

SP1-regulated p27/Kip1 gene expression is involved in terbinafine-induced human A431 cancer cell differentiation: An in vitro and in vivo study

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Abstract

In this study, the differentiation-promoting effects of terbinafine (Lamisil), TB were investigated in human epithelioid squamous carcinoma (A431) cells. The polyhydroxyethylmethacrylate (poly-HEMA)- and type-I collagen-coated culture plate models were adapted to harvest the TB-induced differentiated cells by agitation of the suspension medium. We demonstrated that p27/Kip1, p21/Cip1 and the keratinocyte differentiation marker, human involucrin (hINV), were induced (>25 microM) in TB-induced differentiated A431 cells. Animal studies demonstrated that administration of TB (10 mg/kg body weight) inhibited A431-xenografted tumor growth through differentiation processes as evidenced by expression of pancytokeratin in tumor tissues. Immunocytochemical staining analysis showed that p27/Kip1, but not p21/Cip1, positive-stained cells were detected in the early-differentiated cells of TB-treated tumor tissues. SP1, which regulates p27/Kip1 expression, was induced by TB (>10 microM) in A431 cells. The TB-induced promoter activity and protein expression levels of p27/Kip1 were significantly attenuated by pretreatment with mithramycin A, a SP1 specific inhibitor. We also demonstrated that TB-induced differentiated A431 cells sorted from the poly-HEMA-coated culture plates were arrested in the G1 phase. TB-induced G1 arrest in the suspension-cultured cells was attenuated by mithramycin A pretreatment. Such results suggest that SP1 plays a critical role in the p27/Kip1 gene transcriptional activation that may be subsequently involved in the TB-induced A431 cancer cell differentiation process.