

Pancreatic Stellate Cells and Chronic Alcoholic Pancreatitis

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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

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