膵星細胞と膵がん細胞の新たな関係

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がんの進展にはがん細胞自身の特性に加え、周囲の間質に存在するがん関連線維芽細胞（CAFs）などとの相互作用が関わっていることが知られている。例えば、膵がんに特徴的なデスモプラジア（繊維性組織）は、膵星細胞（pancreatic stellate cell）がオートクライン、あるいはパラクラインによって細胞外基質を産生して形成する。このデスモプラジアはがん細胞にとっては化学療法剤からの隠れ蓑となり、臨床上深刻な問題となっている。一方でデスモプラジアに埋もれて血管が届かない膵がん細胞が栄養飢餓状態をどのように克服しているのかは大変興味深い。今回 Kimmelman らは、①がん-間質間での栄養物の直接的なやりとり、②アラニンを代替源とした代謝リプログラミングを明らかにし、上記の疑問に一つの答えを導いた。

紹介論文

Pancreatic stellate cells support tumour metabolism through autophagic alanine secretion.
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要旨

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive disease characterized by an intense fibrotic stromal response and deregulated metabolism. The role of the stroma in PDAC biology is complex and it has been shown to play critical roles that differ depending on the biological context. The stromal reaction also impairs the vasculature, leading to a highly hypoxic, nutrient-poor environment. As such, these tumours must alter how they capture and use nutrients to support their metabolic needs. Here we show that stroma-associated pancreatic stellate cells (PSCs) are critical for PDAC metabolism through the secretion of non-essential amino acids (NEAA). Specifically, we uncover a previously undescribed role for alanine, which outcompetes glucose and glutamine-derived carbon in PDAC to fuel the TCA cycle, and thus NEAA and lipid biosynthesis. This shift in fuel source decreases the tumour's dependence on glucose and serum-derived nutrients, which are limited in the pancreatic tumour microenvironment. Moreover, we demonstrate that alanine secretion by PSCs is dependent on PSC autophagy, a process that is stimulated by cancer cells. Thus, our results demonstrate a novel metabolic interaction between PSCs and cancer cells, in which PSC-derived alanine acts as an alternative carbon source. This finding highlights a previously unappreciated metabolic network within pancreatic tumours in which diverse fuel sources are used to promote growth in an austere tumour microenvironment.