表觀遺傳藥物對自然殺手細胞之抗膀胱癌免疫治療功能之研究

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膀胱癌是泌尿系統中常見的惡性疾病之一，為全球的第十大癌症。抽菸與重金屬砷污染的水源為罹患膀胱癌的主要危機因子。膀胱癌病人在進行手術後，會再進一步以化學療法或免疫療法治療。雖然免疫療法在最近有很大的進展，但只對部分的病人有效，導致病人的預後並不理想，復發機率也相當高。因此，目前需要找到更有效治療膀胱癌的方式。

自然殺手細胞在先天免疫上及抗癌機制上扮演重要的角色，當其受體 NKG2D 被癌細胞上的配體 ULBP2 活化後，自然殺手細胞會進一步殺死癌細胞。先前有研究發現癌細胞上的 ULBP2 受到表觀遺傳調控，導致基因沉默，從而躲避自然殺手細胞的攻擊。因此，我們想探討表觀遺傳藥物 HDAC 抑制劑，是否能恢復受到表觀遺傳沉默的 ULBP2 的表現，並增加自然殺手細胞之抗癌免疫反應。 從我們初步的細胞實驗結果顯示，經過 HDAC 抑制劑處理後的膀胱癌細胞，其 ULBP2 的 mRNA 及蛋白表現量有上升的趨勢。重要的是，在共培養實驗發現，自然殺手細胞會增加對於表觀遺傳藥物處理過後之癌細胞的毒殺能力。綜合上述所言，透過 HDAC 抑制劑的處理能夠增強膀胱癌細胞上的配體 ULBP2 的表現，增加自然殺手細胞的毒殺能力，以期能夠在膀胱癌的免疫治療上提供新的標的。

Investigation of the effect of epigenetic therapy in the cytotoxicity of NK cells in bladder cancer

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Bladder cancer (BC) is one of the common malignant diseases of the urinary system, and ranks tenth of incidence cancer in the world. Smoking and drink water polluted with arsenic are the risk factors for bladder cancer. Patients with BC will usually undergo surgical treatment followed by chemotherapy and/or immunotherapy. Despite the recent advances in immunology, only less than 20% of the patients demonstrate therapeutic response, resulting in a poor prognosis with high recurrence rate of up to 70%. Therefore, a more efficient treatment is required for bladder cancer.

Natural killer (NK) cells play an important role in innate immunity and anti-tumor immunity. Upon activation of NK receptor, NKG2D by its ligand, ULBP2, presented on the tumor cells, NK cells will be activated to kill cancer cell. Previous studies found that tumor's ULBP2 can be transcriptionally silenced by epigenetic modifications, thus escaping the attack of the NK cells. Thus, we wanted to explore whether epigenetic silencing of ULBP2 could be restored. Therefore, we hypothesize that epigenetic drugs can enhance NK-mediated anti-tumor immunotherapy in BC. Our preliminary results showed that mRNA and protein expression of ULBP2 were upregulated upon treatment with HDAC inhibitors in BC cells. The cytotoxicity of NK92 cells was significantly enhanced in BC cells pretreated with these epigenetic drugs. Taken together, treatment of HDAC inhibitors could enhance the expression of ULPB2 and the cytotoxicity of NK cells. Epigenetic therapy might be provided a new sight for the immunotherapy in BC.