

Pancreatic Stellate Cells and Chronic Alcoholic Pancreatitis

Raffaele Pezzilli

Department of Digestive Diseases and Internal Medicine, Sant'Orsola-Malpighi Hospital.
Bologna, Italy

Chronic pancreatitis is a disease often characterized by recurrent episodes of abdominal pain accompanied by progressive pancreatic exocrine and endocrine insufficiency [1] and it sometimes requires multiple hospitalizations. Obstructive jaundice, duodenal stenosis, left-sided portal hypertension, pseudocyst and mass formation, and pancreatic carcinoma may occur as complications of chronic pancreatitis. The disease is frequently the result of chronic alcohol abuse, even if other factors such as genetic alterations, autoimmune disorders, and obstructive disease of the biliary tract and the pancreas may cause the disease [2]. Medical therapy is the treatment of choice for most patients and it is based on substitutive therapy for either exocrine or endocrine insufficiency and on analgesics for pain control. In the presence of intractable pain, surgical management is the main option [3] even if, in recent years, other therapeutic options such as endoscopic therapy [4], thoracoscopic splanchnicectomy [5], and extracorporeal shockwave lithotripsy have been applied in clinical practice [6].

From a pathological point of view, chronic pancreatitis is characterized by irregular sclerosis with destruction and loss of the exocrine parenchyma, and complete replacement of acinar, ductal and endocrine tissue by fibrotic tissue. It has recently been reported that acute alcoholic pancreatitis develops in a pancreas already affected by chronic pancreatitis [7].

In 1982, Watari *et al.* [8] reported the presence of vitamin A-containing cells in the vitamin A-fed rat pancreas. These were later described and characterized as stellate cells in the rat and the human pancreas [9, 10]. Pancreatic stellate cells are morphologically similar to hepatic stellate cells. They bear long cytoplasmic processes and are situated close to the pancreatic acini. In the quiescent state, these cells contain lipid droplets, store vitamin A and express markers such as desmin, glial fibrillary acidic protein, neural cell adhesion molecule and neurotrophin nerve growth factor just as hepatic stellate cells do. Pancreatic stellate cells contain the enzyme alcohol dehydrogenase [11] and, when activated, they assume a myofibroblast-like phenotype [12]. Activated pancreatic stellate cells are characterized by the disappearance of fat globules and the expression of alpha-smooth muscle actin. These cells have proliferative and migratory [13, 14, 15] functions and they also synthesize and secrete extracellular fibrous tissue matrix proteins, matrix metalloproteinases and their inhibitors [16]; it has also been demonstrated that pancreatic stellate cells have phagocytic activity [17]. Thus, the ability of pancreatic stellate cells to synthesize as well as to degrade extracellular matrix proteins suggests their role in maintaining a normal pancreatic architecture which can shift towards fibrogenesis if the balance is altered. Ethanol, acetaldehyde and oxidant stress are capable of activating activate pancreatic stellate cells via

three mitogen-activated protein kinase pathways [18], namely extracellular signal kinase, p38 kinase and c-jun amino terminal kinase [19, 20, 21], and ethanol and acetaldehyde are also capable of activating phosphatidylinositol 3-kinase and protein kinase C [22]. On the other hand, extracellular signal kinase activation occurs via a signal transduction pathway which involves G-protein Ras and serine threonine protein kinase Raf-1 [23, 24]. The Ras superfamily G proteins undergo post-translational modification involving isoprenylation, a process which requires intermediate substrates of cholesterol biosynthesis [25, 26] which is regulated by HMG CoA reductase [27]. The paracrine pro-fibrogenic effect of TGF-beta on pancreatic stellate cells is mediated via smad while the autocrine effect is mediated through the extracellular signal kinase pathway [28]; furthermore, the role of the peroxisome proliferator-activated receptor-gamma seems to be involved in the activation of pancreatic stellate cells [29,30]. The major part of the studies published on pancreatic stellate cells have been carried out in experimental animals; thus, the study of Suda *et al.* seems of particular interest because it was performed on humans [31]. These authors investigated the distribution of activated pancreatic stellate cells or myofibroblasts using immunohistochemistry and a computer-counting device in relation to fibrogenesis in 24 patients with clinically diagnosed chronic alcoholic pancreatitis. In all cases, fibrosis was patchily distributed in the perilobular or interlobular, areas accompanied by a cirrhosis-like appearance; it had extended into the intralobular area in advanced cases. Seven patients had a massive or confluent loss of exocrine tissue, resulting in extensive interlobular fibrosis; the more extensive the interlobular fibrosis, the smaller the lobules. Immunoreactivity to alpha-smooth muscle actin, a myofibroblast marker, was found mostly in the same areas of the fibrosis, mainly the interlobular, and less often the periacinar, areas; the average percentage area of perilobular myofibroblasts was significantly higher than that of

periacinar myofibroblasts in 20 randomly selected lobules; fibrosis also immunostained positive for collagen types I and III. In conclusion, this study carried out on humans, further supports the hypothesis that the fibrotic alterations in chronic alcoholic pancreatitis are not due to recurrent episodes of necrotizing pancreatitis but the disease is due to a chronic stimulation of alcohol on pancreatic stellate cells which play an important role in pancreatic fibrogenesis.

Keywords Fibrosis; Pancreatitis, Alcoholic; Pancreatitis, Chronic

Correspondence

Raffaele Pezzilli
Department of Digestive Diseases and
Internal Medicine
Sant'Orsola-Malpighi Hospital
Via Massarenti, 9
40138 Bologna
Italy
Phone: +39-051.636.4148
Fax: +39-051.636.4148
E-mail: pezzilli@aosp.bo.it

References

1. Gullo L, Barbara L, Labò G. Effect of cessation of alcohol use on the course of pancreatic dysfunction in alcoholic pancreatitis. *Gastroenterology* 1988; 95:1063-8. [PMID 3410221]
2. Etemad B, Whitcomb DC. Chronic pancreatitis: diagnosis, classification, and new genetic developments. *Gastroenterology* 2001; 120:682-707. [PMID 11179244]
3. Liao Q, Zhao YP, Wu WW, Li BL, Li JY. Diagnosis and treatment of chronic pancreatitis. *Hepatobiliary Pancreat Dis Int* 2003; 2:445-8. [PMID 14599957]
4. Gabbrielli A, Mutignani M, Pandolfi M, Perri V, Costamagna G. Endotherapy of early onset idiopathic chronic pancreatitis: results with long-term follow-up. *Gastrointest Endosc* 2002; 55:488-93. [PMID 11923759]
5. Hammond B, Vitale GC, Rangnekar N, Vitale EA, Binford JC. Bilateral thoracoscopic splanchnicectomy for pain control in chronic pancreatitis. *Am Surg* 2004; 70:546-9. [PMID 15212413]

6. Delhaye M, Arvanitakis M, Bali M, Matos C, Deviere J. Endoscopic therapy for chronic pancreatitis. *Scand J Surg* 2005; 94:143-53. [PMID 16111097]
7. Migliori M, Manca M, Santini D, Pezzilli R, Gullo L. Does acute alcoholic pancreatitis precede the chronic form or is the opposite true? A histological study. *J Clin Gastroenterol* 2004 ;38:272-5. [PMID 15128075]
8. Watari N, Hotta Y, Mabuchi Y. Morphological studies on a vitamin A-storing cell and its complex with macrophage observed in mouse pancreatic tissues following excess vitamin A administration. *Okajimas Folia Anat Jpn* 1982; 58:837-58. [PMID 7122019]
9. 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; 43:128-133. [PMID 9771417]
10. 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]
11. Apte MV, Phillips PA, Fahmy RG, Darby SJ, Rodgers SC, McCaughan GW, Korsten MA, Pirola RC, Naidoo D, Wilson JS. Does alcohol directly stimulate pancreatic fibrogenesis? Studies with rat pancreatic stellate cells. *Gastroenterology* 2000; 118:780-94. [PMID 10734030]
12. Saotome T, Inoue H, Fujiyama Y, Bamba T. Morphological and immunocytochemical identification of periacinar fibroblast-like cells derived from human pancreatic acini. *Pancreas* 1997; 14:373-82. [PMID 9163784]
13. 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]
14. 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]
15. Phillips PA, Wu MJ, Kumar RK, Doherty E, McCarroll JA, Park S, et al. Cell migration: a novel aspect of pancreatic stellate cell biology. *Gut* 2003; 52:677-82. [PMID 12692052]
16. Phillips PA, McCarroll JA, Park S, Wu MJ, Pirola R, Korsten M, et al. Rat pancreatic stellate cells secrete matrix metalloproteinases: implications for extracellular matrix turnover. *Gut* 2003; 52:275-82. [PMID 12524413]
17. Shimizu K, Kobayashi M, Tahara J, Shiratori K. Cytokines and peroxisome proliferator-activated receptor gamma ligand regulate phagocytosis by pancreatic stellate cells. *Gastroenterology* 2005; 128:2105-18. [PMID 15940641]
18. Lopez-Illasaca M. Signaling from G-protein-coupled receptors to mitogen-activated protein (MAP)-kinase cascades. *Biochem Pharmacol* 1998; 56:269-77. [PMID 9744561]
19. 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]
20. McCarroll JA, Phillips PA, Park S, Doherty E, Pirola RC, Wilson JS, Apte MV. Pancreatic stellate cell activation by ethanol and acetaldehyde: is it mediated by the mitogen-activated protein kinase signaling pathway? *Pancreas* 2003; 27:150-60. [PMID 12883264]
21. 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]
22. 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]
23. Lewis TS, Shapiro PS, Ahn NG. Signal transduction through MAP kinase cascades. *Adv Cancer Res* 1998; 74:49-139. [PMID 9561267]
24. Chang L, Karin M. Mammalian MAP kinase signalling cascades. *Nature* 2001; 410:37-40. [PMID 11242034]
25. Rebollo A, Martinez AC. Ras proteins: recent advances and new functions. *Blood* 1999; 94:2971-80. [PMID 10556179]
26. Casey PJ, Solski PA, Der CJ, Buss JE. p21ras is modified by a farnesyl isoprenoid. *Proc Natl Acad Sci USA* 1989; 86:8323-7. [PMID 2682646]
27. Goldstein JL, Brown MS. Regulation of mevalonate pathway. *Nature* 1990; 343:425-30. [PMID 1967820]
28. Ohnishi H, Miyata T, Yasuda H, Satoh Y, Hanatsuka K, Kita H, et al. Distinct roles of Smad2-, Smad3-, and ERK-dependent pathways in transforming growth factor-beta1 regulation of pancreatic stellate cellular functions. *J Biol Chem* 2004; 279:8873-8. [PMID 14688282]
29. 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]

30. Masamune A, Kikuta K, Satoh M, Suzuki N, Shimosegawa T. Protease-activated receptor-2-mediated proliferation and collagen production of rat pancreatic stellate cells. *J Pharmacol Exp Ther* 2005; 312:651-8. [PMID 15367578]

31. Suda K, Fukumura Y, Takase M, Kashiwagi S, Izumi M, Kumasaka T, Suzuki F. Activated perilobular, not periacinar, pancreatic stellate cells contribute to fibrogenesis in chronic alcoholic pancreatitis. *Pathol Int* 2007; 57:21-5. [PMID 17199738]
