C1GALT1 high expression is associated with poor survival of patients with pancreatic ductal adenocarcinoma and promotes cell invasiveness through integrin α_v

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1. 簡述論文概要與重大發現:
   研究發現，醣基化的改變有助於許多癌症腫瘤的進展及抗藥性。而調控 GalNAc-type O-glycosylation 延伸的關鍵酶就是 C1GALT1。作者發現與附近非腫瘤組織相比，高表達 C1GALT1 的 PDAC 腫瘤預後較差，總生存率較低。當 C1GALT1 過表達，便會增強細胞遷移及侵襲能力。反之， knockdown C1GALT1 可以抑制細胞活力、遷移及轉移能力，並增加對 Gemcitabine 的敏感性。在皮下和胰腺原位注射模型中可以看到，knockdown C1GALT1 降低了 NOD/SCID 小鼠中 PDAC 細胞的腫瘤生長和轉移。而研究也發現 C1GALT1 可以修飾多個 integrin subunits 上的 O-glycans，因此作者透過功能性阻斷抗體將 integrin α_v 鑑定為 C1GALT1 介導的 PDAC 細胞侵襲的關鍵因素。最後這項研究表示 C1GALT1 可以是 PDAC 的潛在治療靶點，也為 O-glycosylation 在 integrin α subunits 中的作用提供了新的見解。
2. 對論文內容的疑問:
   調控 GalNAc-type O-glycosylation 延伸的關鍵因素除了 C1GALT1 之外還有嗎?
3. 論文的缺點、評論:
   有些圖中的 western blot 感覺還可以跑得在更漂亮一些，不然結果看起來有點不明確。

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ARTICLE

C1GALT1 high expression is associated with poor survival of patients with pancreatic ductal adenocarcinoma and promotes cell invasiveness through integrin α_v

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Abstract

Pancreatic adenocarcinoma (PDAC) is a leading cause of cancer-related death. Altered glycosylation contributes to tumor progression and chemoresistance in many cancers. C1GALT1 is the key enzyme controlling the elongation of GalNAc-type O-glycosylation. Here we showed that C1GALT1 was overexpressed in 85% (107/126) of PDAC tumors compared with adjacent non-tumor tissues. High expression of C1GALT1 was associated with poor disease-free and overall survival ($n = 99$). C1GALT1 knockdown using siRNA suppressed cell viability, migration, and invasion as well as increased gemcitabine sensitivity in PDAC cells. In contrast, C1GALT1 overexpression enhanced cell migration and invasion. In subcutaneous and pancreatic orthotopic injection models, C1GALT1 knockdown decreased tumor growth and metastasis of PDAC cells in NOD/SCID mice. Mechanistically, C1GALT1 knockdown dramatically suppressed cell-extracellular matrix (ECM) adhesion, which was associated with decreased phosphorylation of FAK at Y397/Y925 and changes in O-glycans on integrins including the β_1, α_v, and α_5 subunits. Using functional blocking antibodies, we identified integrin α_v as a critical factor in C1GALT1-mediated invasiveness of PDAC cells. In conclusion, this study not only reveals that C1GALT1 could be a potential therapeutic target for PDAC but also provides novel insights into the role of O-glycosylation in the α subunits of integrins.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the most common type of pancreatic cancer and characterized by an intense desmoplastic stroma, which contains mainly extracellular matrix (ECM) proteins and regulates cancer growth and metastasis [1]. Rapidly developed radio-chemoresistance, especially to the current first-line gemcitabine-based regimen, remains a critical issue underlying the poor prognosis of PDAC [2]. Abundant crosstalk between malignant epithelial cells and the surrounding desmoplastic stroma results in the proliferation, survival, and resistance to therapy of cancer cells [3]. Growing evidence has demonstrated that targeting the stroma of PDAC is a promising treatment modality in addition to surgery, chemotherapy, radiotherapy, and immunotherapy [1].

The primary cell surface receptors for various ECM proteins are integrins, which include 24 transmembrane heterodimers with 18 α and 8 β subunits [4]. Different combinations of integrins play crucial roles in nearly all steps of tumor progression, from tumorigenesis to

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