ACTN4 promotes metastasis by enhancing the focal adhesion dynamic and chemoresistance in pancreatic ductal adenocarcinoma

Speaker : Qin-Ling Hong
Advisor : Ching-Chieh Weng
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Pancreatic cancer is one of the worst prognostic malignant tumors of all types of cancer, and pancreatic ductal adenocarcinoma (PDAC) is the most common type of pancreatic cancer. PDAC is still associated with high mortality and morbidity for affected patients notwithstanding considerable progress in diagnosis and surgical pharmacological therapy. Focal adhesion complexes (FAs) are the crucial regulator of cell migration, and their overexpression is associated with metastatic tumor behavior. FAs are large dynamic protein complexes that could deliver the signals between cells and extracellular matrix to affect cell's behavior. α-Actinin-4 (ACTN4) is essential to support the FAs complexes, an actin-binding protein that assists in the elongation of actin to maintain the structure of the FAs complexes and make cells move. These studies have pointed out that the changes in ACTN4 expression are associated with tumor invasion and metastasis, but we also unknown the role of ACTN4 in pancreatic cancer. Therefore, we want to explore the role of ACTN4 in PDAC. Our results showed that ACTN4 expression levels increased in the PDAC mouse model during pancreatic cancer progression. We knockdown ACTN4 in the human pancreatic cancer cell line to explore it's functionality and compared with knockdown control, the proliferation of PDAC cells wasn't affected, but the cell migration was significantly affected and inhibited the Epithelial-mesenchymal transition (EMT). Thus demonstrate the functional of ACTN4 in FAs complexes, we found knockdown ACTN4 cause the FAs complexes are unstable, and the protein expression is downregulation such as p-FAK, α-Actinin and Vinculin. Those results indicated ACTN4, one of the critical roles in focal adhesion dynamic. Further, by exploring the association between ACTN4 and chemoresistance, we understand that knockdown ACTN4 sensitizes cells to drug treatment. In this study we demonstrate the ACTN4 promotes metastasis by enhancing the focal adhesion dynamic, and chemoresistance in PDAC.

ACTN4 在胰腺癌中透過增強黏著斑動力及化療耐藥性促進轉移

姓名:洪沁伶
指導教授:翁靖傑
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胰腺癌是所有類型癌症中預後最差的惡性腫瘤之一，胰腺癌（PDAC）是最常見的胰臟癌類型。儘管在診斷和手術藥物治療方面取得了相當大的進步，但 PDAC 仍然與患者的高死亡率和發病率有關。粘著斑複合物 (FAs) 是細胞遷移的關鍵調節因子，它們的過度表達與腫瘤轉移的行為有關。FA 是大型動態蛋白質複合物，可以在細胞和胞外基質之間傳遞信號以影響細胞的行為。α-Actinin-4 (ACTN4)對於支持 FAs 複合物至關重要，ACTN4 是一種肌動蛋白結合蛋白，有助於肌動蛋白的延長以維持 FAs 複合物的結構並使細胞移動。有研究指出 ACTN4 表達的變化與腫瘤的侵襲轉移有關，但我們還不清楚 ACTN4 在胰腺癌中的作用。因此我們想探討 ACTN4 在 PDAC 中的作用為何。我們的結果表明，在胰腺癌進展過程中，PDAC 小鼠模型中的 ACTN4 表達水平增加。我們敲低人胰腺癌細胞系中的 ACTN4 以探索其功能，與對照組相比，PDAC 細胞的增殖不受影響，但細胞遷移受到顯著影響並抑制上皮間質轉化(EMT)。從而證明 ACTN4 在 FAs 複合物中的功能，我們發現敲低 ACTN4 會導致 FAs 複合物不穩定，且蛋白質表達下調，例如 p-FAK、α-Actinin 和 Vinculin。這些結果表明 ACTN4 是粘著斑動態中的關鍵角色之一。此外通過探索 ACTN4 與化療耐藥之間的關聯，我們了解到敲低 ACTN4 可使細胞對藥物治療敏感。在這項研究中，我們證明了 ACTN4 在胰腺癌中透過增強黏著斑動力及化療耐藥性來促進轉移。