TSDH 引起人類前列腺癌細胞凋亡之分子機制探討

Study of the molecular mechanisms of TSDH-induced apoptosis in prostate cancer cells

中文摘要

先前我們的研究已證實 TSDH 能夠使得乳癌細胞生長停滯，並讓細胞週期停滯於 G1 期，且經過依賴 p53 和 RB 腫瘤抑制基因來誘導細胞死亡；此外，在肝癌細胞中會降低 glutathione 的含量而引起大量 ROS 的產生，進而造成細胞凋亡。然而 TSDH 藥物是否也會透過其它細胞凋亡途徑而使細胞死亡至今仍未報導。在本實驗中以 MTT 測定細胞存活度，發現 TSDH 有意義地降低前列腺癌細胞的增生；而且也在 DNA fragm entation 和流式細胞儀中也檢測到 TSDH 會誘導 DU145 細胞凋亡。TSDH 能夠誘導細胞內質網壓力的產生，同時內質網壓力相關恆定蛋白如葡萄糖調節蛋白 (GRP78)，GADD153 (CHOP) 也會被誘導，且會增進真核轉錄起始因子 (eIF????)，內質網上穿膜蛋白 (PERK)，MAPK/JNK 的磷酸化，以及 XBP1 m RNA 的切割型式增加。另一方面，TSDH 能夠活化細胞凋亡相關蛋白，包括 PARP, caspase 9 及 caspase 3。結果顯示 TSDH 可以誘導細胞內質網壓力及未折疊蛋白反應引起前列腺癌細胞的凋亡，因此可能具有治療人類前列腺癌細胞的潛力。

英文摘要

Our previous studies have demonstrated that TSDH could induce cell cycle arrest in G1 phase and cell apoptosis through mitochondrial pathway in human breast cancer. In addition, other study also demonstrated that TSDH induced reactive oxygen species production through depletion of glutathione, and resulted in apoptosis of human hepatoma cells. However, whether TSDH can induce apoptosis through ER (endoplasmic reticulum) stress pathway remains to be examined. In this study, we found that TSDH significantly decreased the proliferation by MTT assay and induced apoptosis by DNA fragmentation and flow cytometry assays in human prostate cancer cells DU145. TSDH was able to induce ER stress, including up-regulation of glucose regulation protein 78 (GRP78), GADD153 (CHOP) and inducing phosphorylation of eIF???? and JNK, and increase XBP1 mRNA splicing form in DU145 cells. In addition, TSDH activated apoptotic relative proteins, including PARP, caspase 9, and caspase 3. The results suggested that TSDH could induce prostate cancer cells apoptosis via induction of ER stress and unfold protein response, and might have therapeutic potential for prostate cancer