Indol 3 carbinol suprime atividade do NF-kappaB e estimula a via p53 em células da leucemia linfoblática B pré-aguda

Indole-3-carbinol suppresses NF-κB activity and stimulates the p53 pathway in pre-B acute lymphoblastic leukemia cells.

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Abstract

B cell precursor acute lymphoblastic leukemia (BCP-ALL) is the most common type of cancer in children. Dramatic improvements in primary therapy for childhood ALL have led to an overall cure rate of 80 %, providing opportunities for innovative combined-modality strategies that would increase cure rates while reducing the toxic side effects of current intensive regimens. In this study, we report that indole-3-carbinol (I3C), a natural phytochemical found in cruciferous vegetables, had anti-leukemic properties in BCP-ALL NALM-6 cells. I3C induced cell growth inhibition by G1 cell cycle arrest and triggered apoptosis in a dose- and time-dependent manner. p53, p21, and Bax proteins showed increased expression after I3C treatment. Real-time PCR analysis of pro-apoptotic p53 target genes revealed up-regulation of PUMA, NOXA, and Apaf-1. I3C also suppressed constitutive nuclear factor-κB (NF-κB) activation and inhibited the protein expression of NF-kappa B-regulated antiapoptotic (IAP1, Bcl-xL, Bcl-2, XIAP) and proliferative (c-Myc) gene products. Coadministration of I3C with the topoisomerase II inhibitor, doxorubicin, potentiates cytotoxic effects compared with either agent alone. Apoptosis induction by the drug combination was associated with enhanced caspase-9 activation and PARP cleavage. Furthermore, I3C abolished doxorubicin-induced NF-κB activity as evidenced by decreased nuclear accumulation of p65, inhibition of IκBα phosphorylation and its degradation, and decreased NF-κB DNA-binding activity. Western blot analysis revealed that doxorubicin-induced Bcl-2 protein expression was inhibited by I3C. Overall, our results indicated that using nontoxic agents, such as I3C, in combination with anthracyclines might provide a new insight into the development of novel combination therapies in childhood BCP-ALL.

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