JOP. J. Pancreas (Online) 2001; 2(2):69-77.

Trypsin Activation Peptide (TAP) in Acute Pancreatitis: From Pathophysiology to Clinical Usefulness

Jean Louis Frossard

Division of Gastroenterology, Geneva University Hospital. Geneva, Switzerland

Acute pancreatitis is a common digestive disease which is usually diagnosed when there is acute abdominal pain associated with a concomitant rise of serum amylase and lipase levels [1, 2]. However, up to 20% of patients with acute pancreatitis may have normal serum enzyme concentrations [3]. After exposure to a trigger event (mainly alcohol and gallstone migration into the common bile duct), injury to the gland occurs extremely rapidly and is usually complete at the time of admission. For the past 10 years, research aimed at understanding the early events which initiate acute pancreatitis has provided new information which has led to the recent development of potentially useful diagnostic tools. In the mid 1990s, the urinary concentration of trypsinogen and trypsinogen activation peptide (TAP) was shown to be more sensitive and specific in diagnosing acute pancreatitis than serum amylase and lipase concentrations [4, 5, 6]. Since then, urinary trypsinogen and urinary TAP represent good alternative tools for clinicians in this situation, but the detection kits are expensive and not available in every hospital.

Acute pancreatitis is also a disease of variable severity, while approximately 80% of patients experience mild attacks which resolve themselves with little morbidity, the remaining 20% [7] suffer from severe disease with mortality rates as high as 30% [8]. Early prediction of the severity of an attack of acute pancreatitis remains the main goal for clinicians in charge of such patients. The complexity of using multifactorial scales, including Ranson [9], Glasgow [10] and APACHE II [11] scoring systems, and the fact that CT scanning is expensive, exposes the patient to ionizing radiation and lacks sensitivity and specificity in the early stage of the disease [12], account for the increasing interest shown in serum markers to predict the severity of an attack. If severe attacks were detected at an early stage, aggressive and efficient measures could be implemented without undue delay. Thus, such patients will probably benefit from admission to tertiary center, prophylactic antibiotic administration [13], early enteral nutrition [14] and early endoscopic retrograde cholangiopancreatography in pancreatitis of suspected biliary origin [15]. In the recent study of Neoptolemos *et al.* [16], urinary TAP concentration measurement is proposed as a valuable predictive factor inasmuch as it provided accurate severity prediction in 172 patients with acute pancreatitis (35 with a severe form) 24 hours after the onset of an attack (70% accuracy at 24 hours).

In this article, we would like to briefly review the pathophysiology of acute pancreatitis and try to determine the effectiveness in using TAP either as a diagnostic tool or prognostic indicator in acute pancreatitis.

TAP: An Indicator of the First Molecular Event during Experimental Pancreatitis ?

Trypsinogens are pancreatic proteases that can initiate the autodigestive cascade characterizing acute pancreatitis. TAP corresponds to the N-terminal region of the peptide released by the

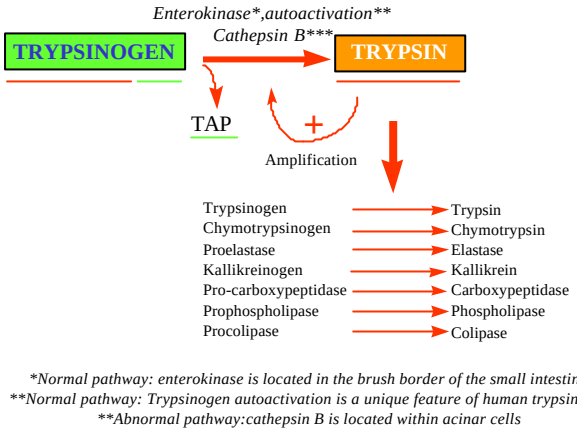

Figure 1. Trypsinogen could be either activated into active trypsin either by the brush-border enzyme enterokinase in the small intestine or by cathepsin B, a lysosomal enzyme present in acinar cells. Another mechanism of trypsinogen activation, which is a unique feature of human trypsinogen, consists of trypsinogen autoactivation. This finding may be more relevant to human pancreatitis whereas cathepsin B mediated trypsinogen activation is more relevant to rodent models of pancreatitis. Once trypsin is activated, it can catalyze the activation of other digestive pro-enzymes as well as trypsinogen itself, initiating the auto-digestion of the gland. Recent reports claim that the colocalization of trypsinogen and cathepsin B in the same compartment could result in premature activation of trypsinogen and leads to acute pancreatitis.

activation of trypsinogen into active trypsin (Figure 1). Normally, this 7-10 amino peptide is released only when trypsinogen has reached the small intestine where it is activated by the brush-border enzyme enterokinase. This small cleavage molecule is immunologically completely distinct from the same sequence within trypsinogen allowing for detection of TAP in situ. In acute experimental pancreatitis, recent reports have shown that one of the first steps during acute pancreatitis consisted of inappropriate and premature activation of trypsinogen into active trypsin within the pancreas resulting in the release of TAP into the peritoneum, plasma and urine [17, 18, 19].

Research directed at understanding the early molecular mechanisms which drive acute pancreatitis from the trigger event to the phase in which it manifests itself is the subject of controversy. There are two major theories which have been postulated as to the site and mechanism of trypsinogen activation: the co-localization theory which may be of relevance only in rodents [17, 20] and the trypsinogen autoactivation [21, 22], a unique feature of human trypsinogen, which may be more relevant to human pancreatitis.

The co-localization theory claims that intraacinar cell activation of digestive enzymes is initiated by lysosomal hydrolases acting on trypsinogen either after fusion of the zymogen granules and lysosomes or because lysosomal enzymes are not segregated from the secretory pathway with complete fidelity (missorting mechanism) [17, 18, 19, 23, 24]. Using very dissimilar models of pancreatitis, co-localization of digestive enzymes with the lysosomal enzyme cathepsin B was found to be an early phenomenon preceding cell injury in rodents [24]. This theory is based on the following findings: 1) adjunction of cathepsin B, a lysosomal enzyme, is capable of activating digestive enzymes from dogs [25] or human pancreatic extracts [26]; 2) cell fractionation experiments show co-localization of these different enzymes in the same sedimentation fraction [17, 27]; 3) inhibition of either trypsin or cathepsin B can effectively prevent trypsinogen activation [24]; 4) this latter speculation is also supported by recent observations that cathepsin B knockout mice are partially protected against cerulein-induced pancreatitis because cerulein-induced cathepsin B-mediated activation of trypsinogen cannot occur in these animals [28]. Taken together, these observations suggest that the initiation of acute pancreatitis occurs in a compartment containing both of these enzymes.

The second theory postulates that trypsinogen activation occurs in the normal pathway under low pH conditions and becomes pathological only with a secretory blockade. Under normal conditions, a fraction of the human trypsinogen autoactivates to active trypsin. Trypsin can catalyze a cascade of trypsinogen activation as well as activate all other proenzymes leading to the autodigestion of the gland. This process is regulated by at least two different lines of defense. The first one is pancreatic secretory

trypsin inhibitor (PSTI) which is now referred to as SPINK1 (serine protease inhibitor, Kazal type 1) [29]. When levels of trypsin activity are low, SPINK1 inhibits trypsin and prevents further autoactivation of trypsin and other proenzymes within the pancreas. During excessive trypsinogen activation, the SPINK1 inhibitory capacity is overwhelmed and trypsin activity keeps increasing. The second line of defense is represented by trypsin itself. Indeed, to prevent uncontrolled enzyme activation, trypsin and trypsin-like enzymes, by means of a feedback mechanism, hydrolyze the chain connecting the two globular domains of the trypsin at R122H. This results in permanent inactivation of trypsin and prevents subsequent activation of other proenzymes. Recent reports by Whitcomb *et al*. [23] have strongly suggested that premature trypsin activation also plays a pivotal role in human acute pancreatitis. This group has identified two trypsinogen mutations that result in inactivation-resistant trypsin in patients with hereditary pancreatitis [23]. During excessive trypsinogen activation, the R122H trypsin recognition site is mutated and, therefore, the trypsin cannot be inactivated leading to autodigestion of the gland and pancreatitis. Furthermore, although SPINK1 mutations are as high as 2% in the general population, they are clearly associated with familial and chronic pancreatitis [30]. The last paper by Whitcomb's group [30] suggests that SPINK1 mutations are disease modifying, possibly by lowering the threshold for pancreatitis from other genetic or environmental factors, but, by themselves, they do not cause disease.

Taken together, all these observations suggest that one of the earliest events during acute pancreatitis consists of inappropriate and premature activation of trypsinogen into active trypsin within the pancreas resulting in the release of TAP into the peritoneum, plasma and urine [17, 18, 19]. Thus, plasma TAP concentration seems to be among the best and earliest markers of acute pancreatitis. In this setting, it is reasonable to consider TAP as a sensitive and specific diagnostic tool of an attack of pancreatitis. However, because TAP is a 7-10 amino-acid peptide, one needs to keep in mind that it is rapidly excreted in urine and its value is therefore limited to the first 24-48 hours after the onset of the symptoms. Moreover, its detection in plasma is more difficult than in urine.

Pancreatic Products as Diagnostic Tools of an Attack of Acute Pancreatitis

Even if most patients with acute pancreatitis have an uncomplicated outcome, early diagnosis of acute pancreatitis is important because 20% of patients will develop the severe disease with local or systemic complications [7]. Therefore, immediate diagnosis of severe pancreatitis should be assessed in order to optimize therapy and to prevent organ dysfunction.

Although amylase and lipase are important for the diagnosis of acute pancreatitis, these enzymes are imprecise in certain cases [31]. In a series of 352 consecutive cases of acute

Table 1. Performance of pancreatic enzymes and pancreatic-related products in the diagnosis of acute pancreatitis.

Marker	Sensitivity	Specificity	PPV	NPV	Author
Amylase	85%	91%	-	-	Kemppainen [35]
Amylase	81-85%	87-89%	-	-	Dominguez-Munoz [57]
Lipase	92-95%	95-97%	-	-	Dominguez-Munoz [57]
Phospholipase	34-57%	75-80%	-	-	Dominguez-Munoz [57]
Pancreatitis-associated protein	45-61%	70-83%	-	-	Dominguez-Munoz [57]
Trypsinogen	91%	95%	-	-	Hedström [34]
Trypsinogen	95%	95%	68%	99%	Kemppainen [35]

PPV: positive predictive value
NPV: negative predictive value

pancreatitis confirmed by CT scan, 19% of the patients had normal amylase concentrations in serum upon admission [3]. Acute pancreatitis with normal amylasemia is characterized by a high prevalence of alcoholic origin [3]. In the study of Pezzilli *et al.* [32], serum amylase and lipase levels were able neither to establish the etiology nor to predict the severity of acute pancreatitis. Recent studies support the view that proteolytic enzymes have a role in the pathophysiology of pancreatitis and the concentration of trypsinogen in serum was shown to reflect pancreatic injury [5, 33]. The accuracy of the urinary trypsinogen-2 dipstick test in differentiating between patients with acute pancreatitis, acute abdominal disease of extrapancreatic origin or no abdominal disease was assessed by Hedström *et al.* [34] with a sensitivity of 91% and a specificity of 95% (Table 1). In a study done by the same group [35] concerning patients with acute abdominal pain, a negative dipstick test for urinary trypsinogen-2 ruled out acute pancreatitis with a high degree of probability (sensitivity 95%, negative predictive value 99%) (Table 1).

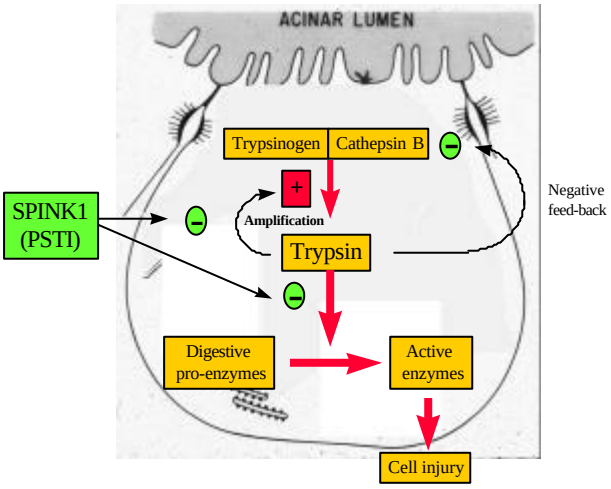

Figure 2. The intrapancreatic activation of trypsinogen into active trypsin is a process regulated by at least two distinct mechanisms. 1. The PSTI (pancreatic secretory trypsin inhibitor), now referred as to SPINK1 (serine protease inhibitor, Kazal type 1), is synthesized with trypsinogen in a ratio of 1:5, and can inhibit the activation of trypsinogen by trypsin. 2. Trypsin itself by means of a feed-back mechanism can inactivate trypsin and trypsin-like enzymes by hydrolyzing the connecting chain between the two globular domains of the trypsin. Interestingly, in patients with hereditary pancreatitis, trypsin cannot be inactivated because of a mutation (R122H) in the connecting chain making its hydrolysis impossible.

TAP assay in urine was first performed in 1990 on 55 patients with acute pancreatitis [6]. A negative result on admission which was maintained over the first 12 to 24 hours suggested that these patients would either have no pancreatitis at all or, if so, a very moderate form. Additionally, in the study by Tenner *et al.* [36], median urinary TAP at admission was lower in controls than in patients with acute pancreatitis.

TAP as a Prognostic Factor of an Attack of Acute Pancreatitis

All of the causes of acute pancreatitis result in a similar pattern of disease, but the severity of each cannot be predicted [37]. Most observers believe that the various causes of pancreatitis converge to the same point which initiates a cascade of events, the nature and extent of which will determine the outcome. TAP has been chosen as a potential marker of severity, because trypsinogen activation starts within minutes after exposure to a causal factor. As a result of trypsinogen activation, the trypsinogen and carboxypeptidase B activation peptides (CAPAP), which are markers of zymogen activation, are released into the serum early in the course of the disease. (Figure 2).

Although TAP utility has been reported in three major papers [6, 16, 36], CAPAP represents another activation peptide that is undergoing evaluation. Indeed, in the last study by Pezzilli *et al.* [38], the overall sensitivity and specificity of CAPAP in assessing the severity of an attack of acute pancreatitis were 84.6% and 59.4% respectively (Table 2).

The first clinical paper referring to TAP use in human beings was published in 1990 [6]. In that study, urinary samples were collected within 48 hours after the onset of symptoms. The concentrations of TAP correlated with subsequent disease severity in 87%. By comparison, C-reactive protein and multifactorial scales at 48 hours were correct in

Table 2. Performance of pancreatic enzymes and pancreatic-related products in the prediction of the outcome of an attack.

Marker	Sensitivity	Specificity	PPV	NPV	Author
CAPAP	85%	59%	-	-	Pezzilli [38]
TAP	80%	90%	67%	-	Gudgeon [6]
CRP	53%	55%	-	-	Gudgeon [6]
TAP	100%	85%	60%	100%	Tenner [36]
TAP at 24 h	58%	73%	39%	86%	Neoptolemos [16]
CRP at 24 h	0%	90%	0%	75%	Neoptolemos [16]
TAP at 48 h	83%	72%	44%	94%	Neoptolemos [16]
CRP at 48 h	86%	61%	37%	94%	Neoptolemos [16]
TAP + CRP	74%	85%	58%	92%	Neoptolemos [16]
APACHE II	56%	64%	30%	85%	Neoptolemos [16]
IL-6	80%	-	71%	-	Leser [54]
IL-6	70%	-	45%	-	Heath [55]
Polymorphonuclear Elastase	93%	-	80%	-	Dominguez-Munoz [47]
Polymorphonuclear Elastase	71%	-	60%	-	Gross [48]

PPV: positive predictive value
NPV: negative predictive value

55% and 84%. The second study by Tenner *et al.* [36] showed that the median urinary TAP within 48 hours after the onset of symptoms was significantly higher in patients with severe pancreatitis than in patients with mild attacks and control patients. Severe pancreatitis was identified in all patients having a urinary TAP greater than 10 ng/mL, whereas only 6 of 40 patients with mild pancreatitis had a TAP greater than 10 ng/mL. The authors conclude that urinary TAP is useful in identifying patients with severe acute pancreatitis if obtained within the first 48 hours following the onset of the symptoms (Table 2). In the third and last study dealing with TAP, the group of Neoptolemos carried out a multicenter study in 246 patients 172 of whom had acute pancreatitis (35 severe) and 74 were controls. This study was aimed at comparing urinary TAP to C-reactive protein (CRP) and three indices scoring systems, but failed to provide more information than the two previous papers published in 1990 and 1997 respectively. This study was original in that it gave the performances of urinary TAP at different time points, including 24 hours after the onset of symptoms. At 24 hours after the onset of symptoms, the sensitivity, specificity, positive predictive and negative predictive values of the test to show severe acute pancreatitis as compared to mild acute disease were 58%, 73%, 39%, and 86% for TAP greater than 35 mmol/L, and 0%, 90%, 0%, and 75% for CRP greater than 150 mg/L, respectively. The results of this study fit well with the concept of Neoptolemos which claims that the preferred characteristics of a prognostic marker have a high negative predictive value, thus allowing a high proportion of patients with the mild form of the disease to be followed at home. In clinical practice, the use of a prognostic marker capable of accurately identifying the patients who will develop severe pancreatitis seems more reasonable and efficient. The comments by Windsor [39], which appeared as an accompanying commentary of the Neoptolemos paper, are most welcome. Windsor elegantly demonstrated that comparing likelihood ratios was more appropriate for identifying the patients who would have a severe outcome than were predictive value or accuracy which are better suited to population studies. When applied to the Neoptolemos study, the likelihood ratios were all of similar amplitude and there appeared to be no difference between TAP, CRP and the three scoring systems. Surprisingly, the likelihood ratio was even better for the combined measurement of TAP and CRP, although Neoptolemos did not claim this [16] (Table 2). In summary, TAP

performed no better than the other methods in terms of overall accuracy.

Perspectives

Traditional severity scores have been used successfully by most clinicians to predict severe acute pancreatitis. These scores, which are complicated to use, measure the multiple physiological derangements induced by the disease. However, to predict the severity of the pancreatic disease itself, before the occurrence of multiple organ failure, other single factors have been measured. Thus, several biological markers of severity have emerged in the past 15 years and their ability to provide additional information on the severity of the disease has been evaluated in numerous clinical studies. Nowadays, CRP [40, 41, 42, 43, 44, 45], neutrophil elastase [46, 47, 48, 49, 50] and interleukin-6 (IL-6) [51, 52, 53, 54, 55] are among the best markers, but they are not immediately available in most institutions.

Measurement of TAP in acute pancreatitis seems appealing because activation of trypsinogen into active trypsin has been reported to be among the earliest molecular events leading to acute pancreatitis. It should be noted that, in experimental pancreatitis, the release of TAP occurs as early as 15 minutes after cerulein administration in rodents [17]. Although very attractive, TAP measurement does not provide additional information for predicting the outcome of an attack of pancreatitis when compared with the results obtained using other markers. Further studies should be performed with larger cohorts of patients in order to determine whether TAP measurement could usefully replace serum amylase and lipase determinations in assessing the diagnosis and the prognosis of acute pancreatitis, since TAP is specific to the pancreas and is liberated within a few hours after the onset of symptoms.

In clinical practice, physicians need a marker able to detect which patient will develop the severe disease [39]. However, in the absence of a clear understanding of the physiopathology of acute pancreatitis [56], other factors, either pancreatic enzymes, or cyto/chemokines, will emerge in the near future and will also prove useful in the early prediction of the severity of an attack of acute pancreatitis.

Received August 21st, 2000 – Accepted October 5th, 2000

Key words Amylases; Causality; Lipase; Predictive Value of Tests; Sensitivity and Specificity; Trypsinogen

Abbreviations CAPAP: carboxypeptidase B activation peptide; CRP: C-reactive protein; IL-6: interleukin-6; PSTI: pancreatic secretory trypsin inhibitor; SPINK1: serine protease inhibitor, Kazal type 1

Correspondence
Jean Louis Frossard
Division of Gastroenterology
Geneva University Hospital
Rue Micheli du Crest
1211 Geneva 14
Switzerland
Phone: +41-22-372.9340
Fax: +41-22-372.9366
E-mail address: jean-louis.frossard@hcuge.ch

References

1. Bradley EL III. A clinically based classification system for acute pancreatitis. Arch Surg 1993; 128:586-90. [93256758]
2. Steinberg W, Tenner S. Acute pancreatitis. N Engl J Med 1994; 330:1198-210.
3. Clavien PA, Robert J, Meyer P, Borst F, Hauser H, Herrmann F, et al. Acute pancreatitis and normoamylasemia. Not an uncommon combination. Ann Surg 1989; 210:614-20.
4. Hedstrom J, Sainio V, Kemppainen E, Puolakkainen P, Haapiainen R, Kivilaakso E, et al. Urine trypsinogen-2 as marker of acute pancreatitis. Clin Chem 1996; 42:685-90.

5. Hedstrom J, Sainio V, Kemppainen E, Haapiainen R, Kivilaakso E, Schroder T, et al. Serum complex of trypsin 2 and alpha 1 antitrypsin as diagnostic and prognostic marker of acute pancreatitis: clinical study in consecutive patients. Br Med J 1996; 313:333-7.
6. Gudgeon AM, Heath DI, Hurley P, Jehanli A, Patel G, Wilson C, et al. Trypsinogen activation peptides assay in the early prediction of severity of acute pancreatitis. Lancet 1990; 335:4-8. [90113538]
7. Steer ML. Classification and pathogenesis of pancreatitis. Surg Clin North Am 1989; 69:467-80.
8. Steinberg WM. Predictors of severity of acute pancreatitis. Gastroenterol Clin North Am 1990; 19:849-61.
9. Ranson JH, Rifkind KM, Roses DF, Fink SD, Eng K, Spencer FC. Prognostic signs and the role of operative management in acute pancreatitis. Surg Gynecol Obstet 1974; 139:69-81.
10. Blamey SL, Imrie CW, O'Neill J, Gilmour WH, Carter DC. Prognostic factors in acute pancreatitis. Gut 1984; 25:1340-6. [85077717]
11. Wilson C, Heath DI, Imrie CW. Prediction of outcome in acute pancreatitis: a comparative study of APACHE II, clinical assessment and multiple factor scoring systems. Br J Surg 1990; 77:1260-4. [91070206]
12. Ranson JH, Balthazar E, Caccavale R, Cooper M. Computed tomography and the prediction of pancreatic abscess in acute pancreatitis. Ann Surg 1985; 201:656-65.
13. Haber PS, Pirola RC, Wilson JS. Clinical update: management of acute pancreatitis. J Gastroenterol Hepatol 1997; 12:189-97.
14. Windsor AC, Kanwar S, Li AG, Barnes E, Guthrie JA, Spark JI, et al. Compared with parenteral nutrition, enteral feeding attenuates the acute phase response and improves disease severity in acute pancreatitis. Gut 1998; 42:431-5.
15. Gupta R, Toh SK, Johnson CD. Early ERCP is an essential part of the management of all cases of acute pancreatitis. Ann R Coll Surg Engl 1999; 81:46-50.
16. Neoptolemos J, Kemppainen E, Mayer J, Fitzpatrick J, Raraty M, Slavin J, et al. Early prediction of severity in acute pancreatitis by urinary trypsinogen activation peptide: a multicentre study. Lancet 2000; 355:1955-60. [20315573]
17. Hofbauer B, Saluja AK, Lerch MM, Bhagat L, Bhatia M, Lee HS, et al. Intra-acinar cell activation of trypsinogen during caerulein-induced pancreatitis in rats. Am J Physiol 1998; 275:G352-62. [98365352]
18. Krims PE, Pandol SJ. Free cytosolic calcium and secretagogue-stimulated initial pancreatic exocrine secretion. Pancreas 1988; 3:383-90.
19. Mayer J, Rau B, Schoenberg MH, Beger HG. Mechanism and role of trypsinogen activation in acute pancreatitis. Hepatogastroenterology 1999; 46:2757-63.
20. Otani T, Chepilko S, Grendell J, Gorelick F. Codistribution of TAP and the granule membrane protein GRAMP-92 in rat caerulein-induced pancreatitis. Am J Physiol 1998; 275:G999-1009. [99032636]
21. Whitcomb DC. Early trypsinogen activation in acute pancreatitis. Gastroenterology 1999; 116:770-2. [99186353]
22. Whitcomb DC. Hereditary pancreatitis: new insights into acute and chronic pancreatitis. Gut 1999; 45:317-22. [99376885]
23. Whitcomb DC, Gorry M, Preston R, Furey W, Sossenheimer M, Ulrich C, et al. Hereditary pancreatitis is caused by mutation in the cationic trypsinogen gene. Nat Genet 1996; 14:141-5. [96438847]
24. Saluja AK, Donovan EA, Yamanaka K, Yamaguchi Y, Hofbauer B, Steer ML. Cerulein-induced in vitro activation of trypsinogen in rat pancreatic acini is mediated by cathepsin B. Gastroenterology 1997; 113:304-10. [97350915]
25. Greenbaum L, Hirschkowitz A. Endogenous cathepsin activates trypsinogen in extracts of dog pancreas. Proc Soc Exp Biol Med 1961; 107:74-6.
26. Figarella C, Miszczuk-Jamska B, Barrett A. Possible lysosomal activation of pancreatic zymogens: activation of both human trypsinogens by cathepsin B and spontaneous acid activation of human trypsinogen 1. Biol Chem Hoppe Seyler 1988; 369 (Suppl):293-8.
27. Saluja A, Hashimoto S, Saluja M, Powers RE, Meldolesi J, Steer ML. Subcellular redistribution of lysosomal enzymes during caerulein-induced pancreatitis. Am J Physiol 1987; 253:G508-16.
28. Halangk W, Lerch M, Brandt-Nedelev B, Roth W, Ruthenbuerger M, Reinheckel T et al. Role of cathepsin B in intracellular trypsinogen activation and the onset of acute pancreatitis. J Clin Invest 2000; 106:773-81. [20453314]
29. Witt H, Luck W, Hennies H, Classen M, Kage A, Lass U, et al. Mutations in the gene encoding the serine protease inhibitor, Kazal type 1 are associated with chronic pancreatitis. Nat Genet 2000; 25:213-6.

30. Pfutzer R, Barmada M, Brunskill A, Finch R, Hart P, Neoptolemos J, et al. SPINK1/PSTI polymorphisms act as a disease modifiers in familial and idiopathic chronic pancreatitis. Gastroenterology 2000; 119:615-23. [20440586]

31. Clavien PA, Burgan S, Moossa AR. Serum enzymes and other laboratory tests in acute pancreatitis. Br J Surg 1989; 76:1234-43.

32. Pezzilli R, Billi P, Miglioli M, Gullo L. Serum amylase and lipase concentrations and lipase/amylase ratio in assessment of etiology and severity of acute pancreatitis. Dig Dis Sci 1993; 38:1265-9.

33. Ohlsson K, Eddeland A. Release of proteolytic enzymes in bile-induced pancreatitis in dogs. Gastroenterology 1975; 69:668-75.

34. Hedstrom J, Korvuo A, Kenkimaki P, Tikanoja S, Haapiainen R, Kivilaakso E, et al. Urinary trypsinogen-2 test strip for acute pancreatitis. Lancet 1996; 347:729-30.

35. Kemppainen EA, Hedstrom JI, Puolakkainen PA, Sainio VS, Haapiainen RK, Perhoniemi V, et al. Rapid measurement of urinary trypsinogen-2 as a screening test for acute pancreatitis. N Engl J Med 1997; 336:1788-93.

36. Tenner S, Fernandez-del Castillo C, Warshaw A, Steinberg W, Hermon-Taylor J, Valenzuela JE, et al. Urinary trypsinogen activation peptide (TAP) predicts severity in patients with acute pancreatitis. Int J Pancreatol 1997; 21:105-10. [97353710]

37. Karne S, Gorelick F. Etiopathogenesis of acute pancreatitis. Surg Clin North Am 1999; 79:699-709.

38. Pezzilli R, Morselli-Labate AM, Barbieri AR, Platè L. Clinical usefulness of the serum carboxypeptidase B activation peptide in acute pancreatitis. JOP. J Pancreas (Online) 2000; 1:58-68.

39. Windsor J. Search for prognostic markers for acute pancreatitis. Lancet 2000; 355:1924-5.

40. Buchler M, Malfertheiner P, Schoetensack C, Uhl W, Beger HG. Sensitivity of antiproteases, complement factors and C-reactive protein in detecting pancreatic necrosis. Results of a prospective clinical study. Int J Pancreatol 1986; 1:227-35.

41. De Beaux AC, Goldie AS, Ross JA, Carter DC, Fearon KC. Serum concentrations of inflammatory mediators related to organ failure in patients with acute pancreatitis. Br J Surg 1996; 83:349-53.

42. De la Pena J, De las Heras G, Galo Peralta F, Casafont F, Pons Romero F. Prospective study of the prognostic value of C reactive protein, alpha 1-antitrypsin and alpha 1-acid glycoprotein in acute pancreatitis. Rev Esp Enferm Dig 1991; 79:337-40.

43. Gross V, Leser HG, Heinisch A, Scholmerich J. Inflammatory mediators and cytokines - new aspects of the pathophysiology and assessment of severity of acute pancreatitis? Hepatogastroenterology 1993; 40:522-30.

44. Imrie CW. Prognosis of acute pancreatitis. Ann Ital Chir 1995; 66:187-9.

45. Isenmann R, Buchler M, Uhl W, Malfertheiner P, Martini M, Beger HG. Pancreatic necrosis: an early finding in severe acute pancreatitis. Pancreas 1993; 8:358-61.

46. Buchler M, Malfertheiner P, Uhl W, Beger HG. Diagnostic and prognostic value of serum elastase 1 in acute pancreatitis. Klin Wochenschr 1986; 64:1186-91.

47. Dominguez-Munoz JE, Carballo F, Garcia MJ, de Diego JM, Rabago L, Simon MA, de la Morena J. Clinical usefulness of polymorphonuclear elastase in predicting the severity of acute pancreatitis: results of a multicentre study. Br J Surg 1991; 78:1230-4.

48. Gross V, Scholmerich J, Leser HG, Salm R, Lausen M, Ruckauer K, et al. Granulocyte elastase in assessment of severity of acute pancreatitis. Comparison with acute-phase proteins C-reactive protein, alpha 1-antitrypsin, and protease inhibitor alpha 2-macroglobulin. Dig Dis Sci 1990; 35:97-105.

49. Ikei S, Ogawa M, Yamaguchi Y. Blood concentrations of polymorphonuclear leucocyte elastase and interleukin-6 are indicators for the occurrence of multiple organ failures at the early stage of acute pancreatitis. J Gastroenterol Hepatol 1998; 13:1274-83.

50. Uhl W, Buchler M, Malfertheiner P, Martini M, Beger HG. PMN-elastase in comparison with CRP, antiproteases, and LDH as indicators of necrosis in human acute pancreatitis. Pancreas 1991; 6:253-9. [91319677]

51. Berney T, Gasche Y, Robert J, Jenny A, Mensi N, Grau G, et al. Serum profiles of interleukin-6, interleukin-8, and interleukin-10 in patients with severe and mild acute pancreatitis. Pancreas 1999; 18:371-7.

52. Bertsch T, Aufenanger J. Interleukin-6 and phospholipase A2 isoenzymes during acute pancreatitis. Pancreas 1998; 16:557-8.

53. Cromwell O, Hamid Q, Corrigan C, Barkans J, Meng Q, Collins P, et al. Expression and generation of interleukin-8, interleukin-6 and granulocyte-macrophage colony stimulating factor by bronchial

epithelial cells and enhancement by IL-1 beta and tumor necrosis factor-alpha. Immunology 1992; 77:330-7.

54. Leser HG, Gross V, Scheibenbogen C, Heinisch A, Salm R, Lausen M, et al. Elevation of serum interleukin-6 concentration precedes acute-phase response and reflects severity in acute pancreatitis. Gastroenterology 1991; 101:782-5.

55. Heath DI, Cruickshank A, Gudgeon M, Jehanli A, Shenkin A, Imrie CW. Role of interleukin-6 in mediating the acute phase protein response and potential as an early means of severity assessment in acute pancreatitis. Gut 1993; 34:41-5.

56. Frossard JL. Trypsinogen activation peptide in acute pancreatitis. Lancet 2000; 356:766-7.

57. Dominguez-Munoz JE. Diagnosis of acute pancreatitis : any news or still amylase. In: Buchler MW, Uhl W, Friess H, Malfertheiner P, eds. Acute Pancreatitis, Novel Concepts in Biology and Therapy. Volume 1. 1st ed. Oxford: Blackwell Science. 1999:171-9.