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Oncogene addiction and pancreatic ductal adenocarcinoma: Where is the way to cure

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Pancreatic ductal adenocarcinoma (PDAC) remains one of the most devastating disease with the 5-year survival rate less than 6%, novel and effective strategies to manage this disease is of urgent need. Previously we have demonstreated that maintaining the stability of central proteome may be a primary mechanism for addicted oncogenes to maintain the survival of cancer cells through various signaling pathways, and quick loss of some of the short-lived members of the central proteome may be the direct reason for the rapid apoptotic response or acute apoptosis following acute inhibition of the addicted oncogenes in cancer cells. In this study, we investigated if inhibiting protein synthesis directly with homoharringtonine (HHT) could induce acute apoptosis in pancreatic cancer cells through quick depletion of multiple short-lived critical members of the central proteome, example, PSMD11(26S proteasome non-ATPase regulatory subunit 11). It was shown that although HHT could inhibit proliferation and growth of MiaPaCa-2 and PANC-1 cells in a time- and dose-dependent manner, only part of pancreatic cancer cells could be induced to die through acute apoptosis. Mechanistic studies showed that HHT could induce quick protein synthesis of PSMD11 through activating MEK1/ERK1/2 signaling pathway in pancreatic cancer cells. Inhibiting MEK1/ERK1/2 pathway with sorafenib could improve the cytotoxity of HHT *in vitro* and in a genetically engineered mouse model of pancreatic cancer. These results suggest that quick induction of PSMD11 or other acute apoptosis inhibitors through activation of the MEK1/ERK1/2 signaling pathway may be one of the important surviving mechanism which can help pancreatic cancer cells avoid acute apoptosis, it may have significant implications for the targeted therapy of pancreatic ductal adenocarcinoma.

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