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• 中文摘要

我們的先前研究發現臨床上治療皮膚病的用藥 Terbinafine (TB)可藉由抑制內皮細胞增生進而抑制血管增生。本研究我們繼續證明 TB 可以抑制內皮細胞的粘附及遷移，且其抑制作用隨著 TB 濃度的增加而漸增。利用西方點墨法我們證實 TB 可以抑制細胞內 Ras 蛋白質的含量以及結合到細胞膜上面 Rho 的含量。同時當細胞給予 farnesol (FOH)及 geranylgeraniol (GGOH)等藥物，可以避免 TB 所引起的內皮細胞遷移的抑制作用。然而這些因爲 FOH 及 GGOH 所引起的作用卻可被 Ras inhibitor peptide 及 ROCK inhibitor (Y27632)所終止。這樣的結果讓我們認爲細胞內 geranylgeranyl pyrophosphate 的耗損會抑制蛋白質的 geranylgeranylation 及 farnesylation (這兩個作用是 Rho GTPases 及 Ras 的活化所必須的)，進而抑制內皮細胞的遷移。我們同時也觀察到 TB 藥物會降低內皮細胞的磷酸化 focaladhesion kinase (FAK)及 paxillin 兩種蛋白質的含量，以及 matrix metalloproteinase (MMP)2 及 MMP 9 的 mRNA 含量。綜合這些研究結果，我們認爲 TB 對內皮細胞遷移作用的抑制現象可能是藉由抑制了 Rho 所調控的訊息傳遞所造成。

• 英文摘要

Our previous studies have demonstrated that terbinafine (TB), a newly synthesized oral antimycotic drug, exerts anti-tumorigenesis and anti-angiogenesis activities. TB treatment caused cell cycle arrest at the G0/G1 phase through up-regulation of the p53 protein, which in turn caused an increase in p21 expression, and finally inhibited the cyclin-dependent kinase 4 (CDK4) activity in various cancer cells including colon and liver cancer cell lines. Moreover, administration of TB reduced the growth of tumors derived from human colon cancer cells in an in vivo setting. (Lee et al. 2003). In the human vascular endothelial cells, treatment with TB also caused growth inhibition through up-regulation of p53 and p21 protein, which in turn inhibited CDK2 kinase activity, and finally arrested cell cycle at the G0/G1 phase. Using tube formation and CAM assays, we further

demonstrated that TB exerts anti-angiogenic activity (Ho et al. 2003). Taken together, we results strongly suggest the potential applications of TB in the treatment of human cancer. Although we are very happy with these exciting findings, several important issues still need to be further addressed before it can be applied for the clinical uses. Accordingly, the proposed grant application is aimed to apply the cellular and molecular biology techniques to further study the anti-cancer activity of TB in detail. In the present study, we found that TB dose-dependently inhibited adhesion and migration of HUVEC. The levels of phosphorylated ERK and FAK were downregulated in the TB-treated HUVEC. Pretreatment of HUVEC with TB prevented TB-induced inhibition of [3H]thymidine incorporation. Taken together, our data suggest that RAS, ERK and FAK might be involved in the TB-induced inhibition of angiogenesis. Using RT-PCR technique, we also demonstrated that the p21 mRNA levels were up-regulated in HUVEC after 6 hr treatment with TB, suggesting that TB-induced increase of p21 protein is at the transcriptional level.