Cancer-associated fibroblasts maintain critical pancreatic cancer cell lipid homeostasis in the tumor microenvironment

Han, Xu, et al. Cell reports 43.11 (2024).

Presenter：Yi-Chia Huang　　**Date/time**：2025/03/13，15:20-16:10

Commentator：Prof. Chu-An Wang　　**Location** ：Room 601, med college building

Background：

Pancreatic ductal carcinoma (PDAC) is one of the leading-cause of cancer-associated mortality in the United States. The PDAC cells are surrounded by dense extracellular matrix (ECM). The situation impairs surrounding vascular function and leads to nutrient and oxygen restriction so called tissue hypoxia. According to the previous studies, the fatty acid desaturation in cancer cells would be inhibited under hypoxia which leads to imbalance lipid homeostasis. Since then, the cancer cells depend on the imports of exogenous unsaturated fatty acids for survival. However, there is little investigation of how hypoxic PDAC cells obtain the unsaturated fatty acids. On the other hand, cancer-associated fibroblasts (CAFs) have been studied in the past few decades as they play a vital role for supporting tumors growth in tumor microenvironments. CAFs are known to improve cancer progression by ECM remodeling and cytokine secretion. But the comprehensive network of metabolic crosstalk between CAFs and PDAC cells has not been completely defined.

Objective：

To investigate hypoxic PDAC cells lipid homeostasis and its metabolic crosstalk with CAFs.

Results：

The author found that inhibiting the utilization of unsaturated LPCs sensitizes PDAC cells to endoplasmic reticulum (ER) stress-induced apoptosis through the activation of IRE1α. They also identified a distinct spatial pattern in the tumor microenvironment, where malignant cell-dominant regions exhibit hypoxia markers, while CAF-rich regions do not. This suggests that CAFs are capable of producing unsaturated LPCs despite the overall hypoxic nature of the tumor. Through whole paper, they indicated that PDAC cells survival rely heavily on unsaturated lysophosphatidylcholines (LPCs) secreted by cancer-associated fibroblasts (CAFs), owing to significantly reduced stearoyl-CoA desaturase 1 (SCD1) activity in tumor cells.

Conclusion：

PDAC cells survive under severe hypoxic conditions with the support of CAFs unsaturated LPCs. The findings may have provided a novel targetable metabolic vulnerability in PDAC tumors.