利用 SYTL3 增強胃癌的抗腫瘤免疫反應

學生: 劉潔婷

指導教授：陳永恩教授

日期: 2023/09/15

近年來由於探究將冷腫瘤轉化為熱腫瘤的方法被認為具癌症治療的潛力。本研究的目的為找出能夠使胃癌腫瘤微環境中 T 細胞浸潤增加的潛在標的。我們利用 TCGA 資料庫，將胃癌患者根據其 T 細胞浸潤及抗腫瘤特性程度分類為熱腫瘤與冷腫瘤族群。在這些表現量有差異的基因當中，囊泡運輸相關蛋白 SYTL3（Synaptotagmin-like protein 3）被發現與 T 細胞浸潤及抗腫瘤反應呈顯著正相關。此外，在臨床患者的腫瘤樣本中 SYTL3 的表現量低於健康的胃組織。鑒於胃癌患者中 SYTL3 並未出現基因缺陷，我們假設 SYTL3 的表現可能受到表觀遺傳所調控。由相關性分析的結果顯示，SYTL3 的表達與多種表觀遺傳調節因子呈負相關，其中包括 HDAC 以及 EZH2。此外，SYTL3 的表現量會在表觀遺傳藥物處理後有顯著的提升。透過 ChIP-qPCR 分析證實 SYTL3 的表達會受到表觀遺傳控制，在胃癌細胞中發現 H3K27ac 和 H3K4me1 的增加且 H3K27me3 則是相對減少。基於 HDAC 抑制劑處理後細胞的染色質開放區域的增加，我們在 ChIP-qPCR 的目標區域內找到 CTCF 的結合位點，並觀察到 chromatin looping 在 HDAC 抑制劑處理後有顯著的減少。值得注意的是，透過小鼠胃癌腫瘤模式可以觀察到 SYTL3 過表達的腫瘤生長明顯受到抑制，且伴隨著較多的 $CD8^+$ T 細胞浸潤。我們後續分析了 YTN5-1 腫瘤細胞株和腫瘤組織的分泌蛋白體，結果顯示 WISP-1 在兩種條件下均有顯著的增加。我們的研究結果顯示 SYTL3 的表觀遺傳修飾可能藉由 CTCF 調控機制將非發炎腫瘤微環境形塑為 $CD8^+$ T 細胞浸潤的腫瘤微環境。

Harnessing SYTL3 to boost anti-tumor immune response in gastric cancer

Student: Low Jie Ting

Advisor: Michael Chan, PhD

Date: 2023/09/15

Since the approaches for switching a "cold tumor" into a "hot tumor" have been recently considered as the potential therapeutic strategies for cancers. This study aimed to identify a potential target that increases T cell infiltration into the tumor microenvironment for gastric cancer. Patients with gastric cancer were classified as two populations displaying hot and cold tumor according to T cell infiltration and anti-tumor signatures, using TCGA gastric cancer cohort. Among the differentially expressed genes, a vesicle trafficking protein SYTL3 (Synaptotagmin-like protein 3) displayed a significantly positive correlation with T cell infiltration and anti-tumor responses. Importantly, SYTL3 was found to be downregulated in gastric cancer tissues, as compared to gastric normal tissues clinically. Given that SYTL3 doesn't shows genetic defects in gastric cancer patients, we hypothesized that gene expression of SYTL3 might be regulated epigenetically. The correlation analysis revealed an inverse association between the expression of SYTL3 and several epigenetic modifiers, including HDAC and EZH2. Furthermore, treatment of epigenetic drugs restored SYTL3 expression. The epigenetic reprogramming of SYTL3 expression was examined by ChIP-qPCR analysis, suggesting the enrichment of H3K27ac and H3K4me1 was increased while H3K27me3 was reduced, in gastric cancer cells. Thus, in terms of increasing chromatin accessibility, we found CTCF binding sites within ChIP target regions, and we observed a significant reduction of chromatin looping after HDAC inhibitor treatment. Notably, overexpression of SYTL3 significantly inhibited tumor growth, accompanied with higher $CD8^+$ T cell infiltration, in a syngeneic mice tumor model. Moreover, secretome analysis of YTN5-1 cell line and tumor tissue revealed a significant enrichment of WISP-1 in both conditions. In conclusion, our findings suggest that epigenetic modulation of SYTL3 may shape the tumor microenvironment from a non-inflamed into $CD8^+$ T cell-enriched contexture, possibly through CTCF-mediated mechanism.