JOP. J Pancreas (Online) 2007; 8(4 Suppl.):495-500.

ROUND TABLE

Action of Antiproteases on Fibrosis in Experimental Chronic Pancreatitis

Yoshikuni Nagashio, Makoto Otsuki

Department of Gastroenterology and Metabolism, University of Occupational and Environmental Health, Japan, School of Medicine. Kitakyushu, Japan

Introduction

Chronic pancreatitis is an irreversible progressive disease characterized by damage to both the exocrine and the endocrine components of the pancreas, eventually resulting in significant exocrine insufficiency and diabetes [1]. The key histopathologic features of chronic pancreatitis are pancreatic fibrosis, acinar atrophy, chronic inflammation, and distorted and blocked ducts [1]. Therapeutic strategies to treat chronic pancreatitis are mostly symptomatic and very limited. In the pancreas, pancreatic stellate cells (PSCs) play a pivotal role in fibrogenesis, and their activation has been recognized as a key event in fibrogenesis [2, 3, 4, 5, 6, 7, 8]. In response to pancreatic injury or inflammation, PSCs transform into myofibroblast-like phenotypes expressing alpha-smooth muscle actin (alpha-SMA) (activated state), proliferate, and synthesize and secrete increased amounts of extracellular matrix (ECM) proteins, particularly collagens and fibronectin. Moreover, it is well-known that the activation of proteases such as trypsin and plasmin is involved in the process of inflammation in the pancreas [9]. For the development of an effective therapy, it is of particular importance to elucidate the mechanisms underlying the processes of inflammation and PSC activation in the pancreas.

Many *in vitro* experiments using PSCs have shown their key roles in the activation and/or proliferation process for cytokines (e.g., transforming growth factor-beta (TGF-beta), platelet-derived growth factor (PDGF), interleukin-1beta (IL-1beta), and tumor necrosis factor-alpha (TNF-alpha) [6, 7]), angiotensin II [10, 11, 12], peroxisome proliferator-activated receptor-gamma (PPAR-gamma) [13], PI 3-kinase [14, 15], and mitogen-activated protein kinase (MAPK) pathways [14, 16, 17, 18, 19]. For example, a blockade of the receptors for TGF-beta, PDGF, and angiotensin II and activation of PPAR-gamma is likely to provide therapeutic benefit in patients with chronic pancreatitis. On the other hand, several *in vivo* experimental studies have shown beneficial effects of antifibrotic drugs on chronic pancreatitis. Agents showing benefit in experimental chronic pancreatitis include angiotensin- converting enzyme inhibitor [20], angiotensin II receptor antagonist [21], PPAR-gamma ligand [22, 23], vitamin E [24], cyclooxygenase-2 (COX-2) inhibitor [25], soluble TGF-beta receptor (blockade of TGF-beta signaling) [26] and the serine protease inhibitor camostat [27, 28, 29, 30]. In this chapter, we focus on the effect of antiproteases on fibrosis in experimental chronic pancreatitis.

Experimental Models of Chronic Pancreatitis

There are several experimental models of chronic pancreatitis for investigating the

mechanisms responsible for the development of chronic pancreatitis. PSCs are the principle effector cells in pancreatic fibrosis of these experimental models.

Trinitrobenzene Sulfonic Acid (TNBS)-Induced Chronic Pancreatitis

Infusion of TNBS into the pancreatic duct of rats causes a pancreatic necroinflammation followed by pancreatic fibrosis within four weeks [31]. In TNBS-treated rats, alpha-SMA-positive PSCs are found in the fibrotic areas.

Dibutyltin Dichloride (DBTC)-Induced Chronic Pancreatitis

This model involves a single intravenous administration of DBTC (6-8 mg/kg body weight) to rats [32]. The rats develop moderate to severe pancreatitis within one week, followed by fibrosis within four weeks after DBTC injection.

Chronic Pancreatitis Induced by Repetitive Intraperitoneal Injections of Cerulein

In mice, the induction of repeated episodes of acute pancreatitis via intraperitoneal injections of cerulein (50 μg/kg body weight every hour for six hours) induces pancreatic fibrosis similar to that of human chronic pancreatitis [26, 33, 34].

Spontaneous Chronic Pancreatitis in WBN/Kob Rats

The characteristic lesions of chronic pancreatitis (acinar atrophy, inflammatory cell infiltration, and fibrosis) develop spontaneously in this strain of rats. These lesions appear focally at approximately 12 weeks of age [35].

Camostat Mesilate

Camostat mesilate, an oral synthetic serine protease inhibitor, inhibits trypsin, kallikrein, thrombin, plasmin and C1 esterase [36], and has been used clinically for the treatment of chronic pancreatitis in Japan [37]. Since the activation of trypsinogen in the pancreas is considered to be a trigger reaction in the development of pancreatitis [9], the pharmacological effect of camostat mesilate on chronic pancreatitis depends on its inhibitory effect on the serine proteases, especially trypsin. In support of the clinical use of camostat mesilate, animal studies have demonstrated both preventive and therapeutic effects on pancreatic exocrine dysfunction and fibrosis in WBN/Kob rats [27, 28]. Oral administration of camostat mesilate increases pancreatic exocrine secretion and causes hypertrophy of the pancreas in normal rats by means of an increase in endogenous cholecystokinin (CCK) release [38, 39, 40]. Several previous studies have revealed that exogenous and endogenous CCK can accelerate pancreatic regeneration after an attack of acute pancreatitis [41, 42, 43]. These results suggest the possibility that camostat mesilate inhibits pancreatic fibrosis via endogenous CCK release in WBN/Kob rats. Thus, we have investigated the effect of camostat mesilate on pancreatic fibrosis and atrophy in Otsuka Long-Evans Tokushima Fatty (OLETF) rats which have a total and selective defect of CCK-1 receptor gene expression [44, 45], and show extreme atrophy and fibrosis of the pancreas with age [46, 47]. In these studies, oral administration of camostat mesilate also inhibits pancreatic inflammation and prevents fibrosis and atropy of the pancreas in the OLETF rats through the suppression of IL-1beta, interleukin-6 (IL-6), TNF-alpha, TGF-beta, and PSCs [48, 49]. Recently, Gibo *et al*. have revealed that the oral administration of camostat mesilate exerts beneficial effects on DBTC-induced chronic pancreatitis in rats by inhibiting monocyte recruitment and PSC activation [30]. In addition, they have demonstrated that camostat mesilate inhibits lipopolysaccharide (LPS)-stimulated productions of monocyte chemoattractant protein-1 (MCP-1) and TNF-alpha in monocytes, and proliferation and MCP-1 production of PSCs *in vitro*. Camostat mesilate can also inhibit PDGF-stimulated proliferation and TGF-beta1-stimulated collagen synthesis of human pancreatic periacinar fibroblast-like cells (hPFCs) [50] which are considered to be PSCs. In all, camostat mesilate is likely to

attenuate experimental chronic pancreatitis by inhibiting chronic inflammation and activation of PSCs induced by cytokines and growth factors.

IS-741

Originally, the N-(2-sulfonylamino-5-trifluoro-methyl-3-pyridyl) carboxamide derivative IS-741 was prepared and evaluated as a phospholipase A2 (PLA2) inhibitor [51, 52]. Moreover, it is shown that IS-741 has an anti-inflammatory effect through its inhibitory action on cell adhesion in a rat colitis model induced by dextran sulfate sodium and in a rat acute necrotizing pancreatitis model [53, 54]. The administration of IS-741 suppresses inflammatory cell infiltration and subsequent pancreatic fibrosis in WBN/Kob rats and DBTC-induced chronic pancreatitis [55, 56]. Recently, Kaku T *et al*. have demonstrated that the administration of IS-741 suppresses macrophage infiltration and PSC activation in DBTC-induced chronic pancreatitis [56]. Therefore, it is likely that the inhibitory effect of IS-741 on pancreatic fibrosis is due to its inhibitory effects on macrophage infiltration into the pancreas and on PLA2 activity.

Conclusion

Among antiproteases, camostat mesilate, an oral synthetic serine protease inhibitor, has been shown to suppress the progression of fibrosis in experimental chronic pancreatitis. However, the amount of camostat mesilate in experimental chronic pancreatitis is about five times as much as a general dose of camostat mesilate used for patients with chronic pancreatitis in Japan [30]. The oral administration of camostat mesilate increases endogenous CCK release, and subsequently stimulates pancreatic exocrine secretion and pancreatic growth in normal rats [38, 39, 40]. In healthy humans, the oral administration of camostat mesilate for four weeks (2 g/day, approximately three times as much as the usual dosage for human chronic pancreatitis) can also increase the size of the pancreas and CCK release after test meal stimulation [57]. From these observations, there is the possibility that camostat mesilate may stimulate pancreatic growth in patients with chronic pancreatitis. This possibility still remains to be seen. It is necessary to clarify in future studies whether camostat mesilate provides therapeutic benefits in patients with chronic pancreatitis.

Keywords Fibrosis; FOY 305; IS 741; Inflammation; Pancreatitis, Chronic; Protease Inhibitors

Abbreviations alpha-SMA: alpha-smooth muscle actin; CCK: cholecystokinin; COX-2: cyclooxygenase-2; DBTC: dibutyltin dichloride; ECM: extracellular matrix; hPFCs: human pancreatic periacinar fibroblast-like cells; IL-1beta: interleukin-1beta; IL-6: interleukin-6; LPS: lipopolysaccharide; MAPK: mitogen-activated protein kinase; MCP-1: monocyte chemoattractant protein-1; OLETF: Otsuka Long-Evans Tokushima Fatty; PDGF: platelet-derived growth factor; PLA2: phospholipase A2; PPAR-gamma: peroxisome proliferator-activated receptor-gamma; PSCs: pancreatic stellate cells; TGF-beta: transforming growth factor-beta; TNBS: trinitrobenzene sulfonic acid; TNF-alpha: tumor necrosis factor-alpha

Conflict of interest The authors have no potential conflicts of interest

Correspondence
Makoto Otsuki
Department of Gastroenterology and Metabolism
University of Occupational and Environmental Health, Japan
School of Medicine
1-1 Iseigaoka, Yahatanishi-ku
Kitakyushu
807-8555, Japan
Phone: +81-93.691.7251
Fax: +81-93.692.0107
E-mail: mac-otsk@med.uoeh-u.ac.jp

Document URL: http://www.joplink.net/prev/200707/30.html

References

1. DiMagno EP, Layer P, Clain JF. Chronic pancreatitis. In: Go VLW, DiMagno EP, Gardner JD,

Lebenthal L, Reber HA, Scheele GA, eds. The pancreas: biology, pathobiology and disease. New York: Pleum Press 1993:665-706.

2. Apte MV, Haber PS, Applegate TL, Norton ID, McCaughan GW, Korsten MA, et al. Periacinar stellate shaped cells in rat pancreas: identification, isolation, and culture. Gut 1998; 43:128-33. [PMID 9771417]

3. Bachem MG, Schneider E, Gross H, Weidenbach H, Schmid RM, Menke A, et al. Identification, culture, and characterization of pancreatic stellate cells in rats and humans. Gastroenterology 1998; 115: 421-32. [PMID 9679048]

4. Apte MV, Haber PS, Darby SJ, Rodgers SC, McCaughan GW, Korsten MA, et al. Pancreatic stellate cells are activated by proinflammatory cytokines: implications for pancreatic fibrogenesis. Gut 1999; 44:534-41. [PMID 10075961]

5. Haber PS, Keogh GW, Apte MV, Moran CS, Stewart NL, Crawford DH, et al. Activation of pancreatic stellate cells in human and experimental pancreatic fibrosis. Am J Pathol 1999; 155:1087-95. [PMID 10514391]

6. Mews P, Phillips P, Fahmy R, Korsten M, Pirola R, Wilson J, Apte M. Pancreatic stellate cells respond to inflammatory cytokines: potential role in chronic pancreatitis. Gut 2002; 50:535-41. [PMID 11889076]

7. Schneider E, Schmid-Kotsas A, Zhao J, Weidenbach H, Schmid RM, Menke A, et al. Identification of mediators stimulating proliferation and matrix synthesis of rat pancreatic stellate cells. Am J Physiol Cell Physiol 2001; 281:C532-43. [PMID 11443052]

8. Omary MB, Lugea A, Lowe AW, Pandol SJ. The pancreatic stellate cell: a star on the rise in pancreatic diseases. J Clin Invest 2007; 117:50-9. [PMID 17200706]

9. Witt H, Apte MV, Keim V, Wilson JS. Chronic pancreatitis: challenges and advances in pathogenesis, genetics, diagnosis, and therapy. Gastroenterology 2007; 132:1557-73. [PMID 17466744]

10. Hama K, Ohnishi H, Yasuda H, Ueda N, Mashima H, Satoh Y, et al. Angiotensin II stimulates DNA synthesis of rat pancreatic stellate cells by activating ERK through EGF receptor transactivation. Biochem Biophys Res Commun 2004; 315:905-11. [PMID 14985098]

11. Reinehr R, Zoller S, Klonowski-Stumpe H, Kordes C, Haussinger D. Effects of angiotensin II on rat pancreatic stellate cells. Pancreas 2004; 28:129-37. [PMID 15028944]

12. Hama K, Ohnishi H, Aoki H, Kita H, Yamamoto H, Osawa H, et al. Angiotensin II promotes the proliferation of activated pancreatic stellate cells by Smad7 induction through a protein kinase C pathway. Biochem Biophys Res Commun 2006; 340:742-50. [PMID 16380081]

13. Masamune A, Kikuta K, Satoh M, Sakai Y, Satoh A, Shimosegawa T. Ligands of peroxisome proliferator-activated receptor-gamma block activation of pancreatic stellate cells. J Biol Chem 2002; 277:141-7. [PMID 11606585]

14. Masamune A, Kikuta K, Satoh M, Kume K, Shimosegawa T. Differential roles of signaling pathways for proliferation and migration of rat pancreatic stellate cells. Tohoku J Exp Med 2003; 199:69-84. [PMID 12705352]

15. McCarroll JA, Phillips PA, Kumar RK, Park S, Pirola RC, Wilson JS, Apte MV. Pancreatic stellate cell migration: role of the phosphatidylinositol 3-kinase (PI3-kinase) pathway. Biochem Pharmacol 2004; 67:1215-25. [PMID 15006556]

16. Jaster R, Sparmann G, Emmrich J, Liebe S. Extracellular signal regulated kinases are key mediators of mitogenic signals in rat pancreatic stellate cells. Gut 2002; 51:579-84. [PMID 12235084]

17. Masamune A, Kikuta K, Satoh M, Satoh A, Shimosegawa T. Alcohol activates activator protein-1 and mitogen-activated protein kinases in rat pancreatic stellate cells. J Pharmacol Exp Ther 2002; 302:36-42. [PMID 12065697]

18. Masamune A, Satoh M, Kikuta K, Sakai Y, Satoh A, Shimosegawa T. Inhibition of p38 mitogen-activated protein kinase blocks activation of rat pancreatic stellate cells. J Pharmacol Exp Ther 2003; 304:8-14. [PMID 12490569]

19. Masamune A, Kikuta K, Suzuki N, Satoh M, Satoh K, Shimosegawa T. A c-Jun NH2-terminal kinase inhibitor SP600125 (anthra[1,9-cd]pyrazole-6 (2H)-one) blocks activation of pancreatic stellate cells. J Pharmacol Exp Ther 2004; 310:520-7. [PMID 15056726]

20. Kuno A, Yamada T, Masuda K, Ogawa K, Sogawa M, Nakamura S, et al. Angiotensin-converting enzyme inhibitor attenuates pancreatic inflammation and fibrosis in male Wistar Bonn/Kobori rats. Gastroenterology 2003; 124:1010-9. [PMID 12671898]

21. Yamada T, Kuno A, Masuda K, Ogawa K, Sogawa M, Nakamura S, et al. Candesartan, an angiotensin II receptor antagonist, suppresses pancreatic inflammation and fibrosis in rats. J Pharmacol Exp Ther 2003; 307:17-23. [PMID 12944495]

22. Shimizu K, Shiratori K, Kobayashi M, Kawamata H. Troglitazone inhibits the progression of chronic pancreatitis and the profibrogenic activity of pancreatic stellate cells via a PPARgamma-independent mechanism. Pancreas 2004; 29:67-74. [PMID 15211114]

23. Van Westerloo DJ, Florquin S, de Boer AM, Daalhuisen J, De Vos AF, Bruno MJ, Van der Poll T. Therapeutic effects of troglitazone in experimental chronic pancreatitis in mice. Am J Pathol 2005; 166:721-8. [PMID 15743784]

24. Gomez JA, Molero X, Vaquero E, Alonso A, Salas A, Malagelada JR. Vitamin E attenuates biochemical and morphological features associated with development of chronic pancreatitis. Am J Physiol Gastrointest Liver Physiol 2004; 287:G162-9. [PMID 15001429]

25. Reding T, Bimmler D, Perren A, Sun LK, Fortunato F, Storni F, Graf R. A selective COX-2 inhibitor suppresses chronic pancreatitis in an animal model (WBN/Kob rats): significant reduction of macrophage infiltration and fibrosis. Gut 2006; 55:1165-73. [PMID 16322109]

26. Nagashio Y, Ueno H, Imamura M, Asaumi H, Watanabe S, Yamaguchi T, et al. Inhibition of transforming growth factor beta decreases pancreatic fibrosis and protects the pancreas against chronic injury in mice. Lab Invest 2004; 84:1610-8. [PMID 15502860]

27. Shimoda I, Koizumi M, Shimosegawa T, Shishido T, Ono T, Sato K, et al. Physiological characteristics of spontaneously developed diabetes in male WBN/Kob rat and prevention of development of diabetes by chronic oral administration of synthetic trypsin inhibitor (FOY-305). Pancreas 1993; 8:196-203. [PMID 8460095]

28. Sugiyama M, Kobori O, Atomi Y, Wada N, Kuroda A, Muto T. Effect of oral administration of protease inhibitor on pancreatic exocrine function in WBN/Kob rats with chronic pancreatitis. Pancreas 1996; 13:71-9. [PMID 8783337]

29. Su SB, Motoo Y, Iovanna JL, Xie MJ, Sawabu N. Effect of camostat mesilate on the expression of pancreatitis-associated protein (PAP), p8, and cytokines in rat spontaneous chronic pancreatitis. Pancreas 2001; 23:134-40. [PMID 11484915]

30. Gibo J, Ito T, Kawabe K, Hisano T, Inoue M, Fujimori N, et al. Camostat mesilate attenuates pancreatic fibrosis via inhibition of monocytes and pancreatic stellate cells activity. Lab Invest 2005; 85:75-89. [PMID 15531908]

31. Puig-Divi V, Molero X, Salas A, Guarner F, Guarner L, Malagelada JR. Induction of chronic pancreatic disease by trinitrobenzene sulfonic acid infusion into rat pancreatic ducts. Pancreas 1996; 13:417-24. [PMID 8899803]

32. Sparmann G, Merkord J, Jaschke A, Nizze H, Jonas L, Lohr M, et al. Pancreatic fibrosis in experimental pancreatitis induced by dibutyltin dichloride. Gastroenterology 1997; 112:1664-72. [PMID 9136846]

33. Neuschwander-Tetri BA, Bridle KR, Wells LD, Marcu M, Ramm GA. Repetitive acute pancreatic injury in the mouse induces procollagen alpha1(I) expression colocalized to pancreatic stellate cells. Lab Invest 2000; 80:143-50. [PMID 10701684]

34. Nagashio Y, Asaumi H, Watanabe S, Nomiyama Y, Taguchi M, Tashiro M, et al. Angiotensin II type 1 receptor interaction is an important regulator for the development of pancreatic fibrosis in mice. Am J Physiol Gastrointest Liver Physiol 2004; 287:G170-7. [PMID 15016612]

35. Tsuchitani M, Saegusa T, Narama I, Nishikawa T, Gonda T. A new diabetic strain of rat (WBN/Kob). Lab Anim 1985; 19:200-7. [PMID 4033061]

36. Tamura Y, Hirado M, Okamura K, Minato Y, Fujii S. Synthetic inhibitors of trypsin, plasmin, kallikrein, thrombin, C1r-, and C1 esterase. Biochim Biophys Acta 1977; 484:417-22. [PMID 143965]

37. Kanoh M, Ibata H, Miyagawa M, Matsuo Y. Clinical effects of camostat in chronic pancreatitis. Biomed Res 1989; 10:145-50.

38. Göke B, Printz H, Koop I, Rausch U, Richter G, Arnold R, Adler G. Endogenous CCK release and pancreatic growth in rats after feeding a proteinase inhibitor (camostate). Pancreas 1986; 1:509-15. [PMID 3562444]

39. Otsuki M, Ohki A, Okabayashi Y, Suehiro I, Baba S. Effect of synthetic protease inhibitor camostate on pancreatic exocrine function in rats. Pancreas 1987; 2:164-9. [PMID 3628222]

40. Otsuki M, Tani S, Fujii M, Nakamura T, Okabayashi Y, Koide M. Differential effects of proteinase inhibitor camostat on exocrine pancreas in fed and fasted rats. Am J Physiol 1993; 265:R896-901. [PMID 7694489]

41. Majumdar AP, Vesenka GD, Dubick MA. Acceleration of pancreatic regeneration by cholecystokinin in rats. Pancreas 1987; 2:199-204. [PMID 3628224]

42. Jurkowska G, Grondin G, Masse S, Morisset J. Soybean trypsin inhibitor and cerulein accelerate recovery of cerulein-induced pancreatitis in rats. Gastroenterology 1992; 102:550-62. [PMID 1370663]

43. Jurkowska G, Grondin G, Morisset J. Involvement of endogenous cholecystokinin in pancreatic regeneration after cerulein-induced acute pancreatitis. Pancreas 1992; 7:295-304. [PMID 1594550]

44. Funakoshi A, Miyasaka K, Shinozaki H, Masuda M, Kawanami T, Takata Y, Kono A. An animal model of congenital defect of gene expression of cholecystokinin (CCK)-A receptor. Biochem Biophys Res Commun 1995; 210:787-96. [PMID 7539259]

45. Nakamura H, Kihara Y, Tashiro M, Kanagawa K, Shirohara H, Yamamoto M, et al. Defects of

cholecystokinin (CCK)-A receptor gene expression and CCK-A receptor-mediated biological functions in Otsuka Long-Evans Tokushima Fatty (OLETF) rats. J Gastroenterol 1998; 33:702-9. [PMID 9773935]

46. Jia DM, Fukumitsu KI, Tabaru A, Akiyama T, Otsuki M. Troglitazone stimulates pancreatic growth in congenitally CCK-A receptor-deficient OLETF rats. Am J Physiol Regul Integr Comp Physiol 2001; 280:R1332-40. [PMID 11294751]

47. Yoshikawa H, Kihara Y, Taguchi M, Yamaguchi T, Nakamura H, Otsuki M. Role of TGF-beta1 in the development of pancreatic fibrosis in Otsuka Long-Evans Tokushima Fatty rats. Am J Physiol Gastrointest Liver Physiol 2002; 282:G549-58. [PMID 11842006]

48. Jia D, Taguchi M, Otsuki M. Preventive and therapeutic effects of the protease inhibitor camostat on pancreatic fibrosis and atrophy in CCK-1 receptor-deficient rats. Pancreas 2005; 30:54-61. [PMID 15632700]

49. Jia D, Taguchi M, Otsuki M. Synthetic protease inhibitor camostat prevents and reverses dyslipidemia, insulin secretory defects, and histological abnormalities of the pancreas in genetically obese and diabetic rats. Metabolism 2005; 54:619-27. [PMID 15877292]

50. Nakamura F, Shintani Y, Saotome T, Fujiyama Y, Bamba T. Effects of synthetic serine protease inhibitors on proliferation and collagen synthesis of human pancreatic periacinar fibroblast-like cells. Pancreas 2001; 22:317-25. [PMID 11291936]

51. Kimura H, Yotsuya S, Yuki S, Sugi H, Shigehara I, Haga T. Synthesis and antipancreatitis activities of novel N-(2-sulfonylamino-5-trifluoromethyl-3-pyridyl)carboxamide derivatives as phospholipase A2 inhibitors. Chem Pharm Bull (Tokyo) 1995; 43:1696-700. [PMID 8536343]

52. Isaji S, Hayashi J, Higashiguchi T, Yokoi H, Ogura Y, Noguchi T, Kawarada Y. Effect of IS-741 (a new synthetic antiinflammatory agent) on acute necrotizing pancreatitis in dogs. Significance of its inhibitory effect on cytosolic phospholipase A2. Digestion 1999; 60:47-51. [PMID 10026431]

53. Yotsuya S, Shikama H, Imamura M. Efficacy of the inflammatory cell infiltration inhibitor IS-741 on colitis induced by dextran sulfate sodium in the rat. Jpn J Pharmacol 2001; 87:151-7. [PMID 11700014]

54. Yamauchi J, Sunamura M, Shibuya K, Takeda K, Kobari M, Matsuno S. A novel diamino-pyridine derivative prevents excessive leukocyte infiltration in aggravation of acute necrotizing pancreatitis. Digestion 1999; 60:40-6. [PMID 10026430]

55. Xie MJ, Motoo Y, Su SB, Iovanna JL, Sawabu N. Effect of carboxamide derivative IS-741 on rat spontaneous chronic pancreatitis. Dig Dis Sci 2002; 47:139-47. [PMID 11837714]

56. Kaku T, Oono T, Zhao H, Gibo J, Kawabe K, Ito T, Takayanagi R. IS-741 attenuates local migration of monocytes and subsequent pancreatic fibrosis in experimental chronic pancreatitis induced by dibutyltin dichloride in rats. Pancreas 2007; 34:299-309. [PMID 17414052]

57. Friess H, Kleeff J, Isenmann R, Malfertheiner P, Buchler MW. Adaptation of the human pancreas to inhibition of luminal proteolytic activity. Gastroenterology 1998; 115:388-96. [PMID 9679044]