黑殭菌素 B (Destruxin B)、愛瑞莎 (Iressa)合併使用對抗肺癌細胞之腫瘤機制探討

The Anti-tumor Mechanism of Combine Destruxin B with Iressa in Human Lung Cancer Cells

中文摘要

全球因癌症死亡的案例中，肺癌首居其位，而肺癌引發的死亡率遠超過前列腺癌、乳癌以及結腸直腸癌等。先前研究指出有許多治療標的針對癌細胞的生長及存活，其一標的爲表皮生長因子接受器(Epidermal growth factor receptor, EGFR)，在許多癌症如頭頸癌、乳癌及咽喉癌可見表皮生長因子接受器(Epidermal growth factor receptor, EGFR)有過度表現的情形，愛瑞莎(Iressa)即爲一種口服的表皮生長因子接受器酪胺酸激?抑制劑(EGFR-TKI)。但服用愛瑞莎受限於劑量及其所產生的副作用。黑殭菌素(Destruxins)爲黑殭菌(Metarrhizium anisopliae)二次代謝物，爲環狀胜?物質(cyclic hexadepsipeptides)。先前研究指出，在人類肝癌細胞黑殭菌素 B (Destruxin B)對於 B 型肝炎病毒表面抗原(HBsAg)之基因表現具抑制效果。故本實驗目的合併使用 Iressa 與黑殭菌素 B(Destruxin B)，觀察對於 A549 肺腺癌(EGFR wild type, K-ras mutaion)、FaDu 鱗狀上皮肺癌(EGFR wild type, K-ras wild type)細胞株，探討合併藥物的抗腫瘤機制。依文獻 K-ras 突變時使用 Iressa (EGFR inhibitor)並不具有反應，本實驗用流式細胞儀分析及粒線體膜電位發現愛瑞莎(7 μM)對 A549 肺腺癌(K-ras mutation)效果較差，符合先前文獻；但在 Destruxin B 合併使用愛瑞莎反而發現 A549 肺腺癌具有良好的反應，此結果顯示 Destruxin B 待未來通過臨床檢測之後，對於肺腺癌(Adenocarcinoma,尤其具 K-ras mutation)的治療，可能使得治療肺癌更具專一性。此外，依西方墨點法分析，可知 A549 細胞透過外在路徑與內在路徑造成細胞凋亡，以及 AIF 的釋放使細胞走向凋亡，即不需由 caspase 活化之 caspase-independent pathway；而 FaDu 細胞則是透過外在路徑造成細胞凋亡。

英文摘要

Lung cancer is the leading cause of cancer deaths worldwide, representing more deaths than those from prostate, breast, and colorectal cancers combined. Recent development in cancer biology have identified many therapeutic target drugs, one of these target drugs is Iressa(Gefitinib), is an orally active EGFR tyrosine kinase (EGFR-TKI) for NSCLC therapy. But efficacy to Iressa is limited to dosage and side effect. Recent studies indicate that Destruxin B is a second metabolite of fungus (Metarhizium anisopliae) In human, Destruxin B could inhibit Hepatitis B surface antigen(HBsAg) gene expression in Hep3B cell. The aim to this report is combine DB

and Iressa to treat human adenocarcinoma cell (A549，K-ras mutation) and human squamous cell (FaDu，K-ras wt), to observe the anti-tumor efficacy. Previous studies indicate that Iressa treatment has resistant to NSCLC patients with K-ras mutation, this corresponds to our results in Flow cytometry. However, combined therapy seemed to be good response in A549 adenocarcinoma, suggests that Destruxin B may be a potential drug in lung cancer therapy after passing clinical trials, particularly in adenocarcinoma cells with K-ras mutaion expression. In other hand, we observed the signal pathway of combined drugs by western blotting, showed that A549 cells induced apoptosis via extrinsic and intrinsic pathway; and release of AIF protein resulting in cells apoptosis via caspase-independent pathway without caspase activation. FaDu cells induced apoptosis via extrinsic pathway.