在膀胱癌中脂質代謝對於巨噬細胞分化之影響

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根據世界衛生組織統計資料顯示，癌症是全球第二大死因，而膀胱癌發生率在所有癌症中佔據第十名。膀胱癌的成因有抽菸、含砷飲用水使用等等。目前膀胱癌的治療方式包含手術切除、化療、放射線治療與免疫療法等，然而其易復發性與抗藥性導致患者五年存活率較低，因此找到新型的治療方式為目前迫切所需要的。腫瘤微環境 (Tumor microenvironment, TME) 中的免疫細胞的種類在對抗癌症的免疫反應裡扮演重要的角色。癌細胞為了逃避免疫攻擊，會釋放多種因子來誘導抑制發炎的免疫細胞分化。近年研究指出，癌症中所調控的脂質代謝可能會透過脂質的受體 CD36 使抗癌的 M1 巨噬細胞轉換成促癌的 M2 巨噬細胞。從這個觀點來看，以癌症中的脂質代謝作為目標可能可以作為一個重新活化抗腫瘤的免疫反應的策略。我們先前的研究發現，脂蛋白酶抑制劑的基因 ANGPTL4 表現量在膀胱癌中透過表觀遺傳的調控給靜默。過度表達 ANGPTL4 基因後，可以抑制腫瘤生長，因此可以推測其為一種腫瘤抑制基因。在本篇研究中，我們要探討表觀基因是否可以回復癌症中 ANGPTL4 的表現量並抑制脂質代謝，也會透過使用不同的表觀基因調控後的膀胱癌細胞來探討 THP-1 往巨噬細胞的分化。此外，也有研究指出 PHB 會增加脂質合成。在本篇研究中，將會利用佩你安 SAHA 此兩種表關基因藥物以及 FL3，一種 PHB 抑制劑進行探討脂質代謝實驗。此外，我們也會使用 FL3 跟 SAHA 的結合化合物 FL65, FL66 and FL67 來加強兩者的功能。在我們的結果中，可以看到我們的藥物都可以有效提高 ANGPTL4 的表現量，但藥物對在脂質合成基因表達並沒有一致性。之後我們將會進行藥物處理後脂蛋白酶抑制劑的功能試驗以及探討在脂質代謝改變後的巨噬細胞分化。

The role of lipid metabolism on the differentiation of macrophages in urothelial carcinoma

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According to the statistical data from World Health Organization, urothelial carcinoma (UC) ranks the tenth most common cancer in the world. The risk factors of urothelial carcinoma include smoking and arsenic-contain drinking water. The standard treatments of urothelial carcinoma include surgery, chemotherapy, radiation therapy and immunotherapy. Nevertheless, because of the chemoresistance accompanied with high recurrence rate, the 5-year survival rate is still low. Therefore, a novel therapeutics for UC is urgently needed. Tumor microenvironment (TME), including various subtypes of immune cells, plays an important role in the immune response against cancer. To escape immune attack, cancer cells may secrete various factors to induce the differentiation of immune cells immuno-suppressive subtypes. Recent studies suggested that lipid metabolism of the cancer cells may turn the M1 anti-tumor macrophage into M2 pro-tumor subtype, via CD36 lipid receptor. In this regard, targeting the lipid metabolism in cancer may be a strategy to “reactivate” the anti-tumor immunity. Our previous study showed that ANGPTL4, a lipoprotein lipase (LPL) inhibitor, was silenced by epigenetic regulation in urothelial carcinoma. Overexpression of ANGPTL4 gene can inhibit tumor growth, suggesting that it is a tumor suppressor. On the other hand, studies also showed that prohibitin (PHB), a protein involved in various function, can activate lipogenesis in various cell types. In this study, we explore the effect of various epigenetic inhibitors, including cyproheptadine (CPH), and vorinostat (SAHA), as well as PHB inhibitor FL3, and its conjugate with SAHA (FL65, FL66, FL67) on the expression of ANGPTL4 and genes involved in lipogenesis. Our result showed that all drugs upregulated ANGPTL4 expression. However, the effect of these drugs on the lipogenesis genes is not consistent. In the future, we will explore the LPL function after drugs treatment and the effect on macrophages differentiation after lipid metabolism changes.