivudine is used for the prevention of chronic hepatitis B exacerbations during chemotherapy for non-Hodgkin's lymphoma. Lamivudine is registered for the treatment of chronic hepatitis B and can be used as a prophylactic prior to chemotherapy or to treat an exacerbation of the hepatitis. It is advisable to systematically test all patients with lymphoma for the presence of the HBsAg. If this is positive, prophylactic administration of lamivudine 100 mg once daily is strongly recommended if chemotherapy is indicated [59].

Etoposide, mitoxantrone and prednisone: a salvage regimen with low toxicity for refractory or relapsed non-Hodgkin's lymphoma. EMP is a new salvage regimen with a relatively low toxicity. It should be considered for patients with relapsed or refractory NHL who are not candidates for standard reinduction therapy and stem cell transplantation [60].

Satraplatin is an oral platinum analog with demonstrated activity in a range of malignancies [61]. Elderly breast cancer patients with a history of cardiac disease and/or diabetes treated with trastuzumab have an increased incidence of cardiotoxicity [62]. Metastatic Ovarian and Primary Peritoneal Cancer: Assessing Chemotherapy Response with Diffusion-weighted MR Imaging--Value of Histogram Analysis of Apparent Diffusion Coefficients [63].

Meta-analysis of ERCC1 C118T/C8092A and MDR1 C3435T Polymorphism is known to predict outcome of platinum-based chemotherapies in advanced non-small cell lung cancer [64]. Glioblastoma (GBM) is a deadly tumor, which in spite of surgery and radio/chemotherapy frequently undergoes relapses related to the infiltration of the normal parenchyma and to resistance to cytotoxic and radiation therapy. Immunotherapy may represent a promising approach, which may complement existing therapies with the aim of eliminating residual tumor cells, through their selective targeting by immune effector cells or antibodies. Cytokine delivery with IL-2 has resulted in long-term disease-free survival in a small proportion of patients with metastatic disease. The continuous understanding of the mechanisms that underlie the immune complex networks has led to the identification of key molecules that play a major role in the immune response process [65]. New targeted agents with novel mechanisms of action are also being studied, including Histone Deacetylase Inhibitors, Angiopoietin/TIE-2 inhibitors, Carbonic anhydrase IX inhibitors, vaccines, and others. Therapies in Metastatic Renal Cell Carcinoma is also known [66]. Evaluation is done on the occurrence of second malignant neoplasms (SMN) following chemoreduction (CRD) with carboplatin, vincristine, and etoposide (CEV) as frontline therapy in patients with retinoblastoma (RB). Interestingly, enhanced midkine expression significantly correlated with a higher propensity and decreased time for primary DT recurrence (log-rank $p = 0.0025$). Thus increased midkine expression correlates with desmoid tumour recurrence: a potential biomarker and therapeutic target [67]. Development of a novel type of angiogenesis inhibitor will be essential for further improvement of therapeutics against cancer patients. Oral administration of AMF-26 significantly blocked VEGF- or IL-1 β -induced angiogenesis in the mouse cornea, and also tumor angiogenesis and growth. AMF-26 could be a promising novel candidate drug for cancer treatments [68].

Radiotherapy is one of the main treatments for esophageal squamous cell carcinoma, but there are still no biomarkers to differentiate patients who will benefit from radiation. Although treatment with a combination of radiotherapy with chemotherapy, and/or surgery improves the prognosis of patients, no biomarkers

can distinguish between the responses obtained with the combined therapies. Therefore studies with patients treated with radiotherapy alone to evaluate survivin as a predictor for radiotherapy. Moreover, in esophageal cancer cell lines, overexpression of survivin reduced the percentage of cell death induced by radiation [69]. SWOG trial S0102 showed significant activity of the combination of docetaxel and vinorelbine in HER2-negative metastatic breast cancer (MBC). The combination of trastuzumab, docetaxel, and vinorelbine is effective as first-line chemotherapy in HER2-positive MBC with minimal toxicity [70]. Postoperative adjuvant chemoradiotherapy was recommended as the standard treatment for patients with rectal cancer because it reduces local recurrence. This paradigm shifted with the use of neoadjuvant chemoradiotherapy, which not only reduces local recurrence but also improves sphincter preservation and surgical outcomes [71]. A small percentage of gliomas are caused by inheritance in cancer syndromes but there is also a general familial aggregation of glioma. Recently, low penetrant genes associated with glioma risk have been identified [72]. Recent findings show that the role of PET with amino acid tracers in the setting of brain lesions of unknown significance has been better defined, reducing the need for invasive procedures. The impact of PET-guided resection of high-grade glioma using C-methionine (C-MET) has been strongly documented. [¹⁸F]Fluoroethyl-L-tyrosine is currently available for glioma management; advances in targeting glial tumor biopsy and monitoring response to standard chemoradiation of malignant glioma have been remarkable. 2-(2-nitro-1H-imidazol-1-yl)-N-(2,2,3,3,3-penta-fluoropropyl)-acetamide is a rationally designed radiotracer with potential for imaging hypoxia in glioblastoma. New insights regarding the predictive value of 3-deoxy-3-[¹⁸F] fluorothymidine in outcome of recurrent malignant glioma treated with bevacizumab/irinotecan have been provided. First steps are being made toward apoptosis PET imaging for early assessment of radiotherapy response in brain metastases [73]. Accuracy of endoscopic ultrasound to assess tumor response after neoadjuvant treatment in rectal cancer is also studied but this study was limited by the lack of comparison with other imaging methods [74]. CD133 confers chemoradioresistance properties to cells and has recently been used to identify cancer-initiating cells. Pretreatment CD133 and Cyclooxygenase-2 Expression as the Predictive Markers of the Pathological Effect of Chemoradiotherapy in Rectal Cancer Patients and revealed the independent predictive values of CD133 and cyclooxygenase-2 expressions in histological tumor regression after preoperative chemoradiotherapy [75]. Poly(ADP-ribose) polymerase-1 is a critical enzyme in the repair of DNA strand breaks. Inhibition of PARP-1 increases the effectiveness of radiation in killing tumor cells. However, while the mechanism(s) are well understood for these radiosensitizing effects in vitro, the underlying mechanism(s) in vivo are less clear. Nicotinamide, a drug structurally related to the first generation PARP-1 inhibitor, 3-aminobenzamide, reduces tumor hypoxia by preventing transient cessations in tumor blood flow, thus improving tumor oxygenation and sensitivity to radiotherapy [76].

Investigation is done on the proliferation-inhibiting and apoptosis-inducing effects of ursolic acid (UA) and oleanolic acid (OA) on multi-drug resistance (MDR) cancer cells in vitro and found both UA and OA have antitumor effects on cancer cells with MDR, and the optimal effect is shown by UA on colonic cancer cells. Also, UA shows cell apoptosis-inducing effect on SW480, possibly by way of down-regulating the expressions of apoptosis antagonistic proteins, Bcl-2, Bcl-xL, and survivin [77].

Conclusion

Thus further investigation on the role of p53 in cancer cell lines and cancer therapy may therefore be one of the most important research fields for uncovering new paradigms in cancer therapy.

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