Meclizine 誘發人類直腸腫瘤細胞(COLO 205)細胞週期停滯及細胞凋亡之分子機制研究

Studies on the molecular mechanisms of Meclizine-induced cell cycle arrest and apoptosis in human colon adenocarcinoma cells

中文摘要

Meclizine (以下簡稱 Mec)是一種用來治療頭暈和暈眩的用藥，爲抗組織胺藥物的一種。在藥物與細胞的交互作用之中，我們發現 Mec 會讓人類直腸腫瘤細胞 COLO 205 誘發細胞凋亡現象。在人類直腸腫瘤細胞 COLO 205 中，以不同濃度的 Mec 處理細胞 24 小時後，觀察到細胞在 50mM 以上濃度有讓細胞走向細胞凋亡 dose-dependent 的情形。同時，在顯微鏡之下觀察可以看到隨著 Mec 藥物濃度增加，細胞數目隨之減少。在流式細胞儀的分析之中，也可以看到處於 G0/G1 phase 的細胞比例會因著 Mec 的作用而增加。在以西方墨點法分析各種相關蛋白質的變化之後，關於細胞週期停滯方面我們觀察到 p53 與 p21 蛋白在 Mec 作用之後都會升高，而 CDK2 和 CDK4 的活性則受到抑制，這就是 Mec 造成細胞週期停滯的機轉。在引起細胞凋亡方面，我們看到 Mec 可以 dose-dependently 造成以下結果: p53 蛋白表現量增加，Bcl-2 蛋白表現量減少，Bad 蛋白表現量不變，cytochrome C 由粒線體釋放到細胞質中，AIF 由粒腺體進入細胞核中，Apaf-1 蛋白表現量不變，Caspase 9，Caspase 8，Caspase 3 活化，PARP 被 degrade。根據這些結果和文獻的探討，我們提出一個模式圖來解釋 Meclizine 引起 COLO 205 細胞走向細胞凋亡和細胞週期停滯的分子機轉。

英文摘要

Meclizine, a kind of histamine H1 antagonist, has been used in the treatment of motion sickness and vertigo. In studying the interaction of drugs and cancer cell lines, we have found that meclizine dose-dependently induced apoptosis in COLO 205 cells. By DNA ladder assay, we demonstrated that DNA ladder appeared with meclizine treatment in COLO 205 cells if dosage larger than 50 μM. Besides, we observed that cell numbers decreased dose-dependently after treatment with meclizine in COLO 205 cells. By flow cytometry, we noticed that the percentage of COLO 205 cells in G0/G1 phase increased dose-dependently. We analyzed the change of associated protein by Western blot. About cell cycle arrest, p53 and p21 were upregulated after treatment with meclizine and resulted in decreasing CDK2 and CDK4 kinase activity. About apoptosis, meclizine induces upregulation of p53, downregulation of Bcl-2, release of cytochrome C into cytosol from mitochondria, translocation of AIF to the

nucleus from mitochondria, and activation of caspase 3, caspase 8, and caspase 9. According to these data and concepts from references, we propose a flowchart to explain the possible mechanism of meclizine-induced apoptosis and cell cycle arrest in COLO 205 cell.