抗黴菌藥抑制人類惡性腫瘤細胞生長之分子機制

Studies on the Molecular Mechanisms of Antifungal Agents-induced Human Malignant Cells Growth Arrest

中文摘要

Ketoconazole 與 Terbinafine 是臨床上時常被使用的口服抗黴菌藥，且 Ketoconazole 已經被用於治療人體某些依賴荷爾蒙生長的癌症上。本研究證實 Ketoconazole 與 Terbinafine 能使癌細胞的生長週期停滯在 G0/G1 時期，進而抑制癌細胞的生長。藉由流式細胞儀的分析以及細胞生長曲線的分析，我們觀察到 Ketoconazole 與 Terbinafine 誘發癌細胞生長週期停滯的效果，在 COLO 205 細胞（具有 wild-type p53）比 HT 29（p53 His 273 突變）和 Hep 3B 細胞（缺少 p53 基因）要好。由此我們推論 p53 的表現和 Ketoconazole 與 Terbinafine 所引發的癌細胞 G0/G1 時期停滯的過程有某些相關性。我們藉由 Ketoconazole 或 Terbinafine 處理的 COLO 205 細胞中加入 p53 antisense oligonucleotides 的實驗來證實這點推論。同時，Ketoconazole 與 Terbinafine 會引起大腸癌細胞株 p53，p21，p27 等蛋白質表現量增加，且相對的抑制 Cyclin D3 及 CDK4 等蛋白質的表現，且 Terbinafine 誘發 HL 60 細胞凋亡的發生。在裸鼠的實驗上也證實 Ketoconazole 及 Terbinafine 抑制 COLO 205 腫瘤生長。本研究提出 Ketoconazole 與 Terbinafine 誘發大腸癌細胞生長週期停滯的分子機制，也因爲 Ketoconazole 與 Terbinafine 具備這些效果，我們認爲 Ketoconazole 與 Terbinafine 可成爲具有潛力的癌症治療藥物。

英文摘要

In this study, we demonstrated that Ketoconazole (KT) and Terbinafine (TB), two widely used oral-antifungal agents inhibit cell cycle progression in human colorectal and hepatic cancer cell lines in G0/G1 phase. Human cancer cells with various p53 statuses were used to investigate the mechanisms of KT- and TB-induced G0/G1 arrest. The results of flow cytometry and cell growth curve analyses revealed that KT and TB-induced growth arrest was more profound in COLO 205 (with wild-type p53) than in HT 29 (p53 His273 mutant) and Hep 3B (with deleted p53). By the way, TB induced apoptosis in HL 60 cells. KT and TB increased the expression of p53, p21, and p27 in cancer cells, and inhibited the expression of CyclinD3 and CDK4 proteins leaded to the growth arrest in human cancer cells. In contrast, the expression of PCNA, as well as cyclin A, D1, and E levels in human cancer cells were not significant change as compared with untreated cells. CDK4 and CDK2 kinase activity from cells treated with KT and TB was markedly inhibited. In nude mice experiments, treated

with KT or TB inhibit the growth of human COLO 205 tumor. Taken together, these results suggest universality of KT and TB in cessation of cell proliferation, also make them very attractive agents for use as potential cancer chemotherapeutic agents.