三氧化二砷對人類皮膚癌細胞所引發之程序性細胞凋亡作用機制之探討

Studies on the Mechanism of Arsenic Trioxide-Induced Apoptosis in Skin Cancer Cell

中文摘要

1996 首次在活體外實驗證實三氧化二砷可抑制急性前骨髓性白血病 NB4 細胞株之增生以及誘發該細胞發生細胞凋亡，臨床上也發現三氧化二砷可以有效的治療再發性急性前骨髓性白血病，之後陸續有研究報告指出三氧化二砷可以誘導許多不同的腫瘤細胞株發生細胞凋亡作用；除了非急性前骨髓性白血病的血液腫瘤細胞株外，在實體腫瘤細胞(solid tumor) 模型上，亦發現三氧化二砷可以藉由不同的作用路徑，誘導不同的腫瘤細胞產生程序性細胞凋亡。爲了要瞭解三氧化二砷對皮膚癌細胞的影響爲何，本研究針對三氧化二砷對各種不同皮膚癌細胞株之存活率，細胞增生率以及誘導細胞凋亡發生之能力進行評估，實驗中所使用的皮膚癌細胞株包括人類基底細胞癌 (BCC1-KMC)，人類鱗狀上皮細胞癌(A431)，人類黑色素腫瘤(Hs695T 及 PRMI 7951)。由偵測細胞核內 DNA 所呈現之階梯狀斷裂的程度、流式細胞儀的定量以及細胞形態分析的結果顯示，三氧化二砷確實會抑制多種皮膚癌細胞之生長。利用西方墨點法來偵測蛋白質表現的變化情形時，我們發現隨著三氧化二砷誘導細胞發生凋亡的時間，細胞內之 P53、P21、CPP32 和 PARP 等蛋白有被活化的情況，而反股 p53-DNA 寡核酸序列可以部分降低三氧化二砷所誘發的細胞凋亡比例，因此，我們認爲誘導 p53 蛋白之大量表現可能在三氧化二砷所誘發的細胞凋亡路徑中扮演相當重要的角色。

英文摘要

Arsenic trioxide (As2O3) was recently found to induce complete remission in the patients with refractory acute promyelocytic leukemia (APL) and to inhibit proliferation and induce apoptosis in the APL cell line NB4. Afterwards, As2O3 was reported to have cytotoxic effects in several human cancers including solid tumors by induction of apoptosis. We wondered whether As2O3 was able to induce apoptosis in skin cancer cells. We demonstrate in this report As2O3 induces apoptosis in skin cancer cell lines such as human basal cell carcinoma (BCC1-KMC), human epidermoid carcinoma (A431), human malignant melanoma (Hs695T) and PRMI 7951 in a dose- and time-dependent manner, as evidenced by internucleosomal DNA fragmentation and morphologic changes. By western blot analysis, we found that the induction of apoptosis involved an early increase in p53 protein and caspase 3

activation; however, the expressions of Bcl-2 and Bax were not changed after the treatment of As2O3. In addition, pretreatment of these skin cancer cells with p53 antisense oligonucleotide could effectively block As2O3—induced apoptosis, but not by p53 sense oligonucleotide. Thus, our findings suggest that the p53-associated signaling pathway is critically involved in As2O3—mediated apoptotic cell death.