

Expression and role of the tumor suppressor pp32 and related pathway genes in pancreatic tumorigenesis.

Brody JR, Witkiewicz A, Cozzitorto J, Yeo CJ

Introduction: Nuclear phosphoprotein pp32 (ANP32A) displays tumor suppressor like characteristics in cancer cell models and has been shown to be a critical ligand of the ELAV protein, Hur. Hur has been shown to stabilize oncogenic mRNAs containing ARE elements in colon and breast tumors. Previously, pp32 mRNA expression correlates with differentiation status in epithelial cancers.

Methods and Results: In this study, we evaluated pp32 protein expression in relation to the differentiation status of pancreatic ductal adenocarcinomas (PDAs) and surveyed Hur expression in PDAs. pp32 expression showed strong nuclear staining in normal pancreatic acini and ducts. The intensity of this staining was maintained in pancreatic intraepithelial neoplasia (PanINs), well differentiated adenocarcinomas, and a subset of moderately differentiated adenocarcinomas, but not in poorly differentiated tumors. We validated pp32 expression by immunoblot analysis of lysates from resected pancreatic ductal adenocarcinomas and pancreatic cancer cell lines. The well differentiated pancreatic cancer cell line HPAC expressed high amounts of pp32, compared to the poorly differentiated pancreatic cancer cell lines MiaPaCa2, P119 and P121 cells. All cancer cell lines and PDAs expressed high amounts of Hur protein.

Conclusions: This is the first evaluation of expression of these related proteins that are critical for pathways involved in pancreatic tumorigenesis. Based on this study and previous functional work, pp32 and Hur expression levels may be a critical event for the fate of differentiation and aggressiveness of pancreatic cancer cells. Since pp32 can inhibit k-ras (mutated in >95% of pancreatic cancers) and Hur can stabilize oncogenic mRNAs, this work reveals this pathway as a novel 'drugable' target in pancreas cancer.