

題名: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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摘要: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 mM) 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 mM) 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.