

Targeting P53 Pathway by Curcumin for Cancer Prevention and Treatment

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Rec date: Jan 03, 2015; **Acc date:** Jan 04, 2014; **Pub date:** Jan 11, 2015

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Editorial

Tumor protein p53, also called as tumor suppressor protein, has been described as "the guardian of the genome". It was identified by Lionel Crawford, David P. Lane, Arnold Levine, and Lloyd Old in 1979. The tumor suppressor p53 family consists of three members, p53, p63 and p73. A tumor suppressor gene, TP53 (better known as p53) controls several cellular stresses, including DNA damage, hypoxia and oncogene activation. Functionally, the p53 proteins acts as a transcription factor and regulate the gene expression by binding to specific DNA sequences. Classically, p53 has been implicated in controlling genes involved in apoptosis, senescence, cell cycle arrest and play roles in necrosis, autophagy, metabolism, Reactive Oxygen Species (ROS) accumulation and stem cell maintenance. Mutation and loss of p53 is common in variety of cancers including cancer of lung, head and neck, bladder, breast and prostate. However, mutation of p63 and p73 are extremely rare in human cancers, although their expression is frequently dysregulated in human tumors [1].

Normally, p53 is maintained at low protein levels during times of homeostasis by its predominant negative regulator Mdm2 through the ubiquitin-proteasome pathway. However, it becomes activated in response to stress, such as DNA damage, oxidative stress, osmotic shock, ribonucleotide depletion, and deregulated oncogene expression [2]. Activated p53 usually binds to specific DNA sequences in the promoter region of its target genes, including Bax, Puma, Noxa (apoptosis); p21, Gadd45a, 14-3-3 delta (cell cycle arrest); p21, E2F7 (senescence); Tigar, PGM (metabolism); Atg2b, Atg4a, Atg7, Dram1 (Autophagy). However, mutated p53 loses these functions and serves as an oncogene by physically interacting with other proteins and thus modulating their cellular function [3]. Mutant p53 is known to associate with p63 and several transcription factors, such as Sp1, Ets-1, and VDR, resulting in the transactivation of their oncogenic target genes [4].

Many natural compounds are reported to exhibit their chemopreventive properties through regulation of p53 expression. This modulation of p53 transcription factor by natural compounds further inhibits COX-2 activity, cyclin D1 and MMPs overexpression, NF- κ B, STAT and TNF- α signaling pathways and subsequently induce of cell cycle arrest and apoptosis [5]. The most extensively investigated natural chemotherapeutic and chemopreventive agent, curcumin, was reported to induce apoptosis via activation of p53 and its transcriptional target in various cancers. Curcumin is the active ingredient of the dietary spice found in the rhizomes of *Curcuma longa*, a plant in the ginger family. Curcumin has shown to induce apoptosis by upregulating the expression of p53, Bax, Bak, PUMA, Noxa, and Bim downregulating Bcl-2, and Bcl-XL and in androgen-dependent and -independent prostate cancer cells, however, it had no effect on normal human prostate epithelial cells. In addition, curcumin induces p53 translocation to mitochondria, and Smac release to

cytoplasm, which strongly suggests its cancer chemopreventive properties [6]. By altering the p53 and its downstream proteins (p21, cyclin B1, CDK1, Cdc25C) and some apoptosis-related proteins (Bcl-2, Bax, Bid, Bad, Apaf1, AIF and Cyt c), curcumin also downregulated the oxidative stress-induced heat shock proteins (HSPs) and histone deacetylase 6 (HDAC6), which further led to apoptosis [7].

In a recent study, HPV18 infected cervical carcinoma has been reported to be treated by curcumin. It restored the p53-mediated transactivation of proapoptotic genes in cervical carcinoma and resulted apoptosis [8]. Curcumin also exhibited inhibitory effects on undifferentiated Nasopharyngeal Carcinoma (NPC) by inhibiting the expression of miR-125a-5p, and subsequently up-regulating the expression of p53 [9]. In addition, curcumin increased the ERK1/2 phosphorylation, and induced protein expression of the tumor suppressors FOXO3a and p53, which leads to the apoptosis in NPC. Curcumin also have the potential to induce the direct interaction of prohibitin (PHB) with p53 in the whole cell and decreased in the nuclear matrix, which induced apoptosis in immortalized human epidermal HaCaT cells. Recently, it was reported that curcumin-based Zn(II)-complex induces conformational change in p53-R175H and -R273H mutant proteins, and restored wtp53-DNA binding and transactivation functions that subsequently results apoptosis [10]. Besides this, hydroxylated biphenyl (D6), a structural analogue of curcumin was also reported for its quick cellular uptake and subsequent block of cell cycle in G2/M phase transition probably through the regulation of p53 signalling pathways as well as by down-regulation of the PI3K/Akt and NF- κ B pathways [11]. Other than the analogues, derivatives and different formulations, curcumin showed the synergistic effects with SiRNA therapies for cancer prevention. Ki-67-7 treated bladder cancer cells potentiate the curcumin-mediated apoptosis and cell cycle arrest by p53- and p21-independent mechanisms [12]. Curcumin was also investigated along with cisplatin for modulation of p53 gene expression and its effect on cisplatin-induced neurotoxicity in NGF-differentiated PC12 cells where, it was indicated that curcumin may reduce cisplatin-induced neurotoxicity [13]. Disruption of p53-MDM2 interaction is also very critical for p53 stabilization. Curcumin downregulated the expression of MDM2 at the transcriptional level in a p53-independent manner, which ultimately up-regulates p21 and induces apoptosis in a prostate cancer cell line [14]. Extensive published literature on the pharmaceutical and nutraceutical value of curcumin revealed that it has potential in the prevention and treatment of degenerative neurologic diseases, cystic fibrosis, and cardiovascular diseases. These studies proved that curcumin and their analogues as well different its formulations could be used as a p53 targeting therapeutic drug without any adverse side effects. However, it also opens a new avenue for the debate on therapeutic values of curcumin particularly in cancer patients.

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