Expression of Pancreatitis-associated Protein (PAP) in Human Pancreatic Ductal Adenocarcinoma

Y. Motoo, M.-J. Xie, S.-B. Su, H. Mouri, K. Ohtsubo, and N.Sawabu

Pancreatitis-associated protein (PAP) is a secretory protein of pancreatic acinar cells. It is almost absent in normal pancreas, but is induced in acute and chronic pancreatitis. It functions as an anti-apoptotic factor in acinar cells exposed to oxidative stress. Cytokines increase PAP mRNA expression in the pancreatic acinar cell line AR4-2J. We have reported the expression of PAP mRNA in cancer tissues, and have measured PAP levels in sera and pancreatic juice of patients with gastrointestinal cancers. We found that serum PAP levels were positive (>55 ng/ml) in 40% of patients with pancreatic cancer. Serum PAP levels were significantly higher in pancreatic cancer than in chronic pancreatitis. The aim of the present study was to determine the frequency and pattern of PAP expression in pancreatic cancer at the tissue level, and to evaluate the clinicopathological significance of its expression.

PAP was overexpressed (>30% of total observed area) in 79% (30/38) of pancreatic cancers, in 19% (7/36) of chronic pancreatitis, and in 29% (2/7) of mucinous cystadenomas. PAP was not expressed in normal pancreas. The rate of expression differed significantly between pancreatic cancer and other pancreatic diseases ($P<0.01$). PAP overexpression was found in 50% (4/8) of liver metastasis and 43% (3/7) of lymph node metastasis specimens from patients with pancreatic cancer. Comparison between primary lesions and metastatic lesions showed that PAP was expressed more in metastases than in primary lesions. At the cellular level, PAP was strongly expressed in the cytoplasm of pancreatic cancer cells. PAP overexpression was significantly correlated with nodal involvement ($P<0.05$), distant metastasis ($P<0.05$) and short survival (<12 months) ($P<0.01$). PAP mRNA was expressed in 2 of 4 pancreatic cancers examined, and two pancreatic cancer cell lines, but not in normal pancreas. Multivariate survival analysis revealed that PAP overexpression ($P<0.05$), nutrition ($P<0.005$), and histological type ($P<0.005$) were significantly correlated with survival.

In summary, the present study demonstrates that PAP is overexpressed in human pancreatic ductal adenocarcinoma and would suggest that PAP expression reflects the aggressiveness of pancreatic cancer cells.