In vitro and in vivo studies of the anti-cancer action of terbinafine in human cancer cell lines

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Abstract

Terbinafine (TB) (Lamisil®), a promising oral antifungal agent used worldwide, has been used in the treatment of superficial mycosis. In our study, we demonstrated that TB dose-dependently decreased cell number in various cultured human malignant cells. Flow cytometry analysis revealed that TB interrupts the cell cycle at the G0/GI transition. The TB-induced cell cycle arrest in colon cancer cell line (COLO 205) occurred when the cyclin-dependent kinase (cdk) system was inhibited just as the levels of p53, p21/Cipl and p27/Kipl proteins were augmented. In the TB-treated COLO 205, the binding between p53 protein and p53 consensus binding site in p21/Cipl promoter DNA probe was increased. Pretreatment of COLO 205 with p53-specific antisense oligodeoxynucleotide decreased the TB-induced elevations of p53 and p21/CipI proteins, which in turn led to arrest in the cell cycle at the G0/GI phase. Moreover, in the p53 null cells, HL60, TB treatment did not induce cell cycle arrest. Taken together, these results suggest an involvement of the p53-associated signaling pathway in the TB-induced antiproliferation in COLO 205. We further examined whether administration of TB could affect the growth of tumors derived from human colon cancer cells in an in vivo setting. COLO 205 cells implanted subcutaneously in nude mice formed solid tumor; subsequent intraperitoneal injections of TB (50 mg/kg) led to obvious decline in tumor size, up to 50-60%. In these tumors, increases in the p21/CipI, p27/KipI and p53 proteins and the occurrence of apoptosis were observed. Combined treatment with TB and nocodazole (ND), a clinically used anticancer agent, potentiated the apoptotic effect in COLO 205. These findings demonstrate for the first time that TB can inhibit the proliferation of tumor cells in vitro and in vivo.