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Abrogation of glutathione peroxidase-1 drives EMT and chemoresistance in pancreatic cancer by activating ROS-mediated Akt/GSK3β/snail signaling

Qingcai Meng, Si Shi, Chen Liang, Jie Hua, Yiyin Zhang, Jin Xu and Xianjun Yu
[1]Shanghai Pancreatic Cancer Institute, China
[2]Fudan University, China

Purpose: Pancreatic Ductal Adenocarcinoma (PDAC) remains one of the deadliest cancers worldwide, partly due to tumor chemoresistance. Numerous studies have shown that Glutathione Peroxidase-1 (GPx1) plays various roles in development and progression of multiple tumors. However, its role in pancreatic cancer remains unclear. In this study, we sought to elucidate the function of GPx1 in pancreatic cancer malignancy and Gemcitabine (GEM) resistance.

Experimental Design: PDAC tissue microarrays was used to evaluate the correlation between GPx1 expression and clinicopathological features. Cytobiology, molecular biology assays and mouse models were performed to investigate the detailed mechanisms. Finally, RNA-sequencing was performed in the scramble-shRNA and GPx1-shRNA MiaPaCa-2 cells to identify core signaling pathways.

Results: The level of GPx1 expression was negatively associated with Overall Survival (OS) in patients with PDAC. Silencing of GPx1 resulted in an Epithelial–Mesenchymal Transition (EMT) phenotype and increased chemoresistance to GEM *in vitro* and *in vivo*. Additionally, activation of Akt/GSK3β/Snail signaling was demonstrated to be involved in this process.

Conclusions: Our results reveal that GPx1 could inhibit EMT and chemoresistance by regulating Akt/GSK3β/Snail axis in PDAC.

15216633283@163.com