AZ-1 造成乳癌細胞死亡原因之探討

Study the AZ-1(Aziridinylnaphthoquinon) on causing the death of the breast cancer cells

中文摘要

乳癌一直是女性癌症死亡的重要原因之一，在美國乳癌死亡率約為 26%，在國內根據衛生署統計乳癌佔女性病患死亡已達到第 2 位，僅次於子宮頸癌，但似乎每年有增加的趨勢，因此乳癌治療乃是女性的健康主題，相信能找到更多的抗癌症的治療方法或藥物是許多人努力的方向，也是癌症患者的福音。在許多的研究報告中可以發現抗癌藥物誘發癌細胞進行 apoptosis 是目前著重的一個研究方向(尤其是 Bcl-2 protein)，而初步研究發現 AZ-1 (Bis-Aziridinoquinonyl thiaethers)對乳癌細胞 BC-M1 具有致死作用，發現 AZ-1 引起細胞死亡率在濃度 0.5 μM 、24 小時對 BC-M1 造成接近 50%的致死率，而且在 48 小時更有接近 99%的致死率。而 AZ-1 對細胞毒性分析則發現在 0.125-1.98 μM 濃度下對 Skin Fibroblast 的死亡並不明顯但對 BC-M1 則毒性明顯，另外以 AZ-1 與 Paciltaxel(Taxol)及 Tamoxifen 比較下，發現再 0.5 μM 濃度以上，AZ-1 對於 BC-M1 致死率比 taxol 和 tamoxifen 高，而對於 Fibroblast 細胞毒性則相差不多。

接下來利用流式細胞儀發現，在低劑量下 AZ-1 能部分抑制細胞週期的進行。利用西方點墨法發現 cdk2 表現量下降而 cyclin B 變化卻不明顯。此外在流式細胞儀的結果中發現，隨著劑量的提高，sub-G1 峰逐漸的升高。利用 DNA 螢光染色亦發現有 DNA 斷裂的現象。在 NMR 的分析上發現隨著劑量的增加，CH3/CH2 的比值也跟著提升;而測得 caspase-3 酵素活性上，發現愈高劑量酵素活性也跟著提高。利用西方墨點法發現，隨著劑量的增高，pro-Caspase 3 與 TIAR 的蛋白表現量隨之下降。綜合以上我們推測 AZ-1 造成乳癌細胞的死亡的方式為細胞凋亡的路徑。

英文摘要

Breast cancer remains a major health issue in many countries. The death rate of breast cancer is about 26% in USA. According to the statistics of department of health, the breast cancer has taken the second place which cause the death of female patients, only next to cervical cancer and increasing by yearly in Taiwan. It is believed that the prevention is most important thing and the other found out more anti-cancer drugs to cure the breast cancer patients. According the recent reports, it is better choice that the anti-cancer drugs could induce the cancer cell death by apoptosis pathway.

In our preliminary data, we found that the Az-1(Bis-Aziridinoquinonyl thiaethers) induce cell death of breast cancer BC-M1 by dose-dependent manner and time-course.

Base on the MTT cytototoxicity assay in our result, the AZ-1 was with lower lethal effect on human fibroblast cell in 2 μM. Comparing the effect of cell death on BC-M1 cell induced by AZ-1、pacilitacel and tamoxifen, we found that the AZ-1 was better than these two compounds. The AZ-1 could induce the BC-M1 cell arrest in G0/G1 phase minor. In western blot, we find cdk2 expression decrease, but cyclin B no effect. The signal of BC-M1 cell progress on apoptosis pathway induced by AZ-1 were including the CH2/CH3 peak ratio increasing by dose-dependent manner determined by NMR analysis, and also in caspase-3 enzyme activity increasing. In western blot, we find pro-caspase and TIAR level were increased. From the above result, we propose that the AZ-1 could induce the BC-M1 cell progress the apoptosis pathway.