Investigation of the role of SLC25A22 in the epigenetic silencing of PCDHB15 in Gastric Cancer

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Gastric cancer is one of the most common causes of cancer death and new cases in the world. According to Ministry of Health and Welfare, over 4000 people were diagnosed with gastric cancer in 2018 and the number is increasing every year. Furthermore, nearly 90% of those patients were infected by H. pylori, one of the main risk factors for gastric cancer.

Upon infection of H. pylori, STAT3 will be activated and translocated to the nucleus to serve as a transcriptional activator or repressor, depending on the context of cis-regulatory elements.

Dysregulated metabolism is recently regarded as a hallmark of cancer. Recent study found that overexpression of SLC25A22, a mitochondrial glutamate symporter, can increase glutamate flux and dysregulation of metabolite for epigenetic machinery, resulting in epigenetic silencing of PCDHB15 in colon cancer. However, the role of SLC25A22 in gastric cancer has never been explored.

We have previously identified several genes, including PCDHB15 that showed promoter hypomethylation in gastric cancer cells and patient samples depleted with STAT3. We therefore hypothesized that overexpression of SLC25A22 may lead to epigenetic silencing of PCDHB15 in gastric cancer.

Our preliminary results showed that a negative correlation between expression of SLC25A22 and PCDHB15 was observed in TCGA gastric cancer RNA-Seq dataset and gastric cancer patient tissue microarray from our own cohort. Colony formation assay found that overexpression of PCDHB15 suppressed tumor growth in gastric cancer cells, suggesting that it is a tumor suppressor.

Further cell line experiments found that PCDHB15 promoter was hypermethylated in gastric cancer cell lines. In the future, we will investigate the role of SLC25A22 in the epigenetic silencing of PCDHB15 in gastric cancer.

胃癌中谷氨酸運輸蛋白 SLC25A22 在表觀遺傳機制之研究

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胃癌是世界上癌症死亡和新發病例最常見的原因之一。據衛生和福利部統計，2018 年有超過 4000 人被診斷出患有胃癌，而且這個數字正逐年增加。

此外，這些患者中有近 90% 感染了幽門螺桿菌，幽門螺桿菌是罹患胃癌的主要危險因素之一。

感染幽門螺桿菌後，STAT3 將被激活並轉移到細胞核中，作為轉錄激活因子或抑制因子，具體取決於順式調節元件的背景。

新陳代謝失調最近被認為是癌症的標誌。最近的研究發現，線粒體谷氨酸轉運體 SLC25A22 的過表達可以增加谷氨酸通量和代謝物表觀遺傳機制的失調，導致結腸癌中 PCDHB15 的表觀遺傳沉默。然而， SLC25A22 在胃癌中的機轉卻尚未明朗。

我們在之前研究結果中已經鑑定了幾個基因，包括 PCDHB15，這些基因在胃癌細胞和用 STAT3 Knock down 的患者樣本中顯示啟動子低甲基化。因此，我們假設 SLC25A22 的過表達可能導致胃癌中 PCDHB15 的表觀遺傳沉默。

我們的初步結果表明，在 TCGA 胃癌 RNA-Seq 數據集和取樣到的胃癌患者組織微陣列中觀察到 SLC25A22 和 PCDHB15 的表達呈負相關。集落形成試驗發現 PCDHB15 的過表達抑制了胃癌細胞中的腫瘤生長，表明它確實是一種腫瘤抑制因子。

進一步的細胞系實驗發現 PCDHB15 啟動子在胃癌細胞系中被高甲基化。未來，我們將研究 SLC25A22 在胃癌 PCDHB15 表觀遺傳沉默中的作用。