Inhibition of hunam vascular endothelial cells proliferation by terbinafine

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Abstract

We have demonstrated previously that terbinafine (TB), an oral antifungal agent used in the treatment of superficial mycosis, suppresses proliferation of various cultured human cancer cells in vitro and in vivo by inhibiting DNA synthesis and activating apoptosis. In our study, we further demonstrated that TB at a range of concentrations (0-120 μM) dose-dependently decreased cell number in cultured human umbilical vascular endothelial cells (HUVEC). Terbinafine was not cytotoxic at a concentration of 120 μM, indicating that it may have an inhibitory effect on the cell proliferation in HUVEC. The TB-induced inhibition of cell growth rate is reversible. [3H]thymidine incorporation revealed that TB reduced the [3H]thymidine incorporation into HUVEC during the S-phase of the cell-cycle. Western blot analysis demonstrated that the protein levels of cyclin A, but not cyclins B, D1, D3, E, CDK2 and CDK4, decreased after TB treatment. The TB-induced cell-cycle arrest in HUVEC occurred when the cyclin-dependent kinase 2 (CDK2) activity was inhibited just as the protein level of p21 was increased and cyclin A was decreased. Pretreatment of HUVEC with a p21 specific antisense oligonucleotide reversed the TB-induced inhibition of [3H]thymidine incorporation. Taken together, these results suggest an involvement of the p21-associated signaling pathway in the TB-induced antiproliferation in HUVEC. Capillary-like tube formation and chick embryo chorioallantoic membrane (CAM) assays further demonstrated the anti-angiogenic effect of TB. These findings demonstrate for the first time that TB can inhibit the angiogenesis.