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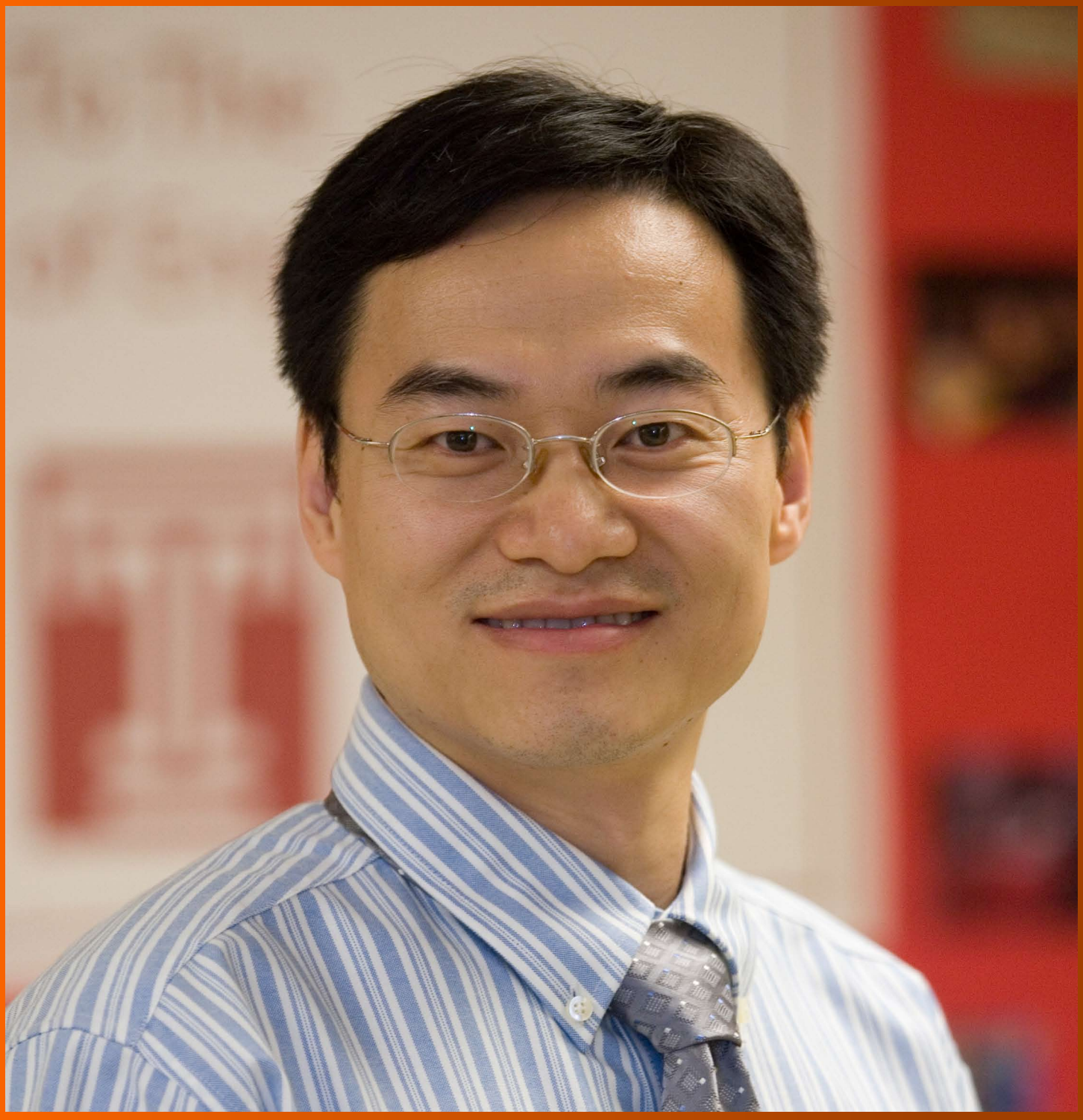

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MINIREVIEWS

Potential prognostic biomarkers in pancreatic juice of resectable pancreatic ductal adenocarcinoma

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Abstract

Despite potentially curative surgery pancreatic cancer has a dismal prognosis. Serum cancer antigen 19-9 (CA 19-9) correlates with tumor burden, resectability and survival in patients with pancreatic ductal adenocarcinoma. Identification of novel biomarkers may facilitate early diagnosis of pancreatic cancer and improve survival. Pancreatic juice is a rich source of cancer-specific proteins rendering it a promising tool for identifying biomarkers. Recent proteomic and microRNA expression analyses have identified several biomarkers of potential diagnostic and prognostic value. Tumor markers CA 19-9 and carcinoembryonic antigen (CEA) are widely used in the characterization of premalignant and malignant lesions of the pancreas. Elevated level of CEA in bile is a marker for malignancy and a predictor of hepatic recurrence. The potential value of CA 19-9, CEA and lactate dehydrogenase as prognostic biomarkers in pancreatic juice and bile is unknown. Specimens of pancreatic juice and bile can be readily collected during surgical resection of the tumor. Profiling of pancreatic juice and bile to identify novel prognostic biomarkers may improve selection of patients for adjuvant therapy with a favorable impact on overall survival in patients diagnosed with pancreatic cancer.

Key words: Prognostic biomarkers; Pancreatic juice; Bile; Pancreatic adenocarcinoma; Surgery

Core tip: Pancreatic juice is a rich source of cancer-specific proteins rendering it a promising tool for identifying novel biomarkers in pancreatic ductal adenocarcinoma. Recent proteomic and microRNA expression analyses have identified several diagnostic and prognostic biomarkers. Elevated carcinoembryonic antigen (CEA) in bile is a marker of malignancy and a predictor of hepatic recurrence. The potential of cancer antigen 19-9, CEA and lactate dehydrogenase as prognostic biomarkers in pancreatic juice and bile is unknown. Specimens of pancreatic juice and bile can be readily collected during pancreatic resection. Profiling of pancreatic juice and bile to identify novel biomarkers may facilitate early diagnosis and improve selection of patients for adjuvant therapy.

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INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer-related mortality in the United States. Despite improvements in adjuvant therapy and identification of novel biomarkers, pancreatic cancer continues to have a dismal prognosis[1]. Pancreatic ductal adenocarcinoma (PDAC) is one of the few cancers for which incidence and mortality rates have changed very little over the past three decades. Surgery is the only potentially curative treatment for prolongation of survival and the use of adjuvant therapy following curative surgery significantly improves 5-year survival[2-4].

Pathologic stage of the tumor is the major determinant of survival after curative resection for PDAC[1]. Serum levels of cancer antigen 19-9 (CA 19-9), carcinoembryonic antigen (CEA) and lactate dehydrogenase (LDH) correlate with the extent of disease and are predictive of survival[5-13]. Serum CA 19-9 correlates with tumor burden, resectability and overall survival. Low preoperative serum CA 19-9, postoperative decline and level < 200 U/mL are independent predictors of survival[5]. Identification of novel diagnostic and prognostic biomarkers in the serum, tissue, bile and pancreatic juice of patients with PDAC may improve early diagnosis and selection of patients for adjuvant therapy.

BIOMARKERS OF PANCREATIC ADENOCARCINOMA

CA 19-9 and CEA in PDAC are well-characterized serum and tissue biomarkers of diagnostic and prognostic value. Recent proteomic and microRNA (miRNA) expression analyses have identified several biomarkers of potential value in the early diagnosis of PDAC and improvement in patient selection for aggressive treatment protocols. Comparative proteomic profiling of tumor and nontumor pancreas samples in patients with PDAC identified a new prognostic biomarker prolargin (PRELP)[14]. Survival analysis demonstrated a significant correlation of protein abundance of PRELP with postoperative survival confirming its value as a candidate prognostic biomarker. Pancreatic juice is a rich source of cancer-specific proteins rendering it a promising tool for identifying novel biomarkers. Additional sources of biomarkers including serum, tumor tissue, pancreatic juice, bile and other body fluids have revealed distinct biomarker patterns in PDAC. These data suggest that analysis of pancreatic juice and bile samples collected at the time of a surgical resection may identify prognostic biomarkers of value in PDAC. Biomarkers may be used to stratify patients based on prognosis and those who will benefit from intensive neoadjuvant protocols or adjuvant hepatic artery infusion therapy.

BIOMARKERS IN PANCREATIC JUICE

Diagnostic biomarkers

During the development of PDAC, malignant ductal cells preferentially shed into the ductal lumen, making pancreatic juice a rich source of cancer-specific proteins. CA 19-9 expression is demonstrated in 90% patients with pancreatic head adenocarcinoma compared to 11%-62% periampullary cancers of duodenal, ampullary or distal bile duct origin[15]. Overexpression of CA 19-9 and CEA in PDAC is shown in Figures 1-4 and it correlates with a higher histologic grade[15,16]. Elevation of CEA level and presence of *K-ras* mutation in pancreatic juice is a strong predictor of PDAC[17]. Increased levels of CA 19-9 and CEA in pancreatic juice are predictive of malignant transformation in benign intraductal papillary mucinous neoplasm (IPMN)[18-21]. Immunohistochemical staining of CEA is strongly positive in invasive IPMN and correlates with the grade of cellular atypia[21,22].

In a comparison of the levels of CA 19-9 in the serum and pancreatic juice of patients with PDAC, the authors reported elevated levels in the pancreatic juice of all patients with normal levels in the sera of several patients[23]. Tumor marker levels are predictive of tumor burden with the level in pancreatic juice correlating with the local tumor and serum level with the systemic burden of disease. This may explain the elevation of tumor markers in pancreatic juice with normal serum levels in patients with malignant IPMN.

Genetic and epigenetic markers such as mutant *K-ras*, *p53* mutations, DNA methylation alterations, mitochondrial DNA mutations and miRNAs in pancreatic juice are under evaluation for their role in distinguishing benign pancreatic pathology or chronic pancreatitis from preinvasive pancreatic neoplasia, IPMN and pancreatic intraepithelial neoplasia (PanIN)[24-33]. Mass spectrometry proteomics of pancreatic juice collected at the time of surgical resection of the tumor suggested distinct proteomic signatures for PDAC[34]. CEA and S100 calcium-binding protein P (S100P) concentrations in duodenal juice were significantly higher in PDAC than the benign conditions and may serve as a useful screening test for the detection of PDAC[35,36]. Immunohistochemical expression of human telomerase reverse transcriptase (hTERT) in preoperative pancreatic juice samples was detectable in 84% PDAC and 88% malignant IPMN and the accuracy of diagnosing PDAC improved when combined with cytology[30,37]. Proteomic analysis of pancreatic juice from patients with PDAC demonstrated three up-regulated proteins, matrix metallo proteinase-9 (MMP-9), oncogene DJ1 (DJ-1) and alpha-1B-glycoprotein precursor (AIBG) indicative of their potential as diagnostic biomarkers in PDAC[38]. Accurate peripheral markers of PDAC are lacking and select miRNAs identified in plasma and bile demonstrated excellent

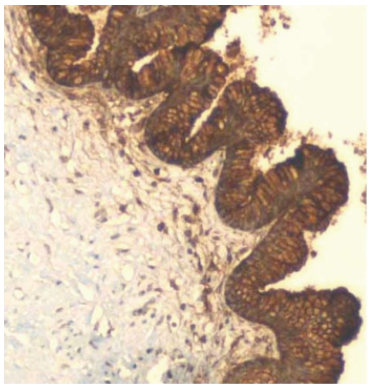

Figure 1 Pancreatic ductal adenocarcinoma with overexpression of carcinoembryonic antigen. The neoplastic cells demonstrate strong cytoplasmic and membranous staining (100 ×). Courtesy, Department of Pathology, Temple University Hospital, Philadelphia, PA, United States.

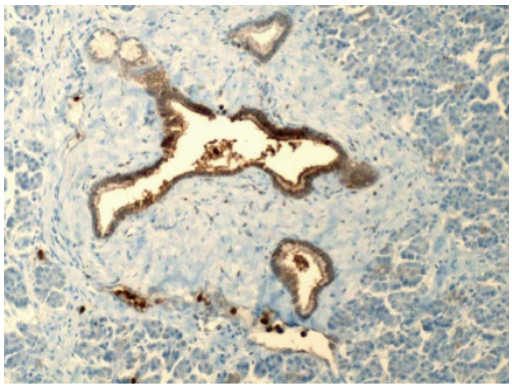

Figure 2 Benign pancreatic ducts and acini with weak staining of the ductal cells for carcinoembryonic antigen (200 ×). Courtesy, Department of Pathology, Temple University Hospital, Philadelphia, PA, United States.

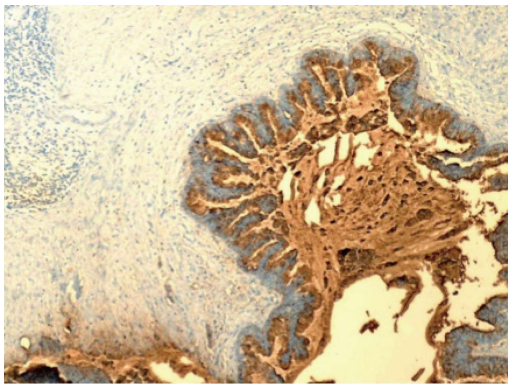

Figure 3 Pancreatic ductal adenocarcinoma with overexpression of cancer antigen 19-9. The neoplastic cells demonstrate strong cytoplasmic staining (100 ×). Courtesy, Department of Pathology, Temple University Hospital, Philadelphia, PA, United States.

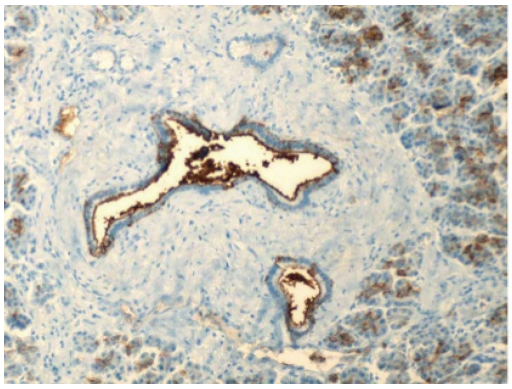

Figure 4 Benign pancreatic ducts and acini with weak staining of the ductal cells for cancer antigen 19-9 (200 ×). Courtesy, Department of Pathology, Temple University Hospital, Philadelphia, PA, United States.

accuracy in distinguishing PDAC from benign conditions[33]. These data highlight the potential value of biomarkers from various biological sources in the early diagnosis of pancreatic cancer.

Prognostic biomarkers

Normal pancreatic juice contains multiple proteins and administration of secretin alters the concentration but not the spectrum of these proteins[39]. The proteome of pancreatic juice in patients with PDAC is markedly altered[39,40]. The proteome of the pancreas after surgical resection contains regenerative and immunomodulatory factors which vary depending on neoadjuvant therapy, history of smoking and vary over time to stimulate restoration of organ function[41]. Profiling of miRNAs in pancreatic juice of patients with PDAC demonstrated higher contents of miR-205 and miR-210 correlating with lymph node metastasis and diminished survival demonstrating their potential value as candidate biomarkers of disease progression and prognosis[42]. Assay of Adnab-9 in pancreaticobiliary secretions and PDAC tumor demonstrated its potential value as a candidate biomarker for diagnosis and prognostication[43]. Elevated level of S100A8 or A9 in pancreatic ductal fluid, a near absence of pancreatic enzymes and high level of mucins (MUC1, 2, 5AC, 5B, 6 and 13) were predictors of poor survival suggesting that pancreatic ductal fluid is a promising tool for identifying prognostic biomarkers[34].

BIOMARKERS IN BILE

Diagnostic and prognostic value

Intraoperative samples of bile from gallbladder in patients with pancreaticobiliary diseases demonstrated significantly higher levels of CA 19-9 in malignancy and correlated with the tumor burden[44]. Biliary CEA > 10 ng/mL in patients undergoing a curative surgery for colorectal cancer is a strong predictor of hepatic recurrence suggesting that it is a marker for occult liver metastases[45,46]. Liver is the site of first recurrence in 50% patients following curative surgery for PDAC[47]. The use of adjuvant liver-directed therapy including hepatic artery infusion chemotherapy (HAI) significantly decreases the incidence of liver metastases with a trend towards improvement in cumulative survival[48,49]. Prediction of the site of early recurrence can impact choice of the optimal modality for adjuvant therapy

Table 1 Potential biomarkers in the pancreatic juice and bile of patients with pancreatic adenocarcinoma

Body fluid	Biomarker
Pancreatic ductal fluid	CA 19-9
	CEA
	K-ras
	p53 mutations
	DNA methylation alterations
	Mitochondrial DNA mutations
	S100 calcium-binding protein P (S100P)
	Human telomerase reverse transcriptase
	Matrix metalloproteinase-9
	Oncogene DJ1
	Alpha-1B-glycoprotein precursor
	MicroRNA- miR-205, miR-210
	Adnab-9
	S100A8 or A9
	Mucins MUC1, 2, 5AC, 5B, 6 and 13
Bile	CEA
	Mac-2-binding protein
	MUC4
	Vascular endothelial growth factor

CA 19-9: Cancer antigen 19-9; CEA: Carcinoembryonic antigen.

following curative surgery for PDAC.

Novel diagnostic biliary biomarkers for biliary tract cancer include Mac-2-binding protein (Mac-2BP) identified in bile using tandem mass spectrometry[50]. Alterations in epithelial mucin expression has identified MUC4 in pancreatic juice as a diagnostic and prognostic marker for pancreatic cancer, biliary MUC4 as a diagnostic biomarker and serum MUC5A as a sensitive diagnostic marker correlating negatively with survival in biliary tract cancer[34,51]. Elevated levels of biliary vascular endothelial growth factor (VEGF-1) distinguishes patients with pancreatic cancer from other etiologies of biliary stricture[52]. Potential biomarkers in the pancreatic juice and bile of patients with pancreatic adenocarcinoma are shown in Table 1. These preliminary data demonstrating the diagnostic and prognostic value of biliary markers in cancer require prospective evaluation and validation in large scale multicenter studies.

SELECTION OF BIOMARKERS

Choice of the optimal biomarker

Biomarkers obtained from readily accessible biological materials *via* non-invasive procedures minimize down-stream investigations and costs[53]. Pancreatic juice and/or bile is readily collected during the course of a pancreatic resection for PDAC. In contrast to the recently identified biomarkers requiring further investigation prior to recommendation for clinical use, CA 19-9 and CEA are widely used and validated markers of diagnostic and prognostic value in PDAC and pre-neoplastic lesions of the pancreas[54]. However, the prognostic value of CA 19-9, CEA and LDH levels in the pancreatic juice and bile of patients with PDAC has not been evaluated. Standardized laboratory protocols are available for the assay of CA 19-9 and CEA in body fluids rendering them optimal biomarkers in the evaluation of patients with PDAC.

CONCLUSION

Pancreatic juice is a rich source of cancer-specific proteins rendering it a promising tool for identifying novel prognostic biomarkers in PDAC. Elevated level of CEA in bile is a marker for malignancy and a predictor of hepatic recurrence. CA 19-9, CEA and LDH are widely used in clinical practice as diagnostic markers of pancreatic cancer however, the prognostic value of their levels in pancreatic juice and bile is unknown. Specimens of pancreatic juice and bile can be readily obtained during surgical resection of the tumor and analyzed according to well-established laboratory protocols for assays of CA 19-9, CEA and LDH to evaluate their prognostic value. Profiling of pancreatic juice and bile to identify biomarkers may improve early diagnosis and selection of patients for the optimal adjuvant therapeutic modality.

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