反轉錄病毒複製載體介導的雙重自殺基因增強動物神經膠質瘤模型的抗腫瘤作用

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膠質母細胞瘤(Glioblastoma,GBM)是最常見且惡性高的原發性腦腫瘤，因 GBM 具有高度的組織浸潤與侵略性，即使接受常規的手術、放射、化療治療後，也難將癌細胞清除乾淨，導致患者預後差，平均壽命也只有 12~15 個月。

近期研究指出，癌症基因治療研究中，可以利用病毒載體進行自殺基因(Suicide gene)的輸送，在給予 Suicide gene 誘導的前驅藥物(produrg)可以有效抑制癌細胞生長，也很有機會成為治療腦癌的新方針。

因此本研究旨在探討，結合兩個自殺基因系統 Cytosine deaminase/5-fluorocytosine (CD/5-FC)＆Nitroreductase(NTR)/CB1954，以可複製型反轉錄病毒(Retroviral)作為輸送載體，評估雙重自殺基因合併療法對於腦癌抗腫瘤作用。我們是選用 ACE vector (改造自 Amphotropic Murine leukaemia virus(MuLVs))攜帶來自於酵母菌 Cytosine deaminase 以及 GS4 vector (改造自 Gibbon ape leukaemia virus(GaLV))攜來自於大腸桿菌的 Nitroreductase，過去實驗室學長已在 *in vitro* 證實，CD 活化 5-FC 以及 NTR 活化 CB1954 之後對於 U87 腦癌細胞具有明顯的毒殺效果以及旁觀者效應。

為了近一步證實結果，未來我會進行裸鼠顱內實驗，先以顱內原位注射方式注入 U87，分別以綠螢光蛋白(GFP)與紅螢光蛋白(dsRed)標記病毒載體，確定了病毒載體在顱內的傳播效率之後，接著使用原位注射在裸鼠顱內建立帶有遠紅外光蛋白(iRFP)的 U87 腦癌細胞，方便後續觀察，再利用 CD 搭配 5-FC 以及 NTR 搭配 CB1954 進行自殺基因系統的抗腦腫瘤治療實驗，再利用非侵入性 3D 螢光斷層掃瞄(Fluorescent molecular tomography,FMT)進行活體造影，觀察給予前驅藥物之後自殺基因系統在裸鼠顱內的治療效果。

Retroviral replicating vector mediated dual suicide gene transfer enhances antitumor effects in an animal glioma model

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Glioblastoma (GBM) is the most common and highly malignant primary brain tumor. Due to its high degree of tissue infiltration and aggressiveness, treating the cancer remains difficult even after conventional surgery, radiation, and chemotherapy, making it challenging to completely eradicate cancer cells. This leads to a poor prognosis for patients, with an average life expectancy of only 12 to 15 months.

Recent studies have suggested that viral vectors can be employed to deliver suicide genes in cancer gene therapy. The prodrug induced by the suicide gene can effectively inhibit the growth of cancer cells and may emerge as a novel treatment strategy for brain cancer.

Therefore, this study aims to explore the combination of two suicide gene systems: Cytosine deaminase/5-fluorocytosine (CD/5-FC) and Nitroreductase (NTR)/CB1954. We will use a replicable retrovirus (Retroviral) as a delivery vehicle to evaluate the anti-tumor effect of dual suicide gene combination therapy on brain cancer. We have chosen the ACE vector (derived from Amphotropic Murine Leukemia Virus, MuLVs) to carry Cytosine deaminase from yeast and the GS4 vector (derived from Gibbon Ape Leukemia Virus, GaLV) to carry Nitroreductase from Escherichia coli. Previous experiments in vitro have confirmed that CD activation of 5-FC and NTR activation of CB1954 have significant cytotoxic effects on U87 brain cancer cells, including bystander effects.

To further validate our findings, I will conduct intracranial experiments on nude mice in the future. Initially, U87 cells will be intracranially injected, and the viral vectors will be labeled with green fluorescent protein (GFP) and red fluorescent protein (dsRed). After optimizing the intracranial propagation efficiency of the viral vectors, we will use in situ injection to establish U87 brain cancer cells with far-infrared photoprotein (iRFP) in the skulls of nude mice for convenient follow-up observations. Subsequently, we will employ CD in combination with 5-FC and NTR in combination with CB1954 to conduct anti-brain tumor treatment experiments using the suicide gene system. Finally, non-invasive fluorescent molecular tomography (FMT) will be utilized for in vivo imaging to observe the therapeutic effects of the suicide gene system in the brains of nude mice after administering precursor drugs.