Griseofulvin 造成人類乳癌細胞(MCF-7)細胞週期停滯與凋亡之分子機制探討

Studies on the Molecular Mechanisms of Griseofulvin-induced G2/M Cell Cycle Arrest and Apoptosis in Human Breast Cancer Cells (MCF-7)

中文摘要

Griseofulvin (GF)目前是一種被廣泛使用的口服抗黴菌藥物，現已知道 GF 有抗癌的效果，其主要的作用機制是經由干擾微小管(Microtubule)的聚合(polymerization)，來達到使細胞凋亡(Apoptosis)的目的。在本研究中，發現到 GF 會誘發人類乳癌細胞 MCF-7 生長週期的停滯(G2/M arrest)及凋亡現象(Apoptosis)。而這樣的現象，會在使用了低濃度的 Paclitaxel (TA)後被加強，同時 GF 的致效濃度也會由原本的 10 M 下降至 5 M。而在其他不同細胞的反應上，實驗中觀察到了這樣的組合對於人類血癌細胞 HL-60、大腸癌細胞 HT-29 這兩株 p53 缺陷的細胞會同時誘發細胞週期停滯和凋亡；在另一株大腸直腸癌細胞 COLO-205，這株 p53 正常的細胞中，則觀察到了高比例的細胞凋亡，並沒有明顯的細胞週期停滯現象。另外本研究中也發現，在 MCF-7 細胞中，隨著 GF 濃度的增加，14-3-3 蛋白有被活化的現象，這樣的現象也在使用了低濃度的 TA 變的更明顯；而在 CDC2 蛋白活性的分析上，實驗中也看到了 CDC2 蛋白活性被抑制，推測是因爲 14-3-3 蛋白被活化而抑制了 CDC2 蛋白之活性。另外，本篇研究也觀察到在 TA 單獨處理細胞時，會使 Akt/PKB 的活性被抑制，而在將 GF 和 TA 共同處理 MCF-7 細胞後，Akt/PKB 的活性被抑制的更明顯。因此本論文最後推測 GF 誘發 G2/M 細胞週期的停滯，與 14-3-3 蛋白的活化有相當密切的關係，且低濃度的 TA 會經由抑制細胞內 Akt/PKB 活化路徑來強化 GF 誘發細胞凋亡的作用。

英文摘要

Griseofulvin (GF) is an antifungal antibiotic produced by various species of Penicillium. It is a spindle poison which could interfere with the organization of microtubules at mitosis or other processes mediated by the microtubules networks. In this study, we found GF could induce G2/M cell cycle arrest and apoptosis in MCF-7 cells. And this effect could be enhanced by low concentration of Paclitaxel (TA). In other cells, including HL-60, HT-29, COLO 205, and A431, we also found the G2/M arrest and apoptosis in the p53-defect cells (HL-60 and HT-29 and A431); but apoptosis in the p53-wild type cells (COLO 205). When MCF-7 cells treated with GF, we found GF can induce 14-3-3 . activation in

dose-dependent manner, and this effect also enhanced by low concentration of TA. We also found when MCF-7 cells cotreated with GF and TA and the CDC2 kinase activity was inhibited, suggested that CDC2 kinase activaity was inhibited by 14-3-3 . Besides that, we found that TA can inhibit the avtivity of Akt/PKB, and when MCF-7 cells cotreated with GF and TA, we saw a dramatically inhibition of activity of Akt/PKB. Our data will support that GF induced G2/M arrest by activated 14-3-3 ..and low concentration of TA will inhibit the Akt/PKB pathway to enhance GF-induce apoptosis in MCF-7 cells.