GOT1 inhibition promotes pancreatic cancer cell death by ferroptosis

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1. 簡述論文概要與重大發現:

胰臟癌被認為是目前最致命的癌症之一，其中又屬胰腺導管腺癌(PDAC)比例最高，那 PDAC 主要是透過 cystine-glutamate shuttle 產生 NADPH 以維持氧化還原平衡，且此種途徑會藉由 Kras mutation 控制 GOT1 的表達來協調，而當氧化還原平衡被破壞，就可能使細胞走向 Ferroptosis，因此作者在這邊想進一步確認如果關掉 GOT1，是不是可以破壞氧化還原平衡，產生 ferroptosis 的現象，進而達到治療PDAC 的效果。從實驗結果顯示關掉GOT1 除了可以有效抑制PDAC 的生長外，同時也可協同抑制 GSH 的合成或是使 GPX4 degradation 等等的方式使細胞走向 Ferroptosis。

2. 對論文內容的疑問:

在 Figure2(b)主要是觀察哪一種藥物對於抑制 PDAC 最有影響，理論上 Paclitaxel 應該是能抑制 PDAC 的生長，但在實驗結果卻發現它的效果很差。

3. 論文的缺點、評論:

胰臟癌本身因為不易被診斷出來，導致治療效果有限，而在本篇論文中雖然作者證明了 Knockdown GOT1 可以誘導 ferroptosis 的發生，進而抑制 PDAC 的生長，但還未在人體實驗得到證實，因此希望研究胰臟癌的學者能藉由此論文的結果，進而找出有效的治療方式。

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GOT1 inhibition promotes pancreatic cancer cell death by ferroptosis

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Cancer metabolism is rewired to support cell survival in response to intrinsic and environmental stressors. Identification of strategies to target these adaptions is an area of active research. We previously described a cytosolic aspartate aminotransaminase (GOT1)-driven pathway in pancreatic cancer used to maintain redox balance. Here, we sought to identify metabolic dependencies following GOT1 inhibition to exploit this feature of pancreatic cancer and to provide additional insight into regulation of redox metabolism. Using pharmacological methods, we identify cysteine, glutathione, and lipid antioxidant function as metabolic vulnerabilities following GOT1 withdrawal. We demonstrate that targeting any of these pathways triggers ferroptosis, an oxidative, iron-dependent form of cell death, in GOT1 knockdown cells. Mechanistically, we reveal that GOT1 inhibition represses mitochondrial metabolism and promotes a catabolic state. Consequently, we find that this enhances labile iron availability through autophagy, which potentiates the activity of ferroptotic stimuli. Overall, our study identifies a biochemical connection between GOT1, iron regulation, and ferroptosis.

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