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Proteomics Profiling of Pancreatic Cancer and Pancreatitis for Biomarkers Discovery

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ABSTRACT

Pancreatic cancer is one of the leading causes of death in the United States. It is considered the 4th most common cancer among both men and women and is ranked as the 11th most common cause of death globally. Pancreatic cancer accounts for 7.2% (43,090) of cases of death in the United States and 331000 deaths annually worldwide [1]. This cancer is lethal because it lacks early symptoms and results in latestage detection and a high mortality rate. Several studies have been undertaken to identify biomarkers for early detection of pancreatic cancer. Among these biomarkers is serum carbohydrate antigen (CA19- 9), which has been extensively studied and widely used for the diagnosis of pancreatic cancer so far. It has a 90% specificity to pancreatic cancer.

However, it is not expressed in Caucasians lacking the Lewis blood group antigen (~5% of the population) whereas an elevation can be observed in chronic pancreatitis and obstructive jaundice. Because of its limitations, CA19-19 is an unreliable screening biomarker and is restricted to the detection of tumor recurrence after surgical resection. Carcinoembryonic antigen (CEA) is another biomarker that has been used to diagnose pancreatic cancer. Since the protein is lacking in most pancreatic tumors and because studies have shown that CA19-9 has a better specificity and sensitivity compared to CEA, scientists have discontinued using CEA to diagnose pancreatic cancer. Nevertheless, combining them has been common in panels. According to researchers from the Mayo Clinic, methylation markers distinguishing pancreatic cancer from benign controls are detected in pancreatic juice. Kisiel et alidentified a panel of methylated biomarkers CD1D, KCNK12, CLEC11A, NDRG4, IKZF1, PKRCB and KRAS resulting in 75% sensitivity and 95% specificity comparing pancreatic cancer to normal pancreas and pancreatitis.

Ten frozen tissues each of pancreatic adenocarcinoma, normal adjacent pancreatic, and pancreatitis tissues were collected from patients that underwent surgery as part of standard care of their condition at Indiana University School of Medicine (Indianapolis, IN). The specimens were obtained and immediately snap frozen using liquid nitrogen. Indiana University and Purdue University Institutional Review Board Committee approved the study and an informed consent was procured from each patient.Laser capture microdissection and protein extraction 2-Dimmensional gel electrophoresis and image analysis MALDI–TOF–TOF analysisImmunohistochemistry Statistical analysis

The purpose of this study was to characterize and compare the protein expression profiles of non-neoplastic pancreas, pancreatitis, and pancreatic adenocarcinoma tissues to determine alterations in proteins expression that can be identified as biomarkers for early detection and/ or therapeutic intervention of pancreatic adenocarcinoma.

Pancreatic cancer, now the fourth leading cause of cancer deaths in the United States for which the 5-year survival rates are 3% , is often dubbed the silent killer because it seldom causes symptoms until advanced. As a result, few pancreatic cancers are operable at diagnosis and surgical excision cures only 10-15% of patients. Furthermore, pancreatic cancer is often resistant to conventional radiotherapy or chemotherapy. Not surprisingly, only 1-4% of patients with pancreatic adenocarcinoma survive 5 years past diagnosis. Recent clinical trials with gemcitabine hydrochloride produced only modest clinical benefits and marginally increased survival in

patients with advanced pancreatic cancer. Much has been learned about the genetics and pathogenesis of pancreatic cancer from studies of biopsy samples from cancer patients, cell lines, and mouse models. However, successful treatment requires more reliable biomarkers of the disease.

In conclusion, the significant factor for the poor prognosis of pancreatic cancer may be attributed to its biological aggressiveness, the difficulty of early diagnosis, and poor response to conventional therapeutics. Additionally, pancreatic masses are sometimes indistinguishable from chronic pancreatitis or benign pancreatic cysts when biopsy is obtained from the lesion. For these reasons, we decided to identify markers differentially expressed between cancer vs. normal pancreas tissues. The comparisons of protein expression profiles of pancreatic cancer and pancreatitis and normal pancreas using laser capture microdissection, 2-dimensional electrophoresis, tandem mass spectrometry (MS/MS) provided important information about the molecular characteristics and revealed some new specific or associated biomarkers of pancreatic cancer including pancreatic Lipase, annexin A1 and ALDH1A1. Our study confirmed these proteins as biomarkers for early detection of pancreatic cancer. Understanding the role of these specific proteins and their mechanistic action will give insights into their involvement in pancreatic cancer.

Keywords: Pancreatic cancer; Proteomic; Pancreatitis; 2D-gel; Biomarkers; Lipase