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Comparison of Pancreas Juice Proteins from Cancer Versus Pancreatitis Using Quantitative Proteomic Analysis

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Abstract

Objectives—Pancreatitis is an inflammatory condition of the pancreas. However, it often shares many molecular features with pancreatic cancer. Biomarkers present in pancreatic cancer frequently occur in the setting of pancreatitis. The efforts to develop diagnostic biomarkers for pancreatic cancer have thus been complicated by the false-positive involvement of pancreatitis.

Methods—In an attempt to develop protein biomarkers for pancreatic cancer, we previously use quantitative proteomics to identify and quantify the proteins from pancreatic cancer juice. Pancreatic juice is a rich source of proteins that are shed by the pancreatic ductal cells. In this study, we used a similar approach to identify and quantify proteins from pancreatitis juice.

Results—In total, 72 proteins were identified and quantified in the comparison of pancreatic juice from pancreatitis patients versus pooled normal control juice. Nineteen of the juice proteins were overexpressed, and 8 were underexpressed in pancreatitis juice by at least 2-fold compared with normal pancreatic juice. Of these 27 differentially expressed proteins in pancreatitis, 9 proteins were also differentially expressed in the pancreatic juice from pancreatic cancer patient.

Conclusions—Identification of these differentially expressed proteins from pancreatitis juice provides useful information for future study of specific pancreatitis-associated proteins and to eliminate potential false-positive biomarkers for pancreatic cancer.

Keywords

pancreatic juice; pancreatitis; ICAT; biomarker; pancreatic cancer; proteomics

Pancreatic cancer is a highly lethal disease.[1,2] The death rate nearly matches the incidence because the diagnosis usually occurs late, after metastases have occurred, and the only chance for a cure (ie, surgical excision) has been eliminated. The problem of early diagnosis is complicated by the obscure location of the pancreas, the absence of reliable symptoms, and the insensitivity and expense of current tests. Better methods of detecting early stages of cancer or precancerous lesions are needed.

In the efforts to develop biomarkers for the early detection of pancreatic cancer, one of the problems is the false-positive involvement of pancreatitis patients. Pancreatitis is an

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inflammatory condition of the pancreas that shares many molecular features with pancreatic cancer. Thus, biomarkers present in the setting of pancreatic cancer frequently occur in pancreatitis, providing an unacceptably low level of specificity for screening. It is therefore important to understand the proteins that underlie pancreatitis, as they could be a source of false-positive biomarkers for pancreatic cancer. Moreover, chronic pancreatitis is risk factor for eventual neoplastic progression; thus, understanding the proteins involved in both diseases may yield some insights into the mechanisms that link these events.

Recently, there has been substantial interest in applying proteomic methods for the discovery of new targets for therapeutics and new biomarkers for diagnosis and early detection.[3] In particular, quantitative proteomics has enabled researchers to use a combination of biochemistry, biology, and bioinformatics to detect proteins that are differentially expressed in cancer. In pancreatic cancer, recent studies using proteomics approach have focused on pancreatic cancer tissues.[4–6] However, from a biomarker's standpoint, pancreatic juice is an excellent starting specimen for the identification of protein biomarkers. Pancreatic juice is a rich source for cancer-specific proteins because the highly proliferative cancer cells are shed into the juice, as they undergo cellular turnover and degradation.[7]

Pancreatic juice was extensively studied in late 1970s and 1980s, primarily by early 2-dimensional electrophoresis analyses, which led to the discovery and description of several pancreatic enzymes.[8–12] Recently, Gronborg and colleagues[13] used a mass spectrometry-based proteomic approach for the analysis of pancreatic juice which used 1-dimensional electrophoresis and liquid chromatography (LC) tandem mass spectrometry (MS/MS). We previously used an isotope-coded affinity tag (ICAT)–based quantitative proteomic approach to identify and characterize potential biomarkers from pancreatic cancer juice.[14] A total of 30 proteins were identified that exhibited greater than 2-fold abundance change in pancreatic cancer juice compared with normal pancreatic juice. Given the false-positive role of pancreatitis in pancreatic cancer, it is important to discover possible pancreatitis specific proteins that can be used to differentiate pancreatic cancer and pancreatitis. In addition, discovery of the proteins in pancreatitis could help identify proteins that might contribute to false-positive findings of pancreatic cancer.

Isotope-coded affinity tag (ICAT) technology provides a comprehensive approach for quantitative proteomic analysis.[15,16] This methodology demonstrates a significant improvement over gel-based methods in identifying low-abundant proteins, and it minimizes problems associated with solubility and extremes of pH.[17] In this study, we used ICAT technology to perform comprehensive quantitative protein profiling of the pancreatitis juice. We performed the analyses by comparing pooled normal pancreatic juice with pancreatic juice from a chronic pancreatitis patient. Identification and quantification of the proteins from pancreatic juice were accomplished by differentially labeling the target proteins (pancreatitis) with heavy ICAT reagents and the normal comparator proteins with light ICAT reagents. The isotopically labeled proteins were then combined, purified, and followed by LC MS/MS analysis. Protein identification and quantification were then accomplished by using a suite of bioinformatics software. The proteomic analysis of pancreatitis juice was then compared with the analysis of pancreatic cancer juice.

MATERIALS AND METHODS

Specimens

Pancreatic juice samples were collected during endoscopic retrograde cholangiopancreatography and immediately stored at −80°C. Pancreatic tissue specimens were collected at surgery and stored in freezing media (10% dimethyl sulfoxide) at −80°C. The specimens were collected in accordance with approved human subject's guidelines at the

University of Washington. Pancreatic juice from a chronic pancreatitis patient and 10 normal controls were included in this study. Pancreatic juices from 10 normal controls were pooled together by equal quantity of total protein. Because endoscopic retrograde cholangiopancreatography is an invasive procedure, it is uncommon to obtain pancreatic juice from patients with a completely normal pancreas. In this study, the normal juices were from the patients who have benign pancreatic diseases such as benign cystic neoplasms. Samples from potentially neoplastic precursor lesions, such as intrapapillary mucinous neoplasia, were not included as normal control. The pancreatitis sample was from a patient with chronic pancreatitis and history of alcoholism, without evidence of malignancy.

Isotope-Coded Affinity Tag Labeling and Mass Spectrometry

The ICAT labeling and mass spectrometry were performed as previously described.[14] Briefly, protease inhibitor, phenyl methyl sulfonyl fluoride, was added to pancreatic juice at a final concentration of 0.5 mmol/L to prevent protein degradation. For each sample, 0.5-mg protein was labeled with the acid cleavable ICAT reagents, either in an isotopically light ^{12}C (pooled normal pancreatic juice) or in heavy ^{13}C (pancreatitis juice) isoforms (Applied Biosystems, Foster City, Calif) as previously described. The labeled 2 samples were then combined and digested into peptides by trypsin (Promega, Madison, Wis). Isotope-Coded affinity tag–labeled peptides were subsequently fractionated by cation-exchange chromatography and purified by avidin-affinity chromatography. The resulting 50 fractions were then combined into 21 fractions and analyzed by microcapillary high-performance LC–electrospray ionization–MS/MS using an ion-trap mass spectrometer (LCQ-DecaXP, ThermoFinnigan, San Jose, Calif) as previously described.[4,14]

Data Analysis

Tandem mass spectrometry spectra were searched against the National Cancer Institute human sequence database using SEQUEST.[18] The database search results were validated using the PeptideProphet program.[19] Peptide-Prophet uses various SEQUEST scores and a number of other parameters to calculate a probability score for each identified peptide. The identified peptides were then assigned a protein identification using the ProteinProphet software.[20] Protein-Prophet allows filtering of large-scale data sets with predictable sensitivity and false-positive identification error rates. In this study, we used ProteinProphet probability score more than or equal to 0.9 as a cutoff value for protein identification. This will ensure that the false-positive rate (error rate) for protein identification in this study less than 0.9%. Quantification of the ratio of each protein (isotopically heavy vs light) was calculated using the ASAPRatio program.[21] Information on the software can be found on line at http://www.systemsbiology.org/Default.aspx?pagename=FullList. The identified proteins were classified based on GO (Gene Ontology) consortium.[22]

RESULTS AND DISCUSSION

Proteins Identified in Pancreatitis Juice

In this study, we used the ICAT approach to identify and quantify proteins in a pair of pancreatic juices: pooled normal pancreatic juice versus pancreatic juice from a patient with pancreatitis. The approach was to label the comparator (pooled normal juice) and target (pancreatitis juice) proteins with the isotopically light and heavy ICAT reagents, respectively. The labeled proteins from the comparator and target proteomes were then combined, digested, fractionated, and purified by multidimensional chromatography and analyzed by MS/MS. The protein identification and quantification were accomplished by using a suite of bioinformatic software tools.[18–21] All together, 72 proteins were identified and quantified in the comparison of pancreatitis juice to pooled normal pancreatic juice, with an error rate of less than 0.9%.

The 72 proteins identified in the pancreatic juices were examined by cellular component, molecular function, and biological process classified accordingly based on GO[22] nomenclature. The distribution of these proteins in cellular component, molecular function, and biological process are presented in Figure 1. Most of the identified proteins was from the extracellular region (72%) or bound to the plasma membrane (12%). This is consistent with the fact that proteins from pancreatic juice are primarily secreted and with a previous study in pancreatic cancer juice and normal pancreatic juice.[14] In addition, about 3% of proteins were from the ductal cell cytoplasm and nucleus. Because pancreatic juice is mainly cell-free, the existent of these cellular proteins supports the assumption that cellular proteins may be shed into pancreatic juice by cell turnover or secretion.[14]

Many of the proteins identified in pancreatic juice were enzymes (catalytic activity, 35%). Other molecular functions identified included: binding function 24%, enzyme regulation 3%, obsolete molecular function 1%, structural molecules 1%, and transporter activity 11%. The molecular functions for 25% of the proteins are still unknown at the present time.

In classifying the proteins by biological process, one third of the proteins identified were involved with metabolism; this finding is consistent with the fact that the major role of pancreatic juice is to provide enzymes for digestion. Other biological functions attributed to the discovered proteins include response to stimulus (24%) (not surprising in the setting of chronic inflammation), developmental (3%), cell communication (4%), regulators of biological processes (3%), and localization (6%).

We have previously identified a total of 105 proteins from pancreatic cancer juice.[14] Comparison of the 2 disease states (pancreatitis and cancer) reveals that 31 of the 72 pancreatitis proteins identified in this pancreatitis study have not been detected in previous studies and are unique to this study of pancreatitis juice. In total, 136 proteins were identified in pancreatic juices in the 2 studies (current and previous) (Table 1).

Proteins With at Least 2-Fold Change in Abundance in Pancreatitis Juice

The use of ICAT technology allows us to perform protein identification and quantification studies in the same experiment. The quantification of each protein is presented as a protein ratio between 2 samples tested. In the comparison of pancreatitis juice/pooled normal juice, 27 proteins showed differential expression in pancreatitis juice by at least 2-fold: 19 were overexpressed, and 8 were underexpressed in pancreatitis juice (Table 2). Below, we will discuss some of the differentially regulated proteins.

Fibrinogen β Chain—Fibrinogen was found to be 3.0-fold up-regulated in pancreatitis juice compared with normal pancreatic juice in this study. The MS/MS spectrum of a unique peptide (PVVSGKECEEIIR) derived from fibrinogen β chain is presented in Figure 2A. Twelve other peptides from this protein were also identified in the experiment (MS/MS spectra not shown). The identification of these 13 peptides gave an explicit identification of fibrinogen β chain in the samples. The relative abundance of each peptide pair was calculated based on the signal intensities for each peptide using ASAPRatio software. The relative abundance data revealed that this peptide was 4-fold more abundant in the pancreatitis sample (heavy) than in the normal sample (light). The ratio of fibrinogen β chain between pancreatitis and pooled normal was eventually calculated to be 3.0 (Fig. 2B) by incorporation of the intensities of all 13 peptides identified.

Blood coagulation/fibrinolytic systems are commonly activated in pancreatic cancer. Immunohistochemical staining of pancreatic cancer sections indicate that fibrinogen exists throughout the tumor stroma, and tumor cells are surrounded by fibrin.[23] Our previous studies also detected overexpression of fibrinogen β chain in pancreatic cancer tissue[4] and elevation

of fibrinogen β chain in pancreatic cancer juice.[24] It has been postulated that local coagulation activation may regulate growth of pancreatic cancer.[23] Alternatively, the up-regulation of fibrinogen in pancreatitis juice discovered in this study may be consistent with the fact that fibrogen is a major acute response protein involved in the inflammation of pancreas. Our study verifies that pancreatic cancer and pancreatitis have some common protein alterations. As such, the consideration of proteins in these 2 diseases should be considered concurringly to avoid false-positive findings in the development of diagnostic biomarkers for cancer.

Plasmin/Plasminogen—Identification of a peptide NYCRNPDGDVGGPW-CYTTNPR derived from plasminogen or plasmin suggested the presence of plasminogen or/and plasmin in the juice samples; however, the exact form of the protein from which the peptide was derived cannot be determined. It is clear that plasminogen/plasmin is elevated in pancreatitis juice by 2.7-fold. In the plasminogen/plasmin system, the inactive proenzyme plasminogen can be transformed into the proteolytically active plasmin mainly by plasminogen activators. Plasmin is involved in fibrinolysis and inflammation. The pathophysiological importance of the plasminogen/plasmin system in classical inflammation diseases has been well established by several studies.[25] Increase level of plasmin activator (uPA) and plasmin–α2-antiplasmin complexes were found in synovial fluid as well as in plasma in patients with rheumatic diseases.[25–27] Involvement of plasmin in inflammatory process has also been demonstrated in plasminogen-deficient mice. In light of these findings, novel approaches were proposed for the treatment of chronic inflammatory diseases. For one example, induction of adenoviral vectors encoding an engineered cell surface-targeted plasmin inhibitor seems to reduce synovial fibroblast-dependent cartilage degradation and invasion in rheumatoid arthritis.[25,28] Enhanced plasminogen activation have also been revealed in pancreatitis.[29,30] However, direct demonstration of enhanced level of plasminogen in pancreatitis juice has not been reported before. In addition to its role in inflammation, plasminogen activation also plays an important role in tumor cell invasiveness and metastasis.[31,32] Plasmin generated at the surface of tumor cells is considered a key event in tumor invasion and metastasis in the pancreatic cancer.[31,32]

Neural Cell Adhesion Molecule L1—Another up-regulated protein in pancreatitis juice is neural cell adhesion molecule L1 (NCAM L1). Neural cell adhesion molecule L1 is a multidomain membrane glycoprotein of the immunoglobulin superfamily[33–36] that is over-expressed by a variety of highly malignant tumors, including neuroblastomas,[37] ovarian tumors,[38] renal cell carcinoma,[39] and endometrial tumors.[40] Neural cell adhesion molecule L1 promotes many cellular activities by interacting through its extracellular domain with other cell adhesion molecules, extracellular matrix molecules, and signal receptors.[41–43] In light of its role in cell proliferation[44] and tumor progression,[41] NCAM L1 has emerged as a promising marker for cancers.[45] Expression of NCAM L1 has not been previously reported in pancreatic cancer or pancreatitis. However, another adhesion molecule, neural cell adhesion molecule, has expression in 66.7% of pancreatic cancer cases.[46] These 2 cell adhesion proteins are generated from different genes on different chromosomes; however, both are membrane glycoproteins belonging to a superfamily of immunoglobulins that mediate cell-to-cell adhesion at the cell surface. The expression of neural cell adhesion molecule has been detected more frequently in lesions where neural invasion was excessive.[46] It is not clear why NCAM L1 was up-regulated in the setting of pancreatitis and not in pancreatic cancer juice. It will be interesting in the future to determine the expression pattern of this protein in normal pancreas and pancreatic disease, such as cancer and pancreatitis.

Caldecrin—One of the down-regulated proteins in pancreatitis juice is caldecrin (2.5-fold decrease). Caldecrin, also known as serum calcium-decreasing factor or chymotrypsin C, is a novel-type serine protease expressed in the pancreas.[47] Its association with pancreatic disease

has not been reported before. Given the fact that several digestive enzymes were differentially regulated in pancreatitis juice presented in this study, it is not surprising to see caldecrin also differentially expressed in pancreatitis juice. Further work is needed to evaluate the role of caldecrin in various pancreatic diseases.

Comparison of Differentially Expressed Proteins in the Pancreatic Juices from Pancreatic Cancer and Pancreatitis

Comparison of the differentially expressed proteins in pancreatitis to those from pancreatic cancer juice and normal juice,[14] revealed 9 proteins (hemoglobin, fibrinogen, trypsin I, trypsin II, chymotrypsinogen b, Ig-α1 chain c region, Ig-μ chain c region, ribonuclease, and human serum albumin) that were both up-regulated in pancreatic cancer juice and pancreatitis juice (Table 3). These proteins should be excluded in future biomarker study for pancreatic cancer. Interestingly, down-regulated proteins in pancreatic cancer do not overlap with those from pancreatitis. There are 21 proteins that were differentially expressed only in pancreatic cancer, whereas 18 proteins were differentially expressed only in the pancreatitis (Fig. 3 and Table 3). In addition, elastase 2b, which was variable in comparison of normal juice with pooled normal juice,[14] was also down-regulated pancreatitis juice but not found in pancreatic cancer juice. These data thus provide useful basis for future development of biomarkers for pancreatic cancer and pancreatitis and reduce the chance of false-positive biomarkers.

Summary

In this study, we performed a comparative and comprehensive proteomic analysis on pancreatic juice from pancreatitis versus pooled normal controls. In total, we identify and quantify 72 proteins in comparison of the pancreatic juice from pancreatitis and pooled normal control, of which 19 were overexpressed, and 8 were underexpressed in pancreatitis juice by at least 2-fold. In these 27 differentially expressed proteins, several proteins (including plasminogen, NCAM L1, and caldecrin) have not been previously associated with pancreatic cancer or pancreatitis, and pancreatic juice. Further study is needed to elucidate the roles of these newly discovered proteins in pancreatitis and pancreatic cancer. In addition, 9 proteins (hemoglobin, fibrinogen, trypsin I, trypsin II, chymotrypsinogen b, Ig-α1 chain c region, Ig-μ chain c region, ribonuclease, and human serum albumin) that were previously shown to be up-regulated in pancreatic cancer juice are also differentially expressed in pancreatitis juice. Thus, these proteins may create false-positive results as biomarkers for pancreatic cancer.

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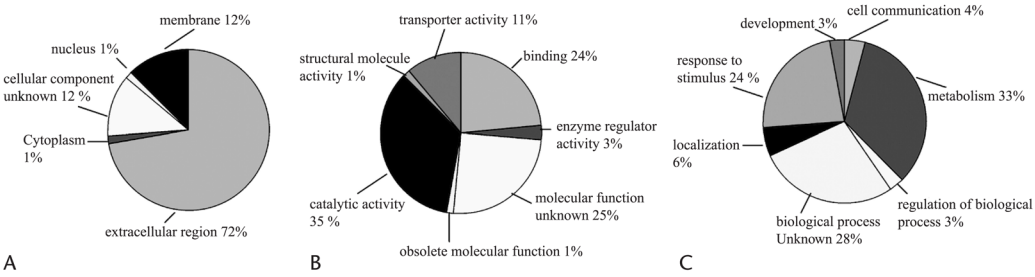

FIGURE 1.

Distribution of the identified proteins from pancreatic juice. The 72 proteins identified and quantified in pancreatic juice were classified into categories based on A, cellular component, B, molecular function, and C, biological process. The assignments were based on GO consortium.

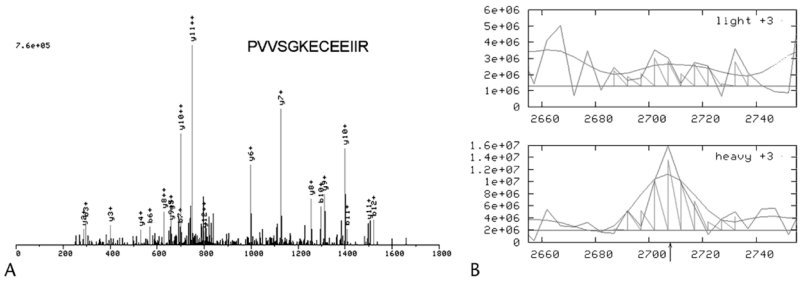

FIGURE 2.

Identification and quantification of fibrinogen beta chain in pancreatic juice by ICAT labeling and MS/MS analysis. A, MS/MS spectrum of a unique peptide (PVVSGKECEEIIR) derived from fibrinogen beta chain. The peptide was identified by sequence database searching using SEQUEST. Twelve other peptides from the same protein were also identified (MS/MS spectra not shown) which lead to conclusive identification of fibrinogen beta chain. B, The relative abundance of each peptide pair was cacculated based on the signal intensities for each peptide using ASAPRatio software. The relative abundance data revealed that this peptide was more abundant in pancreatitis sample (heavy) than in normal sample (light): ratio = 4.0. The ratio of fibrinogen beta chain between pancreatitis and pooled normal was calculated to be 3.0 by incorporation of the intensities of all 13 peptides identified.

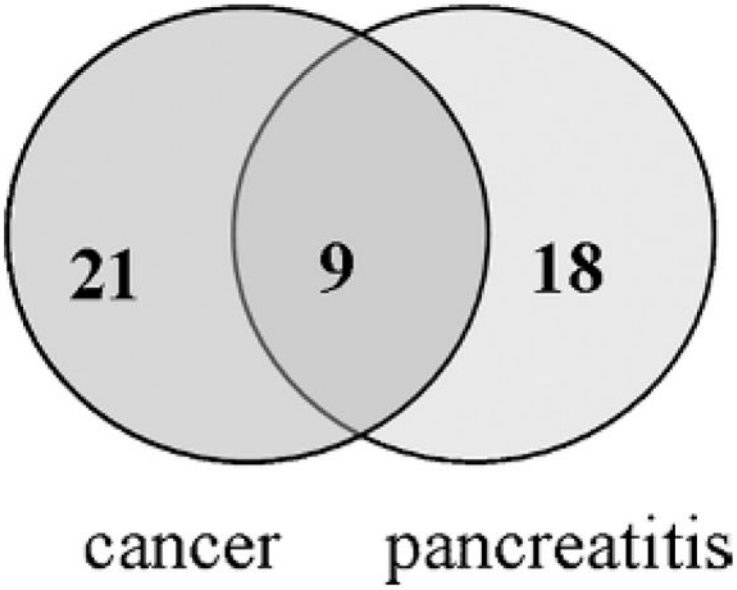

FIGURE 3.

Comparison of protein abundance changes in pancreatic juices from pancreatic cancer and pancreatitis patients. Of the 27 differentially regulated proteins in pancreatitis juice, 9 proteins were also differentially regulated in pancreatic cancer, and they are all up-regulated. Eighteen and 21 proteins are only differentially regulated in pancreatitis and pancreatic cancer, respectively.

TABLE 1

List of Proteins Identified in the Pancreatic Juices

Database ID	Protein Name	Identified in CA/nl	Identified in CP/nl	Identified in nl/nl
3D:1clyH	1clyH IGG FAB (human IgG1, κ)		✓	
SW:W70T_HUMAN	70 kDa WD-repeat tumor rejection antigen		✓	
SW:A1AG_HUMAN	α1-Acid glycoprotein 1 precursor	✓	✓	
SW:A1AT_HUMAN	α1-Antitrypsin precursor		✓	
SW:A1BG_HUMAN	α1b-Glycoprotein precursor	✓	✓	
SW:A2MG_HUMAN	α2-Macroglobulin precursor	✓	✓	
SW:AMYC_HUMAN	α-Amylase 2b precursor	✓		✓
SW:AMYP_HUMAN	α-Amylase, pancreatic precursor	✓	✓	
IPI00025476	Amylase, α2A		✓	✓
SW:APOD_HUMAN	Apolipoprotein D precursor		✓	
GP:AF332505_1	Apoptosis inhibitor–like protein mRNA		✓	
SW:CORI_HUMAN	Atrial natriuteric peptide–converting enzyme	✓	✓	
SW:AXU1_HUMAN	Axin 1 up-regulated 1 protein (TGF-β–induced apoptosis protein 3)	✓		
IPI00179390	β-actin			✓
SW:B2MG_HUMAN	β2-microglobulin	✓		✓
SW:APOH_HUMAN	β2–Glycoprotein 1 precursor (apolipoprotein H)	✓	✓	
GP:BC042510_1	Bile salt–stimulated lipase		✓	
SW:BAL_HUMAN	Bile salt–activated lipase precursor	✓	✓	✓
SW:BMP8_HUMAN	Bone morphogenetic protein 8 precursor		✓	
SW:C4BP_HUMAN	C4b-binding protein α chain precursor	✓		
GP:AF127036_1	Calcium-activated chloride channel protein 1	✓		
SW:CRTC_HUMAN	Calreticulin precursor	✓		
SW:CBP1_HUMAN	Carboxypeptidase a1 precursor	✓	✓	✓
SW:CPB2_HUMAN	Carboxypeptidase a2 precursor	✓	✓	✓
SW:CBPB_HUMAN	Carboxypeptidase b precursor	✓	✓	✓
SW:CATO_HUMAN	Cathepsin o precursor	✓		
SW:CD5L_HUMAN	CD5 antigen–like precursor	✓	✓	
SW:CERU_HUMAN	Ceruloplasmin precursor	✓		
GP:AF287894_1	CFTR-associated ligand (CAL)	✓		
GP:AL512883_3	Chymotrypsin C (caldecrin)	✓	✓	✓
SW:CTRL_HUMAN	Chymotrypsin-like protease ctrl-1 precursor	✓	✓	✓
SW:CTRB_HUMAN	Chymotrypsinogen b precursor	✓	✓	✓
GP:BC005951_1	Clone MGC:14588	✓		
IPI00219642	Clusterin precursor			✓
SW:COL_HUMAN	Colipase precursor	✓	✓	✓
SW:CO3_HUMAN	Complement C3 precursor	✓	✓	
SW:CO4_HUMAN	Complement C4 precursor		✓	
SW:CFAH_HUMAN	Complement factor H precursor		✓	
SW:FHR3_HUMAN	Complement factor H-related protein 3 precursor	✓		
IPI00032293	Cystatin C precursor			✓
SW:EL2A_HUMAN	Elastase 2a precursor	✓	✓	
SW:EL2B_HUMAN	Elastase 2b precursor		✓	✓
IPI00240986	Elastase 3, pancreatic (protease E)			✓
SW:EL3A_HUMAN	Elastase iiia precursor	✓	✓	
SW:EL3B_HUMAN	Elastase iiib precursor	✓	✓	✓
SW:FIBA_HUMAN	Fibrinogen α/αe chain precursor	✓		
SW:FIBB_HUMAN	Fibrinogen β chain precursor	✓	✓	
SW:FIBG_HUMAN	Fibrinogen γ chain precursor	✓	✓	
SW:FGL1_HUMAN	Fibrinogen-like protein 1 precursor	✓		✓
GP:AK074044_1	FLJ00102 protein	✓		
SW:FOL3_HUMAN	Folate receptor γ precursor	✓		
IPI00023673	Galectin 3 binding protein			✓
SW:SGCG_HUMAN	γ-Sarcoglycan (35 kDa dystrophin-associated glycoprotein)	✓		
SW:KLK1_HUMAN	Glandular kallikrein 1 precursor	✓		✓
SW:VGLH_HSV6U	Glycoprotein H precursor	✓		
SW:HPT2_HUMAN	Haptoglobin 2 precursor	✓	✓	
SW:HPTR_HUMAN	Haptoglobin-related protein precursor		✓	
SW:HBB_HUMAN	Hemoglobin β chain	✓	✓	
SW:HEMO_HUMAN	Hemopexin precursor	✓	✓	
GP:M19233_1	Human α-amylase-1 gene	✓		✓
GP:U88581_1	Human transferrin mRNA, C2 allele	✓		
GP:AL136795_1	Hypothetical protein DKFZp434G131		✓	
GP:AB083068_1	Hypothetical protein DKFZp434N1415	✓		
GP:BC027590_1	Hypothetical protein FLJ10261	✓		

Database ID	Protein Name	Identified in CA/nl	Identified in CP/nl	Identified in nl/nl
IPI00168679	Hypothetical protein Tr:Q8NEJ1			✓
IPI00152428	Hypothetical protein Tr:Q8TCS3			✓
SW:ALC1_HUMAN	Ig-α1 chain c region	✓	✓	✓
PIR1:A2HU	Ig-α2 chain C region	✓	✓	
SW:GC2_HUMAN	Ig-γ2 chain c region		✓	
SW:KAC_HUMAN	Ig-κ chain c region		✓	✓
IPI00004574	Ig-κ chain C region			✓
SW:MUC_HUMAN	Ig-μ chain C region	✓	✓	
GP:D84239_1	IgG Fc binding protein		✓	
SW:KAC_HUMAN	IGK mRNA for immunoglobulin κ light chain VLJ region	✓	✓	
GP:AJ294732_1	Immunoglobulin heavy chain constant region γ3 (IGHG3)	✓		
GP:AJ294733_1	Immunoglobulin heavy chain constant region γ4	✓		
GP:AB021510_1	Immunoglobulin heavy chain variable region		✓	
SW:GC1_HUMAN	Immunoglobulin heavy constant γ1	✓		
SW:IBP2_HUMAN	Insulin-like growth factor binding protein	✓		✓
SW:ITH4_HUMAN	Inter–α-trypsin inhibitor heavy chain h4 precursor	✓		
GP:AB040939_1	KIAA1506 protein	✓		
SW:LITA_HUMAN	Lithostathine 1 α precursor pancreatic stone protein)	✓	✓	✓
SW:LITB_HUMAN	Lithostathine 1β precursor	✓		
GP:AY044164_1	Lymphocyte α kinase		✓	
SW:LYC_HUMAN	Lysozyme c precursor	✓		✓
GP:AK009737_1	Moderately similar to gallus gallus syndesmos	✓		
GP:AC003682_1	Most similar to zinc finger protein ZNF132		✓	
IPI00103397	Mucin 5			✓
PIR2:S53362	Mucin 5AC	✓	✓	✓
GP:AF244548_1	Na+ and H+ coupled amino acid transport system N mRNA	✓		
SW:CAML_HUMAN	NCAM L1 (CD171 antigen)	✓		
IPI00220513	P21359 Neurofibromin			✓
SW:PAX7_HUMAN	Paired box protein pax-7 (hup1).	✓		
PIR2:A29934	Pancreatic elastase (EC 3.4.21.36) IIIA precursor	✓		
SW:LIPP_HUMAN	Pancreatic lipase	✓	✓	✓
SW:LIP1_HUMAN	Pancreatic lipase–related protein 1 precursor	✓		✓
SW:LIP2_HUMAN	Pancreatic lipase–related protein 2 precursor	✓	✓	✓
SW:GP2_HUMAN	Pancreatic secretory granule membrane major glycoprotein gp2 precursor	✓	✓	✓
SW:IPK1_HUMAN	Pancreatic secretory trypsin inhibitor precursor (tumor-associated trypsin inhibitor)	✓		✓
GP:AB035542_1	Pancreatic zymogen granule membrane–associated protein GP2β	✓		✓
SW:PAP1_HUMAN	Pancreatitis-associated protein 1 precursor	✓		✓
IPI00022543	Phosphatidylinositol glycan			✓
SW:PA21_HUMAN	Phospholipase a2 precursor	✓	✓	✓
SW:PLMN_HUMAN	Plasminogen precursor		✓	
SW:PIGR_HUMAN	Polymeric-immunoglobulin receptor precursor	✓		✓
SW:SAP_HUMAN	Proactivator polypeptide precursor (contains saposin a)	✓		✓
IPI00022213	Progastricsin (pepsinogen C)			✓
IPI00011694	Protease, serine, 1 preproprotein			✓
IPI00011695	Protease, serine, 2 preproprotein			✓
SW:CLPP_HUMAN	Putative ATP-dependent clp protease proteolytic subunit	✓		
PIR2:S36262	Rearranged Ig-κ region V-domain	✓		
IPI00009197	Regenerating islet–derived 1β precursor			✓
IPI00019176	Retinoic acid receptor responder			✓
SW:RNP_HUMAN	Ribonuclease pancreatic precursor	✓	✓	✓
GP:AK090123_1	RNA binding protein homolog		✓	
IPI00032179	Serine (or cysteine) proteinase inhibitor, clade C (antithrombin)	✓		
SW:TRFE_HUMAN	Serotransferrin precursor (transferrin)	✓	✓	✓
SW:ALBU_HUMAN	Serum albumin	✓	✓	✓
IPI00156237	Similar to chymotrypsinogen B precursor			✓

Database ID	Protein Name	Identified in CA/nl	Identified in CP/nl	Identified in nl/nl
IPI00027722	Similar to elastase 1, pancreatic			✓
IPI00247169	Similar to syncollin			✓
SW:SODC_HUMAN	Superoxide dismutase	✓		
GP:U66061_9	T-cell receptor β chain (human germline)	✓		
GP:AY190093_1	T-cell receptor β chain (clone PSA.S.20)		✓	
IPI00010675	Trefoil factor 2 (spasmolytic protein 1)			✓
IPI00181107	Triacylglycerol lipase			✓
SW:TRY1_HUMAN	Trypsin I precursor	✓	✓	✓
SW:TRY2_HUMAN	Trypsin II precursor	✓	✓	
IPI00015614	Trypsin III precursor			✓
SW:TRY4_HUMAN	Trypsin IV precursor	✓		
IPI00169276	Trypsinogen C			✓
GP:AF305835_1	Uterus-ovary specific putative transmembrane protein UO	✓	✓	✓
SW:VTDB_HUMAN	Vitamin D–binding protein precursor		✓	
GP:U06117_1	Xanthine dehydrogenase		✓	
SW:ZA2G_HUMAN	Zinc α2-glycoprotein precursor	✓		✓

GP indicates GenPept; PIR, Protein information resource; IPI, International Protein Index; SW, SWISS-PROT; CA, cancer; CP, chronic pancreatitis; nl, normal.

TABLE 2

Proteins With at Least 2-fold Change in Abundance in Pancreatic Juice From Pancreatitis

Database ID	Protein Name	Ratio (pancreatitis/nl)	SD	Unique Peptide Identified
More abundant by at least 2-fold				
3D:1clyH	1clyH IGG FAB (human IGG1	7.0	5.1	4
	α1b-Glycoprotein precursor	3.1	0.9	3
SW:A1BG_HUMAN				
	α2-Macroglobulin precursor	2.8	0.3	12
SW:A2MG_HUMAN				
	β2-Glycoprotein I precursor	6.5	6.1	7
SW:APOH_HUMAN	(apolipoprotein H)			
	Chymotrypsinogen b precursor	2.1	0.3	19
SW:CTRB_HUMAN				
SW:FIBB_HUMAN	Fibrinogen β chain precursor	3.0	0.9	13
SW:HPT2_HUMAN	Haptoglobin 2 precursor	2.4	0.3	16
SW:HBB_HUMAN	Hemoglobin β chain	6.8	6.6	12
GP:AF542069_1	Human serum albumin	3.9	1.7	267
SW:ALC1_HUMAN	Ig-α1 chain c region	4.7	1.1	7
SW:MUC_HUMAN	Ig-μ chain c region	2.5	2.1	1
GP:AJ294732_1	Immunoglobulin heavy chain constant region γ3	11.1	8.9	10
GP:AB021510_1	Immunoglobulin heavy chain variable region (IgM)	9.6	1.0	1
	NCAM L1 precursor	34.5	4.8	1
SW:CAML_HUMAN				
	Plasminogen/plasmin	2.7	1.3	1
SW:PLMN_HUMAN				
SW:RNP_HUMAN	Ribonuclease pancreatic precursor	2.3	6.40	2
SW:TRFE_HUMAN	Serotransferrin precursor (transferrin)	2.7	0.4	29
SW:TRY1_HUMAN	Trypsin I precursor	3.8	1.7	16
SW:TRY2_HUMAN	Trypsin II precursor	2.2	0.5	26
Less abundant by at least 2-fold				
	Bone morphogenetic protein 8 precursor	0.2	0.17	1
SW:BMP8_HUMAN				
	Caldecrin precursor	0.4	0.19	3
SW:CLCR_HUMAN				
SW:EL2A_HUMAN	Elastase 2a precursor	0.5	0.06	6
SW:EL2B_HUMAN	Elastase 2b precursor	0.4	0.18	4
	γ-Sarcoglycan	0.1	0.00	1
SW:SGCG_HUMAN				
GP:D84239_1	IgG Fc binding protein	0.3	0.03	5
PIR2:A29934	Pancreatic elastase IIIA	0.3	0.03	27
GP:AY190093_1	T-cell receptor β chain (clone PSA.S.20)	0.1	0.02	1

GP indicates GenPept; PIR, Protein information resource; SW, SWISS-PROT.

TABLE 3

Comparison of Proteins With at Least 2-fold Change in Pancreatic Juice from Pancreatitis and Cancer

Database ID	Protein Name	Ratio (CP/nl)	Ratio (CA/nl)
At least 2-fold change in abundance in both of pancreatic cancer and pancreatitis			
SW:CTRB_HUMAN	Chymotrypsinogen b precursor	2.1	2.8
SW:FIBB_HUMAN	Fibrinogen β chain precursor	3.0	3.8
SW:HBB_HUMAN	Hemoglobin β chain	6.8	3.3
GP:AF542069_1	Human serum albumin	3.9	3.7
SW:ALC1_HUMAN	Ig-α1 chain C region	4.7	4.0
SW:MUC_HUMAN	Ig-μ chain C region	2.5	3.9
SW:RNP_HUMAN	Ribonuclease pancreatic precursor	2.3	2.8
SW:TRY1_HUMAN	Trypsin I precursor	3.8	2.5
SW:TRY2_HUMAN	Trypsin II precursor	2.2	2.9
At least 2-fold change in abundance in pancreatic cancer only			
SW:A1AG_HUMAN	α1-Acid glycoprotein 1 precursor	1.2	0.3
SW:B2MG_HUMAN	β2-Microglobulin		3.3
SW:CPB2_HUMAN	Carboxypeptidase a2 precursor	0.7	0.3
SW:CO3_HUMAN	Complement C3 precursor	1.7	3.0
SW:EL3B_HUMAN	Elastase 3b precursor	1.7	2.2
SW:FIBA_HUMAN	Fibrinogen α/αe chain precursor		0.2
SW:FIBG_HUMAN	Fibrinogen γ chain precursor	1.4	7.1
SW:KAC_HUMAN	Ig-κ light chain VLJ region	1.5	4.7
SW:IBP2_HUMAN	Insulin-like growth factor binding protein 2		4.8
SW:KLK1_HUMAN	Kallikrein 1 precursor		2.7
SW:LITA_HUMAN	Lithostathine 1α (pancreatic stone protein)	0.72	2.3
SW:LITB_HUMAN	Lithostathine 1β precursor		4.8
SW:GP2_HUMAN	Pancreatic secretory granule membrane major glycoprotein	0.72	2.4
SW:PAP1_HUMAN	Pancreatitis-associated protein 1 precursor		3.1
SW:SAP_HUMAN	Proactivator polypeptide precursor		0.2
SW:CLPP_HUMAN	Putative ATP-dependent clp protease proteolytic subunit	0.3	
PIR2:S36262	Rearranged Ig-κ region V-domain		3.7
GP:U66061_9	T-cell receptor β chain (human germline)		10.2
GP:U88581_1	Transferrin, C2 allele		0.4
SW:TRY4_HUMAN	Trypsin IV precursor		5.6
SW:IPK1_HUMAN	Tumor-associated trypsin inhibitor		5.6
At least 2-fold change in abundance in pancreatitis only			
3D:1clyH	1clyH IGG FAB (human IGG1)	7.0	
SW:A1BG_HUMAN	α1b-Glycoprotein precursor	3.1	0.9
SW:A2MG_HUMAN	α2-Macroglobulin precursor	2.8	1.1
SW:APOH_HUMAN	β2-glycoprotein I precursor (apolipoprotein H)	6.5	1.1
SW:BMP8_HUMAN	Bone morphogenetic protein 8 precursor	0.2	
SW:CLCR_HUMAN	Caldecrin precursor	0.4	1.2
SW:EL2A_HUMAN	Elastase 2a precursor	0.5	1.0
SW:EL2B_HUMAN	Elastase 2b precursor	0.4	
SW:SGCG_HUMAN	γ-Sarcoglycan	0.1	
SW:HPT2_HUMAN	Haptoglobin 2 precursor	2.4	2.0
GP:D84239_1	IgG Fc binding protein	0.3	
GP:AJ294732_1	Immunoglobulin heavy chain constant region γ3	11.1	
GP:AB021510_1	Immunoglobulin heavy chain variable region (IgM)	9.6	
SW:CAML_HUMAN	NCAM L1 precursor	34.5	
PIR2:A29934	Pancreatic elastase IIIA	0.3	1.7
SW:PLMN_HUMAN	Plasminogen/plasmin	2.7	
SW:TRFE_HUMAN	Serotransferrin precursor (transferrin)	2.7	1.7
GP:AY190093_1	T-cell receptor β chain (clone PAS.S.20)	0.1	

GP indicates GenPept; PIR, Protein information resource; IPI, International Protein Index; SW, SWISS-PROT; CA, cancer; CP, chronic pancreatitis; nl, normal.