Ketoconazole induces G0/G1 arrest in human colorectal and hepatocellular carcinoma cell lines

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Abstract

Ketoconazole is an oral-antifungal agent that has been used worldwide in the treatment of some hormone-dependent human cancer. In this study, we demonstrated that ketoconazole (20 mM) induced various types of human cancer cell growth arrest in the G0/G1 phase. Our results revealed that ketoconazole-induced growth arrest was more profound in COLO 205 and Hep G2 (with wild-type p53) than in HT 29 (p53 His273 mutant) and Hep 3B (with deleted p53) cells. The protein levels of p53, p21/Cip1, and p27/Kip1 were significantly elevated by ketoconazole (10 mM) treatment in COLO 205 but not in HT 29 cells. The ketoconazoleinduced G0/G1 phase arrest in COLO 205 cells was attenuated by p53-specific antisense oligodeoxynucleotides (20 mM) treatment.These results suggested that the p53-associated signaling pathway is involved in the regulation of ketoconazole-induced cancer cell growth arrest. By Western blot analysis, we demonstrated that cyclin D3 and CDK4 protein but not other G0/G1 phase regulatory protein levels were decreased by ketoconazole-treatment in both COLO 205 and HT 29 cells. Our study provides the basis of molecular mechanisms for ketoconazole in growth inhibition of human cancer cells and such results may have significant applications for cancer chemotherapy.