Indole-3-carbinol mediated cell cycle arrest of LNCaP human prostate cancer cells requires the induced production of activated p53 tumor suppressor protein.

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Abstract
Indole-3-carbinol (I3C), a dietary compound found naturally in cruciferous vegetables of the Brassica genus such as broccoli and brussels sprouts, induces a G1 growth arrest of human reproductive cancer cells. We previously reported that in LNCaP prostate cancer cells, I3C down-regulated cyclin-dependent kinase (CDK) 2 activity. In our current study, Western blotting and quantitative RT-PCR demonstrated that I3C treatment increased both the transcripts and protein levels of the CDK2 inhibitor p21(waf1/cip1) (p21). Transfection of luciferase reporter plasmids containing wild-type and mutated p21 promoter fragments revealed that I3C induced p21 gene transcription through a p53 DNA binding element. Oligonucleotide precipitation showed that I3C increased the level of activated p53 nuclear protein that is competent to bind its DNA target site on the p21 promoter. Ablation of p53 production using short interfering RNA (siRNA) prevented that the I3C induced G1 arrest and up-regulation of p21 expression. Western biots using p53 phospho-specific antibodies revealed that I3C treatment increased the levels of three phosphorylated forms of p53 (Ser15, Ser37, Ser392) that are known to contribute to p53 protein stability and greater transactivation potential. Taken together, our results establish that the I3C induced G1 arrest of human prostate cancer cells requires the induced production of the activated phosphorylated forms of p53, which stimulate transcription of the CDK2 inhibitor p21.

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