Role of STK26-Mediated chemoresistance through anti-Ferroptosis pathway of pancreatic cancer to Gemcitabine.

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Pancreatic cancer is an aggressive tumor that highly metastasizes and is drug-resistant, resulting in a survival rate of only 12% in five years. It has been observed that the STRIPAK complex contains Striatin, CCM3, and GCK-III family, and affects cell apoptosis, adhesion, proliferation, and migration. The complexes are highly active and overexpressed in various cancers, including PDAC. Recent studies show that STK26 (Mammalian Ste20-like Kinase 4, MST4), a member of the GCK-III family, affects the proliferation and migration in PDAC, but the mechanism is still unknown. Initially, we demonstrate that STK26 is overexpressed in the mouse models during the pancreatic cancer process. Then we found that the cell proliferation and migration of Knockdown STK26 decreased significantly, and we also demonstrated that STK26 affects tumor progression. In addition, we explored the ability of chemosensitivity by Knockdown STK26 in vitro and in vivo, and our data indicated the ability of chemoresistance by gemcitabine treatment in PDAC. Furthermore, gemcitabine upregulated STK26 expression, which could limit the anti-tumor activity of gemcitabine, and attenuation of STK26 enhanced gemcitabine sensitivity in vitro and in vivo. Furthermore, knockdown STK26 increased cellular ROS levels and led to ROS-dependent ferroptosis, which resulted in the down-regulation of NRF2, and increased the intracellular free iron level that participates in ferroptosis in PDAC cells. Finally, our results showed that knockdown STK26 enhanced PDAC sensitivity to gemcitabine by inducing ferroptosis death in vitro and in vivo. These findings indicate that STK26 is a potential therapeutic target for PDAC treatment.

STK26 透過抗鐵依賴性死亡的途徑來影響胰臟癌對於 Gemcitabine 的抗藥性

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胰腺癌為一種侵襲能力極強的癌症，高度轉移性以及抗藥性導致其五年存活率僅為 12%。目前研究指出 STRIPAK 的複合體在各種癌症中過度表達，影響了細胞凋亡、黏附、增殖和遷移的能力。STK26（Mammalian Ste20-like Kinase 4，MST4）是 GCK-III 家族的一員，且已有研究證實 STK26 影響胰臟癌的增殖及遷移，但對於 STK26 如何影響其下游機制的過程仍然不清楚。首先我們發現 STK26 在胰臟癌中過度表達，證實了 STK26 可能影響了腫瘤發展過程，緊接著我們證實 Knockdown STK26 的胰臟癌細胞會影響增殖及遷移的能力。為了證實 STK26 在胰臟癌抗藥性中的影響，進一步的我們探討了 Knockdown STK26 在胰臟癌對於 Gemcitabine 處理後的改變。從結果中証實 Knockdown STK26 增強了胰臟癌細胞對於 Gemcitabine 的敏感性並增加細胞 ROS 的含量，導致 NRF2 表現量下降並增加細胞中游離的鐵離子的表現，最後導致鐵依賴性死亡的現象發生。最後我們證實 Knockdown STK26 會透過誘導鐵依賴性死亡來增加胰臟癌對 Gemcitabine 的敏感性，而這些發現也顯示 STK26 可能是胰臟癌的潛在治療標的。