ORIGINAL ARTICLE

The Proteome of Mesenteric Lymph During Acute Pancreatitis and Implications for Treatment

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ABSTRACT

Context The protein fraction of mesenteric lymph during acute pancreatitis and other critical illness is thought to contain toxic factors. However, we do not have a complete description of the mesenteric lymph proteome during acute pancreatitis. **Objective** The aim of this study was to define the proteomic changes in mesenteric lymph during acute pancreatitis. **Setting** Animal Laboratory, University of Auckland, New Zealand. **Design** Mesenteric lymph was collected from sixteen male Wistar rats randomised to Group 1 (n=8) with taurocholate induced acute pancreatitis and Group 2 (n=8) sham control. The lymph was subjected to proteomic analysis using iTRAQTM (Applied Biosystems, Foster City, CA, USA) and liquid chromatography-tandem mass spectrometry. **Results** Two hundred and forty-five proteins including 35 hypothetical proteins were identified in mesenteric lymph. Eight of the 245 proteins had a significant increase in their relative abundance in acute pancreatitis conditioned mesenteric lymph, and 7 of these were pancreatic catabolic enzymes (pancreatic amylase 2, pancreatic lipase, carboxypeptidase A2, chymotrypsinogen B, carboxypeptidase B1, cationic trypsinogen, ribonuclease 1). **Conclusions** This is the first comprehensive description of the proteome of mesenteric lymph during acute pancreatitis conditioned mesenteric lymph. This study provides a clear rationale for further research to investigate the efficacy of enteral protease inhibitors in the treatment of acute pancreatitis.

INTRODUCTION

Acute pancreatitis is a common inflammatory disease that remains a significant clinical challenge. For the third of patients who develop severe acute pancreatitis, the risk of mortality remains high at 20-30% [1, 2] despite improvements in resuscitation and intensive care support [3, 4]. The mortality is due to multiple organ failure, and this has a bimodal time course distribution. Early deaths, during the first week, are due to a fulminant cytokine mediated systemic inflammatory response syndrome and multiple organ dysfunction (MODS), without an overt septic focus [5].

Received October 22nd, 2008 - Accepted December 4th, 2008 **Key words** Lymph; Pancreatitis, Acute Necrotizing; Proteomics; Rats **Abbreviations** IPI: International Protein Index; LC-MS/MS: liquid chromatography-tandem mass spectrometry; MODS: multiple organ dysfunction syndrome; MS: mass spectrometry; NBF: neutral buffered formalin; XO: xanthine oxidase **Correspondence** John A Windsor Department of Surgery, School of Medicine, Faculty of Medical and Health Sciences, University of Auckland, Auckland 1023, New Zealand Phone: +64-9.373.7599; Fax: +64-9.377.9656 E-mail: j.windsor@auckland.ac.nz **Document URL** <u>http://www.joplink.net/prev/200903/04.html</u> Later deaths, after 2 or more weeks, are due to MODS associated with infection of necrotic pancreas [6]. Many pathophysiological processes in acute pancreatitis have been described, but the critical factors that drive the MODS have yet to be fully elucidated [1].

There is a body of experimental work, largely derived from rodent studies, suggesting that mesenteric lymph, collected during critical illness, contains toxic factors [7, 8, 9, 10, 11] that contribute to the development of MODS and might be more important than translocated bacteria [12, 13]. Disease conditioned mesenteric lymph is reported to be toxic and associated with neutrophil dysfunction [14, 15], bone marrow suppression [16], and damage to pulmonary epithelial and endothelial cells [17, 18]. Indeed, Magnotti et al. reported that it was disease conditioned mesenteric lymph and not portal venous blood that caused increased endothelial cell permeability and lung injury [19]. This should not be a surprise because the anatomical route of the mesenteric lymph to the subclavian vein via the thoracic duct bypasses the liver. Therefore, unlike portal blood, mesenteric lymph is able to avoid any hepatic first-pass modification or detoxification, and potentially 'toxic' factors are instead delivered directly to distant organs (especially

the heart and lungs). We have recently reported an increase in the histological severity of experimental acute pancreatitis with the peripheral administration of mesenteric lymph conditioned by mild intestinal ischaemia and reperfusion [1]. Other studies have demonstrated a protection against MODS in a model of hypovolaemic shock when mesenteric lymph is excluded by division [20] or ligation [21] of the main rodent mesenteric lymph duct or by diversion of the thoracic duct [16]. The toxic factors in mesenteric lymph that are responsible for these effects have yet to be identified, although some recent work has suggested the toxic factors are largely carried in the aqueous or protein fraction of mesenteric lymph [8] and that pancreatic enzymes may contribute to the toxicity of disease conditioned mesenteric lymph [10, 22, 23, 24, 25, 26].

We recently published the first comprehensive description of normal rodent mesenteric lymph in the fasted and fed states using the advanced proteomic techniques of isobaric tags (iTRAQTM Reagent Multi-Plex Kit, Applied Biosystems, Foster City, CA, USA) for relative protein quantitation together with LC-MS/MS (liquid chromatography-tandem mass spectrometry) for the identification of the component proteins [27]. The aim of this current study was to use these state-of-the-art proteomic techniques to provide the first comprehensive description of the mesenteric lymph rodent proteome associated with acute pancreatitis, and to determine whether there were any significant increases in the relative abundance of detected proteins compared with sham control mesenteric lymph.

METHODS

Animals

Sixteen inbred male Wistar rats $(466\pm2.9 \text{ g}; \text{mean}\pm\text{SEM})$ fed a standard 18% plant protein derived rodent diet (Harlan Teklad 2018, Madison, WI, USA), were randomised to two groups. Group 1 (acute pancreatitis, n=8) had 90 minutes of acute pancreatitis followed by collection of mesenteric lymph for a further 60 minutes. Group 2 (sham control, n=8) had matched interventions and lymph collection to the pancreatitis. In each case the surgery commenced at the same time each day (09:00) and animals were fed *ad libitum*.

Acute Pancreatitis Model

We used an established model of acute pancreatitis [28, 29, 30, 31]. General anaesthesia was induced by isoflurane (2-5%; 2 L/min O_2 via nasal cone). A tracheostomy was inserted (modified 14g angiocath) and connected to a small animal ventilator (Kent Scientific Corporation, Torrington, CT, USA). Balanced general anaesthesia was maintained with isoflurane (2-3.5%) and buprenorphine (0.05 µg/kg, s.c., Temgesic[®], Reckitt and Coleman, Hull, England). The fraction of inspired oxygen/air was 40%; the

respiratory rate was 50-80 breaths per minute; and the peak inspiratory pressures 11-15 cmH₂O kept the expired CO₂ at 35-45 mL/L as measured by a capnograph (Pryon Corporation, Menomonee Falls, WI, USA). Body temperature was maintained between 36-38°C by use of a warming plate. Maintenance fluid (0.9% sodium chloride, NaCl) was infused at 1-2 mL/h for the duration of the experiment via a femoral intravenous line. Mean arterial pressure was maintained between 80 and 100 mmHg with the use of intravenous NaCl and monitored using a solid-state 2F pressure transducer (Millar Instruments Inc., Houston, TX, USA) placed in the right femoral artery.

The common pancreatic duct was cannulated with a 24g angiocath passed transduodenally into the pancreato-biliary duct through a 1.5 cm abdominal midline incision. The rostral part of the animal was raised 60° to the horizontal for 5 min to allow the biliary tree to drain (about 0.1 mL). During the last 2 min of this procedure, the common hepatic bile duct was occluded at the hilum of the liver (Biemer atraumatic vascular clip, AESCULAP, Center Valley, PA, USA).

Sodium taurocholate (4% w/v in 0.9% NaCl; 0.1 mL/100 g BW; Sigma Aldrich Pty Ltd., Castle Hill, New South Wales, Australia) was infused at 0.1 mL/min by a controlled infusion pump (Genie Precision Pump, Kent Scientific, Torrington, CT, USA). The Biemer clip and angiocath were removed upon completion of the infusion, and the common pancreatic duct was ligated to prevent reflux of taurocholate into the duodenum.

Severe acute pancreatitis was allowed to develop over a 90-minute period. We chose this relatively early time point and careful control of the blood pressure because we wanted to minimise the risk of hypotension and reflex splanchnic vasoconstriction resulting in an intestinal ischaemia-reperfusion injury that is known to occur during the course of severe acute pancreatitis [32, 33]. An intestinal ischaemia-reperfusion injury could potentially have altered the mesenteric lymph composition and confounded our results.

Collection of Mesenteric Lymph

After 90 minutes elapsed from the induction of pancreatitis, the duodenum and intestines were reflected to the left thus exposing the base of the mesentery. The mesenteric lymph duct was then cleared of surface peritoneum and fat. Silastic tubing (0.96 mm internal diameter, pre-soaked in 70% (v/v) ethanol, rinsed Milli-QTM (Millipore, Billerica, MA, USA) water, 18 M Ω) was drawn through the right abdominal posterolateral wall using а 14g angiocatheter. The mesenteric lymph duct was cannulated with the silastic tube and secured in place with a drop of cyanoacrylate tissue glue (Aesculap Inc., Center Valley, PA, USA). The intestines were then returned to their original position and the abdomen closed. Mesenteric lymph was collected for the following 60 minutes. Collection was performed

directly into sterile ice-cold siliconised Eppendorff tubes pre-loaded with protease inhibitors (final: 16.7 μ M bestatin, 8.3 μ M pepstatin and 5 mM EGTA; Sigma Aldrich Pty Ltd, Castle Hill, New South Wales, Australia). We chose to use Eppendorf tubes pre-loaded with protease inhibitors to prevent any *ex-vivo* protein modification of the mesenteric lymph samples. At the end of the experiment the mesenteric lymph was centrifuged (1,700 g, 4°C, 10 min) to remove any cellular material then immediately stored at -80°C until analysis.

Histology and Assays

At the end of the mesenteric lymph collection (150 minutes from the start of the experimental protocol), animals were euthanised for collection of organs and blood. A 1 cm³ piece of the pancreatic tail was fixed (10% neutral buffered formalin, (NBF)), and histological severity scoring was performed by a blinded consultant histopathologist on 5 μ m thick longitudinal paraffin sections using haematoxylin and eosin stain. Pancreatic histology was assessed using a published 5 point scale (from 0=normal to 4=severe) for each of the following criteria: leukocyte infiltration, pancreatic oedema, haemorrhage, fat necrosis, and acinar necrosis for a total score out of 20 [34].

A 5 cm length of small intestine, 20 cm from the caecum, was fixed (10% NBF) and histological severity scoring was performed by a blinded consultant histopathologist on 5 μ m thick longitudinal paraffin sections using haematoxylin and eosin stain. The small intestine histology was assessed on a published 6 point scale (from 0, normal to 5, severe) for mucosal injury, inflammation and haemorrhage respectively for a total score out of 15 [35].

Biochemical assays were performed on rodent serum using a Roche/Hitachi MODULAR[®] analytical system (Roche Diagnostics GmbH, Mannheim, Germany) in accordance with the manufacture's methods.

Depletion of the Major Proteins in Mesenteric Lymph

IgY immunoaffinity columns were used to deplete the most abundant proteins and enhance the detection of lower abundance proteins [36]. In this study, the expected major abundant proteins of mesenteric lymph IgG, fibrinogen, transferrin, alpha1-(albumin, antitrypsin, and haptoglobin) were depleted using ProteomeLab IgY-R7 affinity spin columns (Beckman Coulter, Fullerton, CA, USA). Each of the samples from the 16 rats was individually depleted. The protein concentration of the mesenteric lymph samples was determined using the EZQ[®] protein assay (Molecular Probes, Eugene, OR, USA). The depleted samples were concentrated by ultrafiltration using Vivaspin 4 concentrators with a 5 kDa polyethersulfone filter (Sartorius AG, Goettingen, Germany).

LC-MS/MS Based Proteomics

The mesenteric lymph samples underwent LC-MS/MS based proteomics both with and without

immunodepletion of the top 6 most abundant proteins. Each sample underwent reduction (incubation of 100 μ g protein with 10 mM DTT at 56°C for one hour) and alkylation (incubation with 20 mM iodoacetamide at pH 8.0 in the dark for one hour). Protein was then digested by incubation with 1 μ L trypsin (Promega, Madison, WI, USA) at 1 mg/mL and incubated at 37°C overnight. The peptides were then desalted on 10 mg Oasis SPE cartridges (Waters Corporation, Taunton, MA, USA), eluted with 70% acetonitrile and completely dried using a speed vacuum concentrator (Thermo Savant, Holbrook, NY, USA).

iTRAQTM has previously been evaluated and validated against SDS-PAGE and western blotting as a method of tracking relative concentrations of proteins in four different samples [37, 38]. The dried protein digests were reconstituted with 30 μ L of dissolution buffer from the iTRAQTM and labelled with iTRAQTM reagents according to the manufacturer's instructions. Labelled material was then combined, acidified by addition of 10% (v/v) formic acid, concentrated to approximately 200 μ L, and then diluted to 2 mL with 0.1% formic acid. This sample was desalted as above, the eluate then concentrated to 100 μ L, and finally diluted to 270 μ L with 0.1% (v/v) formic acid.

Samples were then fractionated on-line on a BioSCX II 0.3x35 mm column (Agilent Technologies, Santa Clara, CA, USA). A 20 salt-step protocol was performed using 10 µL injections of 10, 20, 40, 60, 70, 80, 90, 100, 110, 120, 130, 140, 160, 180, 200, 220, 240, 260, 400 and 500 mM KCl. Peptides were captured on a 0.3x5 mm PepMap cartridge (LC Packings, Dionex Corporation, Sunnyvale, CA, USA) before being separated on a C18 300SB 0.3x100 mm Zorbax column (Agilent Technologies, Santa Clara, CA, USA). The HPLC gradient between Buffer A (0.1% formic acid in water) and Buffer B (0.1% formic acid in acetonitrile) was formed at 6 µL/min as follows: 10% B for the first 3 min, increasing to 35% B by 80 min, increasing to 95% B by 83 min, held at 95% until 91 min, back to 10% B at 91.5 min and held there until 100 min. The liquid chromatography effluent was directed into the ion spray source of a QSTAR XL hybrid mass spectrometer (Applied Biosystems, Foster City, CA, USA) scanning from 300-1,600 m/z. The three most abundant, multiply-charged peptides were selected for MS/MS analysis (80-1,600 m/z). The mass spectrometer and HPLC system were under the control of the Analyst OS software package (Applied Biosystems, Foster City, CA, USA).

Sequence Database Searches

ProteinPilot (version 1.0, Applied Biosystems, Foster City, CA, USA) [39] was used to search the MS/MS data against the International Protein Index (IPI) Rat database v3.27 (http://www.ebi.ac.uk/IPI/IPIhelp.html) with the following search parameters: Cys alkylation -Iodoacetamide; Digestion - Trypsin; Instrument -QSTAR ESI; Search Effort - Rapid. The data were also searched against the above database using Mascot 2.0.5 software (Matrix Science, London, UK), and a similar set of protein hits obtained (data not shown). Proteins that were identified as potentially hypothetical by the ProteinPilot IPI Rat database v3.27 search were then subjected to a NCBI Basic Local Alignment Search Tool search against the 'UniProt Clusters 100%' database (BLAST; http://www.ncbi.nlm.nih.gov/blast/).

Validation of Protein Identifications

A search of the IPI Rat database v3.27 with the reversed amino acid sequence of each entry was carried out to determine the minimum required ProteinPilot score for the proteins that would yield an overall confidence greater than 97%. Protein matches were considered valid if their ProteinPilot scores were equal to or above the minimum required score for each run.

Validation of Protein Changes

After immunodepletion and LC-MS/MS, only small volumes (10-20 μ L per animal) of the original mesenteric lymph samples were available for cross-validation of protein changes reported by iTRAQTM LC-MS/MS. Despite the small sample volumes, we were able to measure albumin, pancreatic amylase, and lipase in mesenteric lymph using commercial reagents (Pointe Scientific, Canton, MI, USA) on a COBAS MIRA analyser (Roche, Basel, Switzerland) in accordance with the manufacturer's instructions.

STATISTICS

Protein abundance was calculated from the peptide summary data generated by ProteinPilot. Strict criteria were applied when calculating the protein abundance from peptide data - peptides identified as belonging to more than one protein were eliminated, and any spectra below the confidence threshold set by ProteinPilot were also eliminated. The remaining peak areas were log-transformed and, for each sample, average log peak areas were calculated from the spectra within each reporter region for every identified protein. Differences in relative abundance were calculated as differences in log peak areas (acute pancreatitis - sham) and reported as fold differences between the two.

The statistical analysis was carried out using the LIMMA package v2.9.17 [40] in the R software v2.6.1 (R Development Core Team, 2007) [41]. The analysis for differential expression was performed on a proteinby-protein basis using a linear model that included run, label and treatment effects. A moderated t-statistic, in which the standard errors were moderated across proteins using a Bayesian model, was used for the significance analysis [42]. P values were adjusted for multiple testing using Benjamini and Hochberg's false discovery rate setting the expected proportion of false discoveries to 5% [43]. Changes in protein abundance with an adjusted P value less than 0.05 were considered significant.

For non-proteomic data, such as histology scores and biochemical parameters, the non-parametric Mann-Whitney U test was used to derive statistical significance and two-tailed P value less than 0.05 was considered significant.

Bioinformatics

Proteins that were found to have a statistically significant difference in abundance between sham and acute pancreatitis conditioned mesenteric lymph were then further analysed for functional and biological relevance. With the help of Gaggle [44], an open-source Java software environment, and Gene Ontology (GO) provided free by the Gene Ontology Consortium (http://www.geneontology.org/index.shtml) [45], these proteins were classified by their molecular function and cellular location.

ETHICS

This study was approved by the University of Auckland Animal Ethics Committee. All animals received humane care in keeping with the "Guide for Care and Use of Laboratory Animals (1996)" prepared by the National Academy of Sciences.

	Table 1. Histological and serum biochemical	parameters in the two experimental groups.
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	Acute pancreatitis	Sham	P value
	(n=8)	(n=8)	
Pancreas histology score [34]	7.20±0.57	1.20 ± 0.20	< 0.001
Intestinal histology score [35]	0.47±0.16	0.31±0.15	0.541
Sodium (mmol/L)	141.9±0.35	139.7±0.58	0.012
Potassium (mmol/L)	6.31±0.22	6.22±0.17	0.515
Chloride (mmol/L)	111.6±0.93	108.8±0.98	0.099
Glucose (mmol/L)	14.85±1.61	14.8±0.96	0.959
Urea (mmol/L)	10.2±0.39	10.5±0.41	0.460
Creatinine (µmol/L)	42.13±6.64	42.4±2.75	0.274
Calcium (mmol/L)	2.2±0.06	2.4±0.34	0.027
Amylase (U/L)	3,829±302	2,053±81	< 0.001
Lipase (U/L)	4,377±1,088	310±61	< 0.001
Bilirubin (µmol/L)	<2.0	<2.0	-
GGT (U/L)	<2.0	<2.0	-
ALP (U/L)	47±3	56±4	0.101
AST (U/L)	592±267	101±15	0.019
ALT (U/L)	120±34	46±5	0.009

Values listed are mean±SEM. P values derived using Mann-Whitney U test. Bilirubin and GGT had values below the lower limits of the assays.

RESULTS

Acute Pancreatitis Model

The taurocholate model produced acute pancreatitis with the expected elevation in serum amylase $(3,829\pm302 \text{ U/L } vs. 2,053\pm81 \text{ U/L}; \text{ sham } vs. \text{ acute pancreatitis, respectively; P<0.001) and serum lipase <math>(4,377\pm1,088 \text{ U/L } vs. 310\pm61 \text{ U/L}; \text{ sham } vs. \text{ acute pancreatitis, respectively; P<0.001)}$ (Table 1). The histology of the pancreas confirmed severe acute pancreatitis (Table 1). There was no significant difference between the two groups for histology of the intestine.

Mesenteric Lymph Proteomics

There were 245 proteins identified in mesenteric lymph from all the mass spectrometry runs (with and without depletion) that met the validity criteria. All of the proteins were identified in both experimental groups, and there were no proteins unique to either experimental group. A non-redundant list of these proteins is provided (Supplementary Table 1).

Forty-seven of the 245 identified proteins (19.2%) were listed as potentially hypothetical proteins according to the International Protein Index (Rat database v3.27). These proteins were then subjected to a NCBI BLASTP analysis. Thirty-five proteins (14.3%) were confirmed as hypothetical but 12 proteins were not, being identical to other rat proteins (Supplementary Table 2). Nine of these 35 proteins were previously identified in a recent proteomic study of normal mesenteric lymph [27] but continue to be listed as hypothetical according to the International Protein Index (Rat database v3.27) (Supplementary Table 2).

Prior to the immunoaffinity depletion, the 6 proteins removed by this process (albumin, fibrinogen, transferrin, alpha1-antitrypsin, IgG and haptoglobin) were investigated using mass spectrometry data and there were no statistically significant differences between the two experimental groups (Supplementary Table 1).

There was a statistically significant increase in the relative abundance of 8 proteins in the mesenteric lymph of the acute pancreatitis experimental group after immunoaffinity depletion (Table 2). An additional 2 proteins (hemoglobin beta chain complex and phosphoglycerate mutase 1) had changes in their relative abundance that approached significance (P<0.05 and an adjusted P<0.10).

The 8 proteins that were significantly increased in acute pancreatitis conditioned mesenteric lymph were then classified by their cellular location and molecular function using the Gene Ontology classification system. Seven of the proteins were extracellular pancreatic enzymes and one was cytosolic (Table 2). In regards to their molecular function, all 8 were catabolic enzymes and 4 were also ion binding (Table 2). Of the 7 extracellular pancreatic catabolic enzymes, four had peptidase activity (carboxypeptidase B1, chymotrypsinogen B, carboxypeptidase A2 and cationic trypsinogen), one had ester hydrolase activity (pancreatic lipase), one had endoribonuclease activity (ribonuclease), and one acted on glycosyl bonds (pancreatic amylase 2).

The results of the specific biochemical assays performed for albumin, pancreatic amylase and lipase in mesenteric lymph are consistent with the LC-MS/MS findings. Albumin was not different between the two groups (mean±SEM; 14.7 ± 2.8 g/L vs. 14.0 ± 1.8 g/L; acute pancreatitis vs. sham, respectively; P=0.867) while both pancreatic amylase (7,024±2,079 U/L vs. 901±196 U/L; acute pancreatitis vs. sham, respectively; P<0.001) and lipase (1,424±367 U/L vs. 272±132 U/L acute pancreatitis vs. sham, respectively; P=0.036) were significantly increased.

DISCUSSION

This study provides the first comprehensive description of the changes that occur in the proteome of mesenteric

Table 2. List of the 8 proteins that	had an adjusted P value less	s than 0.05 in their relative	abundance between th	ne pancreatitis and sham	experimental
groups					

Name	Gene symbol	Protein	Location	Molecular	No. of a	nimals ^a	Fold	P value	Adjusted
		identifier		function	AP ^c	Sham	change ^b		P value
Amylase 2, pancreatic	Amy2	IPI00211904	Extracellular	Catabolic Ion binding	7	6	46.96	< 0.001	< 0.001
Pancreatic lipase	Pnlip	IPI00198916	Extracellular	Catabolic	6	5	38.09	< 0.001	< 0.001
Carboxypeptidase A2 (pancreatic)	Cpa2_predicted	IPI00193391	Extracellular	Catabolic Ion binding	6	5	34.64	< 0.001	< 0.001
Chymotrypsinogen B	Ctrb	IPI00206309	Extracellular	Catabolic	6	5	18.22	< 0.001	< 0.001
Carboxypeptidase B1 (tissue)	Cpb1	IPI00193393	Extracellular	Catabolic Ion binding	6	5	22.89	< 0.001	< 0.001
Cationic trypsinogen	LOC286911	IPI00211212	Extracellular	Catabolic Ion binding	6	5	29.64	< 0.001	< 0.001
Glutathione S-transferase, mu 2	Gstm2	IPI00411230	Intracellular	Catabolic	8	8	3.52	< 0.001	0.012
Ribonuclease, RNase A family, 1 (pancreatic)	Rnase1	IPI00211902	Extracellular	Catabolic	3	2	40.50	< 0.001	0.024

^a Number of animals in each group where the protein was identified (maximum n=8 for each group)

^b Fold change: acute pancreatitis *vs*. sham group

^c Taurocholate induced acute pancreatitis group

lymph during acute pancreatitis. A total of 245 proteins were identified in mesenteric lymph using strict acceptance criteria and with greater than 97% confidence. All identified proteins were present in both the acute pancreatitis and sham control groups. There were 8 proteins that were significantly more abundant in acute pancreatitis conditioned mesenteric lymph. All 8 of these proteins were catabolic enzymes with 7 being secreted pancreatic catabolic enzymes. Also identified in the mesenteric lymph of both groups were 35 hypothetical proteins.

Severe acute pancreatitis is associated with hypotension and reflex splanchnic vasoconstriction resulting an intestinal ischaemia-reperfusion injury [32, 33]. It has previously been hypothesized that pancreatic enzymes which are normally present in the intestinal lumen in high concentration may be able to pass through a compromised intestinal barrier and cause remote organ injury [22, 46]. In the current study, we controlled the mean arterial pressure to help prevent ischaemic injury of the intestine, and this was confirmed by the normal intestinal histology scores in the acute pancreatitis group. Thus, we show for the first time that high levels of several pancreatic catabolic enzymes are present in acute pancreatitis conditioned mesenteric lymph early in disease process in the presence of normal intestinal histology.

A strength of this study is the use of state-of-the-art iTRAQTM LC-MS/MS techniques used to define the proteome of acute pancreatitis conditioned mesenteric lymph. Previous studies have used enzyme specific biochemical methods to identify amylase, lipase and trypsin in the thoracic duct lymph of animals [47] and humans [7, 26] with acute pancreatitis. In addition to confirming the presence of these three catabolic enzymes, we report for the first time the presence of ribonuclease 1, carboxypeptidase B1, chymotrypsinogen B and carboxypeptidase A2 in acute pancreatitis conditioned mesenteric lymph. The most abundant protein class identified in normal mesenteric lymph was previously reported to be protease inhibitors [27]. It is striking that despite a substantial increase in the relative abundance of proteases in acute pancreatitis conditioned mesenteric lymph identified here, there was no concomitant rise in relative abundance of protease inhibitors.

A study published in 2008 by Mole *et al.* used two different proteomic techniques to investigate acute pancreatitis conditioned mesenteric lymph [9]. The SELDI-TOF (surface-enhanced laser desorption ionization time-of-flight mass spectrometry) technique generated spectra that differentiated acute pancreatitis conditioned mesenteric lymph from sham mesenteric lymph, but this could not perform identification of individual proteins [48]. In a separate experiment they used 2D-PAGE (two-dimensional gel electrophoresis) to identify just 4 proteins (transferrin, haptoglobin, alpha1-protease inhibitor and apolipoprotein A1) that showed a relative increase or decrease in acute pancreatitis conditioned mesenteric lymph. Using these techniques it was not possible for Mole *et al.* to demonstrate any numerical fold change data or statistical measures of significance. If immunodepletion had been used to deplete the major abundant proteins prior to 2D-PAGE it might have been possible to achieve a higher level of resolution and identification of additional protein changes. Another limitation of the study by Mole *et al.* [9] is that mean arterial pressure was not controlled. This raises the possibility that the reported proteomic changes in acute pancreatitis conditioned mesenteric lymph might have been due, at least in part, to concomitant hypotension and intestinal ischaemia.

Pancreatic enzymes contribute to the development of distant organ injury and MODS by the proteolytic cleavage of cellular membranes and extracellular proteins, and by activating leucocytes to generate reactive oxygen species (ROS) [49, 50, 51, 52, 53]. Pancreatic proteases are also thought to contribute to the generation of ROS by the limited proteolytic conversion of the enzyme xanthine dehydrogenase to xanthine oxidase (XO) [54]. In the oxidase form, this enzyme produces the superoxide anion and thus generates ROS [55]. It is recognized that pancreatic proteases are not the only factor responsible for the development of MODS in acute pancreatitis. Pancreatic amylase has also been implicated as a potentially toxic factor. It is now thought that high levels of pancreatic amylase disrupt the binding of tissue XO by hydrolyzing the internal alpha1-4 linkages of some of the glycoproteins present in the extracellular space. Once mobilized, XO is able to concentrate in distant organs with low intrinsic XO activity and produce ROS contributing to organ dysfunction [56].

There is evidence that pancreatic enzymes contribute to the toxicity of mesenteric lymph in acute pancreatitis and other critical illnesses. In a human study of severe acute pancreatitis, diversion of trypsin rich thoracic duct lymph reduced lung injury [26]. In the setting of haemorrhage it was found in animal models that shock conditioned mesenteric lymph caused neutrophil dysfunction [14, 15], bone marrow suppression [16], and damage to endothelial cells of the pulmonary microvasculature [17, 18]. These effects were prevented by either ligation of the pancreatic duct prior to the induction of shock [10, 22] or by the intraintestinal inhibition of pancreatic serine proteases [23, 24, 25, 50] thereby implicating pancreatic proteases as toxic factors in mesenteric lymph.

The findings of this study support the proposal that pancreatic catabolic enzymes in mesenteric lymph during acute pancreatitis could be therapeutic targets. The history of intravenous anti-protease treatment in acute pancreatitis, using gabexate and nafamostat, is disappointing [57]. After more than 70 clinical trials and several meta-analyses, there is no convincing evidence to recommend the use of intravenous protease inhibition in acute pancreatitis [58]. Of the 16 recently published clinical guidelines there are only two, from Japan and China, that recommend the use of intravenous protease inhibitors [58, 59], and not on the basis of high level evidence. The findings of the present study would suggest that protease inhibition might be more effective if given by the enteral rather than the intravenous route, especially if it were lymphotropic and concentrated in mesenteric lymph. To our knowledge, there is only one clinical trial that investigated the use of oral protease inhibition (FOY 305) in acute pancreatitis [60] and showed significant improvement in abdominal pain scores and urinary amylase in the treatment arm. Further studies to evaluate the efficacy of protease inhibition delivered by the enteral route appear to be justified in this context. There have been previous reports of enteral protease improving inhibitor treatment haemodynamic parameters, reducing intestinal injury and leukocyte activation in models of intestinal ischaemia-reperfusion injury [24, 25] and septic shock [61].

One of the challenges of proteomics is that high abundance proteins mask low abundance proteins when compositional analysis is attempted. This problem was addressed in the present study by the immunodepletion of the highly abundant proteins using a validated method [36, 62, 63, 64, 65]. Unfortunately, unintentional protein loss inevitably occurs during immunodepletion because of non-specific binding to the column, specific binding to immunoglobulin with structural homology to the proteins being depleted, and/or binding to the proteins that are being depleted [36, 62]. Given the modest amount of lymph that can be collected from a rat during the experimental protocol (750-1,000 µL), only 10-20 µL of the original sample is left after immunodepletion and LC-MS/MS for further evaluation thus prohibiting further analyses by complementary gel-based proteomic methods. The protein fraction of mesenteric lymph is unlikely to contain all of the factors responsible for the toxicity found in acute pancreatitis and other critical illnesses, although it has been found to be more toxic than the lipid fraction [8]. Delineating the composition of the lipid fraction of acute pancreatitis conditioned mesenteric lymph is the focus of further studies.

CONCLUSION

This is the first comprehensive description of the proteome of mesenteric lymph conditioned by acute pancreatitis. It has demonstrated a significant increase in the relative abundance of 8 proteins amongst the 245 proteins identified using state-of-the-art iTRAQTM based LC-MS/MS techniques, 7 of which are secreted pancreatic catabolic enzymes. This study provides a clear rationale for further research to investigate the efficacy of enteral protease inhibitors in the treatment of acute pancreatitis.

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Supplementary	Table 1. Non-redundant list of 245	proteins identified in the mesenteric	ymph from the	pancreatitis and	sham expe	rimental groups.
Name		Gene symbol	Protein No.	of animals ^a	Fold P	value Adjusted

Name	Gene symbol	Protein	No. of a	nimals ^a	Fold	P value	Adjustee
		identifier	AP ^c	Sham	change ^b		P value
Ab1-018	Hps5	IPI00382131	8	8	-1.03	0.797	0.98
Ig gamma-2B chain C region	Igh-1a	IPI00655256	3	2	NA	NA	NA
22 kDa protein ^d	-	IPI00204640	8	8	1.07	0.742	0.961
Actin alpha cardiac 1	Actc1	IPI00194087	1	1	NA	NA	NA
Actin, alpha 1, skeletal muscle	Actal	IPI00189813	3	3	1.80	0.150	0.589
Actin, gamma, cytoplasmic 1	Actg1	IPI00764461	4	4	1.90	0.160	0.589
Adiponectin, C1Q and collagen domain containing ^d	Adipoq	IPI00202515	6	5	1.20	0.380	0.833
Afamin	Afm	IPI00777658	2	2	NA	NA	NA
AHNAK nucleoprotein ^d	Ahnak	IPI00769072	3	5	1.35	0.653	0.930
Albumin	Alb	IPI00191737	8	8	-2.12	0.026	0.242
Alcohol dehydrogenase1	Adh1	IPI00331983	2	3	NA	NA	NA
Alcohol dehydrogenase 4 (class II), pi polypeptide	Adh4	IPI00476212	1	2	NA	NA	NA
Aldolase A	Aldoa	IPI00231734	6	6	1.32	0.269	0.745
Aldolase B	Aldob	IPI00471911	2	3	NA	NA	NA
Alpha 1 microglobulin/bikunin	Ambp	IPI00210900	8	8	1.04	0.778	0.975
Alpha-1-inhibitor III	A1i3	IPI00201262	8	8	-1.07	0.601	0.902
Alpha-2-glycoprotein 1, zinc	Azgp1	IPI00211103	8	8	-1.05	0.790	0.974
Alpha-2-HS-glycoprotein	Ahsg	IPI00327469	8	8	-1.10	0.560	0.875
Alpha-2u globulin PGCL1	LOC259246	IPI00400456	6	6	1.80	0.121	0.589
Amiloride binding protein 1	Abpl	IPI00204571	2	2	NA	NA	NA
Amylase 1 salivary	Amvl	IPI00198466	8	8	2.24	0.010	0.121
Amylase 2. pancreatic	Amv2	IPI00211904	7	6	46.96	< 0.001	< 0.001
Angiotensinogen	Agt	IPI00209744	8	8	1 04	0.816	0.986
Anolinoprotein A-I	Anoal	IPI00563778	8	8	-1.02	0.905	0.986
Apolipoprotein A-II	Apoa2	IPI00197700	7	6	-1.24	0.466	0.876
Apolipoprotein A-IV	Apoa4	IPI00324272	8	8	-1.03	0.896	0.986
Anolinoprotein B	Anob	IPI00555161	8	8	1.03	0.947	0.986
Apolipoprotein D	Anocl	IPI00200102	8	8	-1.00	0.995	0.999
Apolipoprotein C-II	Apoc2	IPI00194583	8	8	-1.30	0.448	0.873
Apolipoprotein C-III	Apoc3	IPI00206600	8	8	-1.45	0.440	0.745
Apolipoprotein C-IV	Apoc/	IPI00191952	7	7	-1.22	0.521	0.876
Apolipoprotein E	Apoe	IPI00190701	8	8	1 15	0.521	0.870
Apolipoprotein H	Apob	IPI00778633	8	8	-1 78	0.200	0.121
B-cell CLI //wmboma 10	Rel10	IPI00776589	2	1	-1.70 NA	NA	NA
Beta 2 microalobulin	B2m	IDI00204350	8	1 Q	1.03	0.802	0.086
Haemoglobin beta chain isoform	MGC72073	IDI00207146	8	8	7.66	0.030	0.980
Pataina homoaystaina mathultrangfaraga	Dhmt	IDI00222027	2	2	7.00 NA	0.039 NA	0.304 NA
Bilivardin raduatasa P (flavin raduatasa (NADDH)) (pradiatad)	Dillin Diverb prodicted	IF 100332027	2	1	NA	IN/A NA	NA
Cadharin 1	Gdb1	IP100392070	2	1	1 20	0.605	0.020
Cadhenin 17	Cdn1	IP100206062	3	4	-1.20	0.095	0.930
Cadnerin 17	Call /	IP100215558	1	2	NA 1.22	NA 0.520	NA 0.97(
	Calmi	IP100231955	2	4	1.55 NIA	0.539	0.870
Carbonia anhydroga 1 ^d	Carl mardiate 1	IP100191/28	4	1	NA 2.16	INA 0.07(INA 0.4(7
Carbonic annyarase 1		IP100360930	ð	8	2.10	0.076	0.46/
Carbonic annydrase 3	Cas	IP100230788	8	8	-1.03	0.940	0.986
Carboxypeptidase A1	Cpal	IPI00327713	2	3	NA	NA	NA
Carboxypeptidase A2 (pancreatic) "	Cpa2_predicted	IP100193391	6	5	34.64	<0.001	<0.001

Carboxypeptidase B1 (tissue)	Cpb1	IPI00193393	6	5	22.89	< 0.001	<0.001
Carboxypeptidase B2 (plasma)	Cpb2	IPI00190501	8	8	-1.53	0.313	0.773
Carboxypeptidase N, polypeptide 1	Cpn1	IPI00190500	7	7	-1.06	0.690	0.927
Cathepsin B	Ctsb	IPI00562653	2	3	NA	NA	NA
Cationic trypsinogen ^d	LOC286911	IPI00211212	6	5	29.64	< 0.001	< 0.001
Gastrotropin	Fabp6	IPI00231649	2	3	NA	NA	NA
Ceruloplasmin	Ср	IPI00476292	8	8	-1.11	0.513	0.876
Chymotrypsinogen B	Ctrb	IPI00206309	6	5	18.22	<0.001	<0.001
Clusterin	Clu	IPI00198667	8	8	1.08	0.563	0.876
Coagulation factor II	F2	IPI00189981	8	8	-1.11	0.537	0.876
Coagulation factor IX	F9	IPI00765267	4	4	1.07	0.779	0.975
Coagulation factor X	F10	IP100206786	8	8	-1.13	0.339	0.852
Coagulation factor XI	F11	IPI00569754	4	2	NA	NA	NA
Coagulation factor XII	F12	IPI00365752	8	8	-1.21	0.178	0.615
	Cfll	IP100327144	3	4	1.72	0.247	0.728
Coloas_predicted	Coloa3_predicted	IP100360737	1	1	NA	NA	NA
Complement component 1, q subcomponent, alpha polypeptide	Clqa	IPI00215296	1	2	NA 1.10	NA 0.(25	NA 0.012
Complement component 1, r subcomponent	Clr	IP100301108	о 0	0	-1.18	0.625	0.913
Complement component 2		IF100199519 ID100104044	0	0	1.07	0.610	0.927
Complement component 3	C2 C3	IF100194044 IP100480630	0	0 8	-1.07	0.019	0.913
Complement component 4 binding protein alpha	C4bpa	IPI00200073	8	8	1.03	0.455	0.870
Complement component 4 gene 2	C4-2	IPI00422037	6	7	1.03	0.900	0.986
Complement component 4a	C4 2 C4a	IPI00213036	8	8	-1.09	0.500	0.927
Complement component 5	C5	IPI00764698	8	8	1.07	0.044	0.986
Complement component 6	C6	IPI00331776	8	8	1.01	0.542	0.927
Complement component 7 ^d	C7	IPI00766303	8	8	1.07	0.876	0.986
Complement component 8 alpha polypeptide ^d	C8a predicted	IPI00358382	8	8	-1.01	0.928	0.986
Complement component 8, beta polypeptide	C8b	IPI00387929	7	8	-1.04	0.834	0.986
Complement component 8, gamma polypeptide ^d	C8g predicted	IPI00373395	8	8	1.00	0.999	0.999
Complement component 9	C9	IPI00231423	8	8	1.08	0.594	0.898
Complement component factor H	Cfh	IPI00208659	7	7	-1.02	0.907	0.986
Complement component factor h-like 1	Cfh11	IPI00554226	7	6	1.12	0.503	0.876
Complement factor B	Cfb	IPI00422011	5	5	-1.10	0.617	0.913
Complement factor D	Cfd	IPI00212480	8	8	1.21	0.336	0.804
Complement factor I	Cfi	IPI00204451	8	8	-1.06	0.680	0.927
C-reactive protein, pentraxin-related	Crp	IPI00188225	8	8	-1.35	0.281	0.745
Creatine kinase, brain	Ckb	IPI00470288	8	8	-1.06	0.862	0.986
Creatine kinase, muscle	Ckm	IPI00211053	8	8	1.50	0.245	0.728
Cystatin C	Cst3	IPI00231801	6	7	1.55	0.192	0.632
Desmoglein 2 ^d	Dsg2_predicted	IPI00358687	1	2	NA	NA	NA
Diazepam binding inhibitor	Dbi	IPI00231069	1	1	NA	NA	NA
Dmx-like 1 ^a	Dmx11_predicted	IPI00367836	4	2	NA	NA	NA
Enolase 1, alpha	Enol	IPI00464815	2	3	NA	NA	NA
Enolase 1, alpha pseudogene	LOC688509	IPI00767147	2	3	NA	NA	NA
Enolase 3, beta	Eno3	IP100231631	8	8	1.59	0.205	0.658
Epidermal growth factor receptor	Egir	IPI00212694	8	8	-1.12	0.400	0.851
Esterase 2	ESZ	IP100195148	8	2	-1./U	0.124	0.589
Eukaryotic translation initiation factor 5A	Elloa Nmo2	IP100211210 IP100225180	1	2	NA	NA	NA
Expressed in non-inclustance certs 2	Vlkd1 predicted	IPI00320109	1	1	NA	NA	NA
Extracellular matrix protein 1	Fcm1	IPI00231772	6	7	-1.13	0.516	0.880
Fatty acid binding protein 1 liver	Fabril	IPI00190790	2	3	-1.15 NA	NA	NA
Fatty acid binding protein 3	Fabn3	IPI00231971	1	1	NA	NA	NA
Fatty acid binding protein 4 adipocytes	Fabp4	IPI00207890	8	7	1 27	0.516	0.876
Fetuin beta	Fetub	IPI00212708	7	6	-1.24	0.353	0.822
Fibrinogen, alpha polypeptide	Fga	IPI00382317	7	7	1.18	0.416	0.858
Fibrinogen, B beta polypeptide	Fgb	IPI00382134	1	3	NA	NA	NA
Fibrinogen, gamma polypeptide	Fgg	IPI00190759	4	4	1.03	0.945	0.986
Fibrinogen-like 2	Fgl2	IPI00324102	3	2	NA	NA	NA
Fibronectin 1	Fn1	IPI00231982	3	5	-2.47	0.077	0.467
Follistatin-like 1	Fstl1	IPI00207063	2	1	NA	NA	NA
Four and a half LIM domains 1 ^d	Fhl1	IPI00780699	3	2	NA	NA	NA
Gelsolin	Gsn	IPI00363974	8	8	-1.03	0.902	0.986
Globin, alpha ^a	LOC287167	IPI00213611	7	6	3.11	0.149	0.589
Glucose phosphate isomerase	Gpi	IPI00364311	8	8	-1.01	0.961	0.986
Glutathione peroxidase 1	Gpx1	IPI00192301	1	2	NA	NA	NA
Glutathione peroxidase 3	Gpx3	IPI00476458	8	8	-1.33	0.133	0.589
Glutathione S-transferase, mu l	Gstml	IP100231639	6	7	4.61	0.007	0.109
Glutathione S-transferase, mu 2	Gstm2	IP100411230	8	8	3.52	< 0.001	0.013
Giutatnione-S-transferase, alpha type2	Gsta3	1P100231150	6	4	2.41	0.022	0.221

Glutathione-S-transferase P	Gstp1	IPI00231229	4	5	2.54	0.037	0.297
Glycerol-3-phosphate dehydrogenase 1 (soluble)	Gpd1	IPI00231148	2	3	NA	NA	NA
Glycosylphosphatidylinositol specific phospholipase D1	Gpld1	IPI00325157	7	6	1.41	0.121	0.589
Group specific component	Gc	IPI00194097	8	8	-1.13	0.361	0.824
Guanine deaminase	Gda	IPI00325884	2	3	NA	NA	NA
Isoform 1 of Haptoglobin	Hp	IP1004//59/	2	4	NA	NA	NA
Heat snock protein 8	Hspa8	IP100208205	2	2	NA 5 79	NA 0.064	NA 0.424
Hemoglobin alpha 2 chain	LUC300504	IP100205036	/ 8	0 9	5.78 20.54	0.004	0.434
Hemoglobin subunit alpha 1/2	Hba a1	DI00287835	1	2	20.54 NA	NA	0.000 NA
Hemonexin	Hnx	IPI00195516	8	8	-1 14	0.410	0.858
Hepatocyte growth factor activator	Hgfac	IPI00364125	5	4	-1.21	0.304	0.772
Histidine-rich glycoprotein	Hrg	IPI00201347	8	8	-1.27	0.149	0.589
Hypothetical protein LOC678701 ^d	LOC678701	IPI00557598	2	3	NA	NA	NA
Igh-1a protein ^d	Igh-1a	IPI00202440	2	3	NA	NA	NA
Igha_mapped protein	LOC366747	IPI00553949	4	5	-9.46	0.134	0.589
Insulin-like growth factor 1	Igfl	IPI00831729	4	3	1.12	0.669	0.927
Insulin-like growth factor binding protein 3	Igfbp3	IPI00209369	2	3	NA	NA	NA
Insulin-like growth factor binding protein, acid labile subunit	Igfals	IPI00202416	8	8	-1.09	0.448	0.872
Inter alpha-trypsin inhibitor, heavy chain 4	Itih4	IPI00188541	4	5	1.21	0.511	0.876
Inter-alpha trypsin inhibitor, heavy chain 1 ^a	Itih1_predicted	IPI00188338	7	7	-1.03	0.832	0.986
Inter-alpha trypsin inhibitor, heavy chain 3	ltih3	IPI00326984	8	8	-1.05	0.748	0.961
Interleukin I receptor accessory protein	IIIrap	IPI00211004	4	4	-2.28	0.022	0.220
Kallikrein B, plasma I	KIKDI	IPI00203384	8	8	-1.01	0.961	0.986
K-kiningen isotorm	LOC25087	IPI0018//99	8	8	-1.10	0.227	0.720
K-Killillogen 1	LUC23087	IP100313829 ID100107711	0 2	0	-1.07 NA	U.770	0.975 NA
Lactate dehydrogenase B	Lulla I dhb	IPI00231783	1	1	NA	NA	NA
Lecithin cholesterol acyltransferase	Lano	IPI00191754	1	2	NA	NA	NA
Lectin galactose binding soluble 1	L gals1	IPI00231275	8	8	1 32	0.329	0.804
LOC366772 BWK3 ^d	LOC366772	IPI00368397	4	5	1.92	0.52)	0.884
LOC494499 protein	LOC494499	IPI00555178	5	3	2.62	0.156	0.589
LOC498793 protein ^d	LOC498793	IPI00389806	8	8	1.03	0.817	0.986
LOC500180 Ig kappa chain C region, B allele ^d	LOC500180	IPI00388002	4	5	-1.97	0.271	0.745
LRRGT00046	LOC679040	IPI00454264	1	2	NA	NA	NA
Lumican	Lum	IPI00206403	8	8	1.30	0.173	0.615
Lysozyme	Lyz	IPI00421714	5	4	1.27	0.564	0.876
Malate dehydrogenase 1, NAD (soluble)	Mdh1	IPI00198717	7	7	1.50	0.263	0.745
Mannose binding lectin 1, protein A	Mb11	IPI00325371	7	4	-1.22	0.284	0.745
Murinoglobulin 1 homolog (mouse)	Mug1	IPI00212666	8	8	-1.00	0.992	0.999
Murinoglobulin 2	Mug2	IPI00564327	8	8	-1.11	0.529	0.876
Muscle glycogen phosphorylase	Pygm	IPI00190181	1	l	NA 1.55	NA	NA
Myoglobin	MD Maille and distant	IPI00214517	8	8	1.55	0.293	0.760
Nyosin, light polypeptide kinase	Myrk_predicted	IP1003/0/03	8	8	-1.42 NA	0.450 NA	0.8/3
Oresemueoid 1	Orm1	IP100207723 IP100101715	2	2 0	1 1 A	NA 0.522	INA 0.976
Pangroatic linese	Pnlin	IPI00191/15	6	0 5	-1.14 38.00	0.555 -0.001	0.870
Paraovonase 1	Pon1	IPI00555200	8	8	1.09	0.657	0.927
Parkinson disease7	Park7	IPI00212523	3	5	1.07	0.037	0.927
Pentidylprolyl isomerase A	Pnia	IPI00387771	8	8	1.14	0.236	0.721
Peroxiredoxin 1	Prdx1	IPI00211779	5	4	1.37	0.384	0.834
Peroxiredoxin 2	Prdx2	IPI00201561	8	6	2.94	0.007	0.109
Peroxiredoxin 5	Prdx5	IPI00205745	4	4	2.10	0.151	0.589
Peroxiredoxin 6	Prdx6	IPI00231260	6	5	2.17	0.005	0.109
Phosphoglucomutase 1	Pgm1	IPI00780332	7	5	-1.00	0.990	0.999
Phosphoglycerate kinase 1	Pgk1	IPI00231426	8	8	1.41	0.279	0.745
Phosphoglycerate mutase 1	Pgam1	IPI00421428	5	6	2.68	0.004	0.094
Phosphoglycerate mutase 2	Pgam2	IPI00231506	4	4	2.48	0.032	0.285
Plasma glutamate carboxypeptidase	Pgcp	IPI00388265	4	6	-1.32	0.312	0.773
Plasminogen	Plg	IPI00206780	8	8	-1.06	0.680	0.927
Platelet factor 4	Cxcl4	P100206634	1	2	NA	NA	NA
Pregnancy-zone protein	Pzp	IP100326140	8	8	-1.11	0.64	0.92
PIOIIIII I Drobul 4 hydroxydese, bate polymentide	ዮጠ1 ወለቤዬ	IP100231358	ð	0	1.41	0.182	0.018
Properdin factor, complement ^d	r4no Dfa	IP10019888/ IDI00265806	4	د ہ	15.49	0.005	0.104
Protein S (alnha)	FIC Pros1	IF 100303890	0 ⊿	03	1.04 _1.02	0.047	0.980
Protein 7 vitamin K-dependent plasma glycoprotein ^d	Proz predicted	IPI00213093	+ 8	2	-1.02	0.950	0.900
Putative uncharacterized protein (Fragment) ^d	-	IPI00454446	6	6	1 39	0.281	0.727 0.747
Pyruvate kinase, muscle	Pkm2	IPI00231929	1	2	NA	NA	NA
Regenerating islet-derived 3 gamma	Reg3g	IPI00200614	5	3	-1.03	0.967	0.986
Ribonuclease, RNase A family, 1 (pancreatic)	Rnase1	IPI00211902	3	3	40.50	<0.001	0.024

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S-adenosylhomocysteine hydrolase	Ahcy	IPI00476295	1	2	NA	NA	NA
Selenium binding protein 2	Selenbp1	IPI00208026	6	7	1.56	0.164	0.593
Selenoprotein P plasma 1	Sepp1	IPI00188060	8	8	1 10	0 719	0.941
Series (an exercise) neutidade inhibitan alada A (alaba 1	Sepp1	ID100210240	5	5	1.10	0.990	0.097
Serine (or cysteine) peptidase innibitor, ciade A (alpha-1	Serpinaro	IP100210340	3	5	-1.03	0.889	0.980
antiproteinase, antitrypsin), member 10							
Serine (or cysteine) peptidase inhibitor, clade A, member 3K	Serpina3k	IPI00200593	5	5	1.05	0.905	0.986
Serine (or cysteine) pentidase inhibitor clade A member 3N	Sernina3n	IPI00211075	8	8	-1.08	0 749	0.961
Serine (or cysteine) peptidase inhibitor, elade <i>C</i>	Serpinal	IDI00272272	0	0	1.00	0.114	0.500
Serine (or cysteine) peptidase innibitor, clade C	Serpiner	IP1003/23/2	8	8	-1.34	0.114	0.589
(antithrombin), member 1 ^a							
Serine (or cysteine) peptidase inhibitor, clade D, member 1	Serpind1	IPI00210947	8	8	-1.08	0.566	0.876
Serine (or cysteine) pentidase inhibitor clade F member 1	Seminfl	IPI00777549	2	3	NA	NA	NΔ
Serine (or cysteme) peptidase minoror, clade 1, member 1	Scipiiiri	II 100////J+/	2	5	114	0.527	0.07(
Serine (or cysteine) peptidase inhibitor, clade F, member 2	Serpinf2	IP100199695	8	8	-1.11	0.537	0.8/6
Serine (or cysteine) peptidase inhibitor, clade G, member 1	Serping1	IPI00372792	8	8	-1.27	0.133	0.589
Serine (or cysteine) proteinase inhibitor clade A (alpha-1	Serpina1	IPI00324019	4	4	1 2 4	0.422	0.856
antiprotoinaga antitrungin) mombar 1	Serpinar	1110052.017		-		0	0.000
anuprotemase, anutrypsin), memoer i	~						
Serine (or cysteine) proteinase inhibitor, clade A (alpha-l	Serpina4	IPI00205568	8	8	-1.02	0.889	0.986
antiproteinase, antitrypsin), member 4							
Serine (or cysteine) proteinase inhibitor, clade A (alpha-1	Serpina6	IPI00551705	6	5	-1.42	0.129	0.589
antiprotoinaga antitrungin) mombar 6	Selpinuo	111000001700	Ū	U		0.12)	0.007
anuprotemase, anutrypsin), memoer o	~		_	_			
Serine (or cysteine) proteinase inhibitor, clade A, member 3M	Serpina3m	IPI00210091	7	7	-1.15	0.432	0.858
Serine peptidase inhibitor, Kunitz type 1	Spint1	IPI00454389	4	3	-1.03	0.965	0.986
Serine protease inhibitor	LOC299282	IPI00200591	8	8	-1.12	0.478	0.876
		ID100250202	1	1	N.A.	0.470	0.070
SH3-binding domain glutamic acid-rich protein like (predicted)	Sh3bgri_predicted	IP100358292	1	1	NA	NA	NA
Signal recognition particle receptor, B subunit	Srprb	IPI00476177	5	6	-2.70	0.008	0.112
Similar to Actin extoplasmic 2 (Gamma-actin) ^d	LOC295810	IPI00765011	4	4	1 46	0 461	0.876
Similar to ADD riboxylation factor like 1	LOC(99211	IDI00766220		2	1.07	0.616	0.012
Similar to ADP-moosylation factor-like f	100088311	IP100/00239	4	3	-1.27	0.010	0.915
Similar to alpha-1 major acute phase protein prepeptide	MGC108747	IPI00679245	8	8	-1.18	0.554	0.876
Similar to amylase 2, pancreatic ^d	LOC499694	IPI00563187	1	2	NA	NA	NA
Similar to B7-like protein GI 50-B ^d	RGD1562791 predicted	IPI00301338	1	2	NΔ	NΔ	NΔ
		ID1005/1550	2	2			
Similar to carboxylesterase 5	LUC6/9368	IP100/63603	2	1	NA	NA	NA
Similar to Carboxypeptidase N 83 kDa chain	RGD1305170_predicted	IPI00769284	8	8	-1.14	0.422	0.858
(Carboxypeptidase N regulatory subunit) ^d							
Similar to Cysteine rich protein 1 ^d	LOC601657	IDI00102188	1	2	NA	NA	NΛ
	LOC091037	II 100192188	1	2			11/1
Similar to GTPase activating protein testicular GAP1"	RGD1563562_predicted	IPI00367684	2	3	NA	NA	NA
Similar to heat shock protein 8 ^d	LOC689908	IPI00566672	3	3	-1.77	0.160	0.589
Similar to heat shock protein 8 ^d	LOC680121	IPI00764197	1	2	NA	NA	NA
Similar to histiding rish glygonratain d	100691544	IDI00760165	0	0	1.22	0.141	0.590
Similar to institutie-ficil grycoprotein	LOC081344	IP100/09103	0	0	-1.55	0.141	0.389
Similar to L-lactate dehydrogenase A chain "	RGD1562690_predicted	IPI00203823	3	3	2.30	0.154	0.589
Similar to mKIAA0386 protein ^d	RGD1306939	IPI00382226	6	4	1.11	0.906	0.986
Similar to Murinoglobulin 1 homolog ^d	RGD1566313 predicted	IPI00368704	8	8	-1.09	0.526	0.876
		II 100506704	0	0	-1.07	0.520	0.070
Similar to Myh11 protein	RGD1564935_predicted	IPI00/65351	2	1	NA	NA	NA
Similar to peptidoglycan recognition protein 2 ^d	LOC687320	IPI00779290	3	2	NA	NA	NA
Similar to RIKEN cDNA 1300017J02 ^d	RGD1310507	IPI00655254	8	8	-1.55	0.128	0.589
Similar to tronomyosin 1 embryonic fibroblast rat ^d	MGC109519	IDI00187731	6	4	1 30	0.577	0.883
Similar to tropomyosin 1, emoryonic horobrast – rat	NIGC109319	11100187731	0	4	1.59	0.377	0.885
Similar to Vanin-3 (predicted)"	RGD1560609_predicted	IP100212508	5	5	-1./1	0.278	0./45
SPARC-like 1	Sparc11	IPI00203494	8	8	1.54	0.068	0.433
Superoxide dismutase 3 extracellular	Sod3	IPI00200507	8	8	1.01	0.929	0 986
This and a single 1		ID1002212(0	7	6	1.01	0.050	0.252
I nioredoxin I	1 xn 1	IP100231308	/	0	1.70	0.050	0.352
Thymosin, beta 4	Tmsb4x	IPI00230925	1	2	NA	NA	NA
Transaldolase 1	Taldo1	IPI00190377	1	2	NA	NA	NA
Transferrin	Tf	IPI00679202	3	5	-1.06	0.879	0.986
	11 T. Q.	II 100079202	5	5	-1.00	0.879	0.980
I ransforming growth factor, beta induced "	I gfbi	IPI00188622	8	8	1.19	0.506	0.8/6
Transgelin	Tagln	IPI00231196	8	8	-1.04	0.921	0.986
Transgelin 2	TagIn?	IPI00555171	1	1	NA	NA	NA
Transkatalasa	TI-+	IDI00221120	'n	2	NA	NA	NIA
Transkeiolase	I KL	11100231139	2	3	INA	INA	INA
Transthyretin	Ttr	IPI00324380	7	6	-1.01	0.963	0.986
Triosephosphate isomerase 1	Tpi1	IPI00231767	8	8	1.63	0.121	0.589
Tronomyosin 1 alpha	Tnm1	IPI00204206	2	2	NA	NΔ	NA
	1 21 1	IDI00421057	4	4	1 1 7 7	0.170	0.615
i ype ii keratin Kol	KDI	1P100421857	4	4	1.65	0.179	0.615
14-3-3 epsilon polypeptide	Ywhae	IPI00325135	3	4	3.37	0.042	0.314
14-3-3 gamma polypeptide							
Ominin PolyPopular	Ywhag	IPI00230835	2	2	NA	NA	NA
14.3.3 zeta polypentide	Ywhag Ywhag	IPI00230835	2	2	NA	NA 0 246	NA 0.914
14-3-3 zeta polypeptide	Ywhag Ywhaz	IPI00230835 IPI00324893	2 8	2 8	NA 1.23	NA 0.346	NA 0.814

Highlighted in bold are proteins with an individual P value less than 0.05 and an adjusted P value less than 0.1 for differences in their abundance between the pancreatitis and sham experimental groups.

NA: not available (when proteins were found in only one or two animals in one of the groups, the P value is not reported as the sample size was too small to gain statistical confidence.)

^a Number of animals in each group where the protein was identified (maximum n=8 for each group) ^b Fold change: acute pancreatitis *vs.* sham group

° Taurocholate induced acute pancreatitis group

^d Potentially hypothetical proteins as per International Protein Index (Rat database v3.27)

Supplementary Table 2. Non-redundant list of potentially hypothetical proteins identifications and NCBI BLASTP analysis results (n=47). Pro	oteins
listed as hypothetical are as per IPI Rat database v3.27. NCBI BLASTP search against the 'UniProt Clusters 100%' database.	

identifier opecies 2 kbg protein - PI00204640 C-type lectin domain family 3, member b Rat 100% Adiponestin, C1Q and collagen domain containing - PI00201420 Cationic trypsin-3 Rat 100% Carboxypeptidase A2 (pancreatic) Cpa2_predicted PI00170809 Four and a half L1M domains 1 Rat 100% Similar to 87-like protein GL50-B RGD1562791 IP10021303 Carboxypeptidase A2 (pancreatic) Rat 100% Similar to 87-like protein GL50-B RGD1652791 IP100212400 Ig gamma-2B chain C region Rat 100% Similar to 87-like protein 1 LOC69157 IP00212400 Ig gamma-2B chain C region Rat 100% Similar to black MD456 protein Rat 100% Carboxypeptidase Cysteme-rich protein 1 Rat 100% Similar to roponyposin 1, subposinci fibrohalat MCC109371 PI0075105 Histidine-rich glycoprotein Rat 100% Similar to roponyposin 1, subposinci fibrohalat MCC1093713 Cprotein Rat 99% Similar to roponyposin 1, subposonci fibrohalat	Name	Gene symbol	Protein	Highest scoring protein from BLAST	BLAST	Similarity
22 kDa protein			identifier		species	
Adiponcetin, C1Q and collagen domain containing Carboxyeptidase A2 (pancreatic) Four and a half L1M domains 1 Four and a half L1M domains 1 Four and a half L1M domains 1 Four and half L1M domains 1 Proteins (alpha)Rat 100% Four and half L1M domains 1 Rat 100% Similar to System-rich protein 1 Rat 100%Rat 100% Rat 100%Similar to Cysteine-rich protein 1 Similar to Actin, cytoplasmic 2 (Gamma-actin) Similar to Actin, cytoplasmic 2 (Gamma-actin) Similar to Actin, cytoplasmic 2 (Gamma-actin) Similar to Actin, cytoplasmic 2 (Gamma-actin) L0C29810 Similar to Actin, cytoplasmic 2 (Gamma-actin) L0C29810 Similar to anylase 2, pancreatic L0C68809 Similar to anylase 2, pancreatic L0C68809 L0C68809 L0C68809 L0C68809 L0C68908 L0C68908 L0C68908 L0C68908 L0C68908 L0C68908 L0C68908 L0C69908 L0C69908 L0C69908 Production 2 L0C498793 Protein 8 L0C69908 L0C699093 L0C699	22 kDa protein	-	IPI00204640	C-type lectin domain family 3, member b	Rat	100%
Cationic trypsinogen LoC286911 [P10021212] Cationic trypsin-3 Rat 100% Four and a half L1M domains 1 Rat 100% Cysteme-rich protein 1 LoC691657 1P100192185 Cysteme-rich protein 1 Rat 100% Similar to histidine-rich glycoprotein Rat 100% Similar to rogenoyosin 1, embryonic fibroblast Complement component 1, subcomponent Complement component 1, subcomponent Complement component 1, subcomponent Complement component 3, alpha polypeptide Complement component 3, alpha polypeptide Complement component 3, alpha polypeptide Complement component 3, alpha polypeptide Complement component 4, subca polypeptide Similar to algue 2, pancreate LOC688020 IP10005318 Pancreate Complement component 8, alpha polypeptide Similar to bart abock protein 8 LOC689010 IP10025351 Pancreate Component 7 Mouse 99% Similar to bart abock protein 8 LOC689010 IP10025351 Pancreate Compare 1, Mouse 99% Similar to bart abock protein 8 LOC689010 IP10025351 Pancreate Component 7 Mouse 99% Similar to bart abock protein 8 LOC689010 IP10025852 IP10076331 Pancreate 1 Mouse 99% Similar to batt abock protein 8 Rat 99% Similar to bart abock protein 8 R	Adiponectin, C1Q and collagen domain containing	Adipoq	IPI00202515	30 kDa adipocyte complement-related protein	Rat	100%
Carboxypeptidase A2 (pancreatic) Cpa2_predicted [P1001339] Carboxypeptidase A2 (pancreatic) Rat 100% Similar to P3-like protein G1.50-B RGD1562791 [P10039138] Icos ligand Rat 100% [gh-1a protein to P3-like protein G1.50-B RGD156279] [P10039138] Icos ligand Rat 100% Similar to Cysteine-rich protein 1 Rat 100% Similar to Cysteine-rich protein 1 Rat 100% Similar to Cysteine-rich protein 1 Rat 100% Similar to Asing A0386 protein RGD1306399 [P10057254] Vitamini K-dependent protein 2 Rat 100% Similar to Asing A0386 protein RGD1306399 [P10057254] Vitamini K-dependent protein 2 Rat 100% Similar to Asing A0386 protein RGD1306399 [P10035226] Ab2-162 Rat 100% Similar to Actin, cytoplasmic 2 (Gamma-actin) LOC295810 [P10075011] Actin, gamma, cytoplasmic 1 Mouse 100% Complement component 8, alpha polyeptide' Rat 99% Similar to anylase 2, pancreatic LOC688199 [P10057147] Enolase-alpha Rat 99% Similar to anylase 2, pancreatic LOC689101 [P100751382 Complement component 8, alpha polyeptide Rat 99% Similar to anylase 2, pancreatic LOC680121 [P100751382 Complement component 8, alpha polyeptide Rat 99% Similar to anylase 2, pancreatic LOC680121 [P100751387 Pancreatic alpha-amylase Rat 99% Similar to negatok protein 8 LOC680908 [P10056723 [Lactate dehydrogenase A chain Rat 98% Similar to head shock protein 8 LOC680912 [P10075735] Lactate dehydrogenase A chain Rat 98% Similar to head shock protein 8 LOC680913 [P10056672 [Head shock coganet 71 KDa protein Mouse 98% Similar to head shock protein 8 LOC680913 [P10056672 [Head shock coganet 71 KDa protein Mouse 97% _predicted LOC498793 [P10035806 [htter-alpha-trypsin inhibitor heavy chain H2 Rat 98% Carbonic anhydrase 1 Mouse 97% Similar to head shock protein 8 LOC680913 [P10056672 [Head shock coganet 71 KDa protein Mouse 97% _predicted 1P100358306 [htter-alpha-trypsin inhibitor, heavy chain Mause 93% Similar to Admino, heavy chain 1 Kith [Predicted 1P10036735 [P10075735] Myh1 protein Mouse 93% Similar to Admino, heavy chain 1 Kith [P100358306 [htter-alpha-trypsin inhibitor, heavy chain M	Cationic trypsinogen	LOC286911	IPI00211212	Cationic trypsin-3	Rat	100%
Four and a half LIM domains 1Fh11IP1007980699Four and a half LIM domains 1Rat100%glab-la protein GL50-BRGD15279IP1003133Icos IgandRat100%Protein S (alpha)ProstIP100221409Ig amma-2B chain C regionRat100%Similar to Systemerich protein 1LOC691627IP100192149Viramin K-dependent protein SRat100%Similar to Agha-I major acute phase protein prependsLOC691674IP100679245T-Kninogen 2Rat100%Similar to MixIAA038 proteinRGD15207945IT4Kninoen-rich glycoproteinRat100%Similar to mixIAv036 proteinRGD15207945IT4Kninoen-rich glycoproteinMouse100%Similar to topomyosin 1, embryonic fibroblastMGC109519IP10075711Actin gamma, cytoplasmic 1Mouse100%Similar to topomyosin 1, embryonic fibroblastMGC109519IP10075711Actin gamma, cytoplasmic 4100%Similar to anytopse 2, panceriacLOC688012IP100767147Foalasa-alpha anytasRat99%Similar to hardy back protein 8LOC68800IP100767417Foalasa-alpha anytasRat99%Similar to hardy back protein 8LOC688721IP0076635Heat shock cognate 71 kDa proteinMouse99%Similar to AdvArgorgenase A chainPredictedIP100765351Myosin, light polypeptide kinaseMuuse95%Similar to back protein 8LOC689723IP10036930Camplement component 7Rat95%Similar to Advargenase 1*Deredict	Carboxypeptidase A2 (pancreatic)	Cpa2_predicted	IPI00193391	Carboxypeptidase A2 (pancreatic)	Rat	100%
Similar to b7-like protein RCD156279 [P10023138 Leos ligand Rat 100% Igh-la protein Igh-la [P10021363 Vitamin K-dependent protein Rat 100% Similar to Cysteine-rich protein 1 LOC691657 [P100192188 Cysteine-rich protein Rat 100% Similar to Actin, cytoplasmic 2 Gamma-actin) LOC681544 [P100769165 Histidine-rich glycoprotein Rat 100% Similar to Actin, cytoplasmic 2 Gamma-actin) LOC295810 [P100765011 Actin, gamma, cytoplasmic 1 Mouse 100% Complement component 1, r subcomponent LOC688540 [P100377131 Tym2 protein Rat 99% Similar to Actin, cytoplasmic 2 Rat 100% 10075011 Actin, gamma, cytoplasmic 1 Mouse 100% Similar to Actin, cytoplasmic 2, pancreate LOC688001 [P100377137 Tym2 protein Rat 99% Similar to Actin cytoplasmic 4 Mouse 19007703 Myosin, light polypeptide kinase Nause 99% Similar to Actin cytoplasmic 4 LOC689009 IP100767147	Four and a half LIM domains 1	Fhl1	IPI00780699	Four and a half LIM domains 1	Rat	100%
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Igh-1a IPI0022440 Ig gamma-2B schnic Yegion Rat 100% Similar to Cysteine-rich protein 1 LOC691657 IPI00192188 Cysteine-rich protein 1 Rat 100% Similar to Actin. Parjorauet phase protein preprior Rat 100% Cysteine-rich protein 1 Rat 100% Similar to MitA.03366 protein LOC681544 IPI00759165 Histidine-rich gytoportein 2 Rat 100% Similar to Actin., extoplasmic 2 (Gamma-settin) LOC295810 IPI0075711 Actin., gamma, eytoplasmic 1 Mosse 100% Complement component 1, r subcomponent Chr IPI00351108 C1T protein Rat 99% Similar to anybas 2, pancratic LOC689019 IPI0017717 Fendase 1, alpha pseudogene Nyk, predicted IPI0035187 Pancratic alpha-maylase Rat 99% Similar to anybas 2, pancratic LOC6890508 IPI00763187 Pancratic alpha-maylase Rat 98% Similar to heat shock protein 8 LOC6890508 IPI00763187 Pancratic alpha-maylase Rat 98% Similar to Matha edu bydrogenase A chain RGD 1562690		_predicted				
Protein Prosl <	Igh-1a protein	Igh-1a	IPI00202440	Ig gamma-2B chain C region	Rat	100%
Similar to Cysteine-rich protein 1LOC691657IP00192188Cysteine-rich protein 1Rat100%Similar to MixA0386 proteinMGC108717IP00079165Histdine-rich glycoprotein 2Rat100%Similar to NixA0386 proteinRGD1306399IP00382226Ab2-162Rat100%Similar to Actin, cytoplasmic 2 (Gamma-actin)LOC295810IP00765011Actin, gamma, cytoplasmic 1Mouse100%Complement component 1, rsubcomponentClar proteinMGC1087731Tpm2 proteinMouse100%Complement component 8, alpha polypeptide*Ca predictedIP10037033Myosin, light polypeptide kinaseMylkProteinMouse99%Similar to anythyse 2, pancreticLOC680964IP100767147Enolase-alphaRat99%Similar to hart shock protein 8LOC680960IP10023822L-lactate dehydrogenase A chainRat99%Similar to hart shock protein 8LOC680908IP100766105Mylt IproteinMouse98%Similar to hart shock protein 8LOC6498793IP100376351Mylt I proteinMouse97%Similar to Myh11 proteinCarl predictedIP1003666672Heat shock cognate 71 kDa proteinMouse95%Similar to Myh11 proteinCarl predictedIP100367351Myh11 proteinMouse95%Similar to Myh11 proteinRatPiP00372372Antithrombin-III precursorMouse95%Similar to Myh11 proteinCarl predictedIP10036786Dra-hik1Mouse95%Similar	Protein S (alpha)	Pros1	IPI00213693	Vitamin K-dependent protein S	Rat	100%
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Similar to histidine-rich glycoproteinLOC681544IP100769165Histidine-rich glycoprotein 2Rat100%Similar to NchA0386 proteinRGD130699IP100382226Ab2-162Rat100%Similar to Actin, cytroplasmic 2 (Gamma-actin)LOC295810IP100785011Actin, gamma, cytoplasmic 1Mouse100%Complement component 1, r subcomponentC1rIP1003781108C1r proteinRat99%Complement component 8, alpha polypeptideRat99%ID0C688509IP100767147Enolase-1, alphaRat99%Similar to anylise 2, pancreaticLOC490641IP100370703Myosin, light polypeptide kinaseMouse99%Similar to hast shock protein 8LOC688509IP100767147Heat shock const 71 kDa proteinMouse99%Similar to hast shock protein 8LOC680212IP100766187Pancreatic alpha-amylaseRat99%Similar to hast shock protein 8LOC680908IP10056672Heat shock cognate 71 kDa proteinMouse97%Similar to Myh11 proteinRGD1564935IP100766313Carbonic anhydrase 1Mouse97%Dmx-like 1DmxL1 predictedIP10036930Carbonic anhydrase 1Mouse95%Similar to Complement component 7C7IP100766303Complement component 7Rat96%Carbonic anhydrase 1*Mouse97%Imtra-lipha-trypsin inhibitor, heavy chain 1*Rat96%Similar to Murinoglobulin 1 homolog*Loc49879IP100372372Antithrombin-III precursorMouse9	Similar to alpha-1 major acute phase protein prepeptide	MGC108747	IPI00679245	T-kininogen 2	Rat	100%
Similar to mKLAA0386 proteinRGD1306939IPI00382226AL2-162Rat100%Similar to tropomyosin 1, embryonic fibroblastLOC283810IPI00765011Actin, gamma, cytoplasmic 1Mouse100%Complement component 1, rsubomponentClar proteinMate100%100100100Complement component 8, alpha polypeptideEnclase 1, alpha pseudogeneClar proteinMouse99%Mysin, light polypeptide kinaseMylk predictedIPI0070703Myosin, light polypeptide kinase8499%Similar to anylase 2, pancraticLOC688509IPI00767147Enclase-alphaRat99%Similar to Lactate dehydrogenase A chainRGD1562600IPI00203823L-lactate dehydrogenase A chainRdD1562600IPI00203823L-lactate dehydrogenase A chainRdD1562690Similar to heat shock protein 8LOC689083IPI00566672Heat shock cognate 71 kDa proteinMouse97%LOC498793 protein*LOC489793IPI0037836Inter-alpha-trypsin inhibitor heavy chain H2Rd96%Dmx-like 1LOC488793IPI00372372Antitrombin-limbitor, heavy chain 1*Mouse93%Similar to Aunn-3 (predicted)*RdD1566019IPI00372372Antitrombin-limbitor, heavy chain 1Mouse93%Similar to Murinoglobulin 1 homolog*RdD1566019IPI00372372Antitrombin-limbitor, heavy chain 1Mouse93%Similar to Complement 1Ith1_predictedIPI00372372Antitrombin-limbitor, heavy chain 1*Mouse93%Similar to Complement	Similar to histidine-rich glycoprotein	LOC681544	IPI00769165	Histidine-rich glycoprotein 2	Rat	100%
Similar to Actin, extroplasmic 2 (Gamma-actin)LOC29810[P100765011Actin, gamma, extroplasmic 1Mouse100%Complement component 1, r subcomponentCIrPP10035119PP100187731Tpm2 proteinMouse100%Complement component 8, alpha polypeptideRat99%C8a, predictedPP100370703Myosin, light polypeptide kinaseMouse99%Similar to anylase 2, pancreaticLOC68809PP100767147Enolase: alpha polypeptide kinaseMouse99%Similar to hard shock protein 8LOC6800121IP1003663187Pancreatic alpha-amylaseRat99%Similar to heat shock protein 8LOC68908IP100765151Mouse98%Similar to heat shock protein 8LOC689793IP100566672Heat shock cognate 71 kDa proteinMouse98%Similar to Myh11 proteinLOC649793IP100765151Myh11 proteinMouse95%LOC498793 protein*LOC48973IP10038906Inter-alpha-trypsin inhibitor heavy chain H2Rat96%Drw.Hik 1Dmx-Like 1Dmx1.predictedIP10038906Inter-alpha-trypsin inhibitor heavy chain H2Rat95%Carbonic anhydrase 1*Dmx1.predictedIP10038906Inter-alpha-trypsin inhibitor, heavy chain H2Rat95%Carbonic anhydrase 1*Dmx1.predictedIP10038903Carbonic anhydrase 1Mouse95%Similar to Amirob polytidase inhibitor, elade CSerpinc1IP100456326Proteinic anhydrase 1Mouse93%Similar to Amirob pint H2Taraforming growh fa	Similar to mKIAA0386 protein	RGD1306939	IPI00382226	Ab2-162	Rat	100%
Similar to tropomyosin 1, embryonic fibroblastMCC 109519IPI00187731Tpm2 proteinMouse100%Complement component 1, subcomponentCla proteinCla proteinRat99%Mossin, light polycoptide kinaseMylk predictedIPI00358382 Complement component 8, alpha polypeptide kinaseMouse99%Similar to anylase 2, pancreaticLOC689509IPI00767147Enalase-alphaMat99%Similar to heat shock protein 8LOC689069IPI00767197Pancreatic alpha-amylaseRat99%Similar to heat shock protein 8LOC689069IPI00203823L-lactate dehydrogenase A chainRat98%Similar to heat shock protein 8LOC689008IPI0056672Heat shock cognate 71 kDa proteinMouse97%Similar to Myh11 proteinmouse97%predictedIPI00356336Dmx-like 1Mouse97%LOC498793 protein*LOC6498793IPI00369303Carbonic anhydrase 1Mouse95%Similar to Omplement component 7Carl predicted IPI00367836Dmx-like 1Mouse95%Similar to Complement component 7Carl predicted IPI00367836Dmx-like 1Mouse93%Similar to Vanin-3 (predicted)*-IPI00369303Carbonic anhydrase 1Mouse93%Similar to Vanin-3 (predicted)*Serpinci 1PI0037237Antithrombin-III precursorMouse93%Similar to Munoglobulin 1 bomolog*RGD1566313IPI00388867Desmoglein 2Mouse93%Similar to Munoglobulin 1 bomolog*RGD1566313	Similar to Actin, cytoplasmic 2 (Gamma-actin)	LOC295810	IPI00765011	Actin, gamma, cytoplasmic 1	Mouse	100%
$ Complement component 1, r subcomponent C1r P100361108 C1 protein Rat 99% \\ Complement component 3, alpha polypeptide 'Cas_predicted P100358382 Complement component 8, alpha polypeptide Rat 99% \\ Enolase 1, alpha pseudogene LOC688509 P100767147 Enolase-alpha Rat 99% \\ Similar to anylase 2, parceratic LOC490694 P100370703 Myosin, light polypeptide kinase Mouse 99% \\ Similar to heat shock protein 8 LOC680121 P100761197 Heat shock cognate 71 kDa protein Mouse 99% \\ Similar to heat shock protein 8 LOC680121 P100764197 Heat shock cognate 71 kDa protein Mouse 99% \\ Similar to heat shock protein 8 LOC680121 P100765137 Heat shock cognate 71 kDa protein Mouse 98% \\ Similar to heat shock protein 8 LOC680721 P100368362 P100366672 Heat shock cognate 71 kDa protein Mouse 98% \\ Similar to heat shock protein 8 LOC689793 P100358366 Inter-alpha-trypsin inhibitor heavy chain H2 Rat 96% \\ LOC498793 protein * LOC489793 P10038906 Inter-alpha-trypsin inhibitor heavy chain H2 Rat 96% \\ Carbonic anhydrase 1 * CO478973 P10038906 Inter-alpha-trypsin inhibitor heavy chain H2 Rat 96% \\ Carbonic anhydrase 1 * Co478973 P10038906 IP10036030 Carbonic anhydrase 1 Mouse 94% \\ Carbonic anhydrase 1 * Carl_predicted P10036030 Carbonic anhydrase 1 Mouse 94% \\ Carbonic anhydrase 1 * Carl_predicted P100368704 P100188338 Inter-alpha trypsin inhibitor, heavy chain 1 & Mouse 93% \\ Similar to Marinoglobulin 1 homolog * L_Terdicted P10038874 P100188086 P100212508 Vania 3 Mouse 93% \\ Similar to Murinoglobulin 1 homolog * RGD1560431 P10038874 P10018867 P10018842 P10048674 P10038876 P10018867 P10018867 P10018867 P10018867 P10018867 P10018867 P10018867 P100036876 P1000$	Similar to tropomyosin 1, embryonic fibroblast	MGC109519	IPI00187731	Tpm2 protein	Mouse	100%
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Dimension	Dmy_like 1	Dmvl1 predicted	IPI00367836	Dmx-like 1	Mouse	95%
Similar to Complement of any drass of the sector of the	Similar to Complement component 7		IDI00766303	Complement component 7	Pat	95%
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	GAP1	_predicted				

^a Previously identified in a proteomic study of normal mesenteric lymph (Mittal et al. 2008, [27])