Pancreatic Adenocarcinoma-- a Novel Tumor Marker

Parathyroid hormone-related protein (PTHrP) can act as an oncoprotein to regulate the growth and proliferation of many common malignancies, including pancreatic cancer. Previous studies have shown that PTHrP is produced by human pancreatic cancer cell lines, can be shown in the cytoplasm and nucleus of paraffin-embedded pancreatic adenocarcinoma tumor specimens, and is secreted into the media of cultured pancreatic adenocarcinoma cells. PTHrP could therefore serve as a tumor-marker for growth of pancreatic cancer in vivo.

To test this hypothesis, an orthotopic model was developed and used in the laboratory of the PTHrP-producing human pancreatic cancer line, BxPC-3.

This tumor was stably transduced with green fluorescence protein (GFP) to facilitate visualization of tumor growth and metastases. At early (5 weeks) and late (13 weeks) time points after surgical orthotopic implantation, serum PTHrP was measured and primary and metastatic tumor burden was determined for each mouse by assessing GFP expression.

By 5 weeks after surgical orthotopic implantation (early group), the mean serum PTHrP level was 33.3 pg/mL. In contrast, by 13 weeks after surgical orthotopic implantation (late group), the mean serum PTHrP level increased to 158.5 pg/mL. These differences were highly significant ($p < 0.001$, Student t test).

Numerous metastatic lesions were readily visualized by GFP in the late group. Serum PTHrP levels measured by immunoassay correlated with primary pancreatic tumor weights and serum calcium levels ($p < 0.01$). PTHrP levels were not detectable (<21 pg/mL) in any of the 10 control mice with no tumor. Western blotting of BxPC-3-GFP tumor lysates confirmed the presence of PTHrP. BxPC-3-GFP tumor tissue stained with antibody to PTHrP.

These results indicate that PTHrP can serve as a tumor marker in animal models of pancreatic cancer and may be a useful tumor marker for clinical pancreatic adenocarcinoma.

Parathyroid hormone-related protein (PTHrP) is an oncoprotein that regulates the growth and proliferation of essentially every tissue in which it is expressed, including many common malignancies such as breast, colon, gastric, melanoma, and prostate cancer. In these tumors, PTHrP is processed into distinct peptides that mediate its unique biologic effects through intracrine (nuclear localization) and endocrine (autocrine and paracrine cell surface receptor) pathways.

In addition to its endocrine effects, several studies have shown that increased expression of PTHrP in cancer is associated with accelerated tumor growth and a more malignant phenotype, suggesting that PTHrP may play a role in promoting tumor progression.

Recently, it was shown that PTHrP is produced by human pancreatic adenocarcinoma cell lines and is present in the cytoplasm and nucleus of paraffin-embedded pancreatic adenocarcinoma tumor specimens. It was also observed that PTHrP is secreted into the media of cultured pancreatic adenocarcinoma cell lines and could be measured by radioimmunoassay. Because of these findings, it was hypothesized that PTHrP could serve as a tumor marker for growth of pancreatic cancer. To test this hypothesis in vivo, we used an orthotopic model, developed in our laboratory (16), of the PTHrP-producing pancreatic cancer cell line, BxPC-3, which expresses the green fluorescence protein (GFP) to facilitate visualization of tumor growth and metastases.

In summary, we have shown that PTHrP is secreted into the blood of mice that have undergone surgical orthotopic implantation of PTHrP-expressing human pancreatic tumors. Furthermore, serum

PTHrP correlated with the primary pancreatic tumor weight and the extent of metastatic burden. Future studies will determine whether there is differential expression of PTHrP in the primary tumor and specific metastatic sites. Additional studies are needed to elucidate the role of PTHrP in the development and progression of pancreatic cancer and to determine whether PTHrP could be useful in the early detection or clinical treatment of patients with this disease.