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PANCREAS NEWS

Alcohol, Inflammation and Gene Modifications in Chronic Pancreatitis

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The etiology of chronic pancreatitis in Western countries is associated with chronic alcohol abuse in a high percentage of cases. In fact, we found that, in 190 Italian patients with proven chronic pancreatitis who were studied in the 2005, the etiology was alcohol abuse (more than 80 g/day for at least 5 years) in 77.4% of the cases and due to other causes in 5.8% (hereditary pancreatitis in 2.6%, pancreatic malformation in 2.1%, cystic fibrosis transmembrane conductance regulator gene mutation in 0.5%, autoimmune pancreatitis in 0.5%); in 16.8% of the cases, a definite etiology of the pancreatitis was not recognized [1]. Although alcohol abuse is the main factor associated with chronic pancreatitis development, the pathological mechanisms involved in the initiation the disease remain obscure. One of the reasons for our difficulty in understanding the trigger mechanism between alcohol abuse and chronic pancreatic damage is the lack of animal and cellular models simulating the lesions such as those observed in humans. Gukovsky *et al*. [2] have recently found that rats which had been fed ethanol for 8 weeks, which had received cyclosporin A for the last two2 weeks and in which acute pancreatitis had been cerulein-induced had a massive loss of acinar cells, persistent inflammatory infiltration and fibrosis as compared to the control animals. Furthermore, macrophages in the treated rats were prominent in the inflammatory infiltrate and showed a marked increase in pancreatic NF-kappaB activation, cytokine/chemokine mRNA expression, collagen and fibronectin, in the expression and activities of matrix metalloproteinases 2 and 9 and in the activation of pancreatic stellate cells. Therefore, this study shows the possible mechanism by which alcohol sensitizes the pancreas to chronic injury. The crucial role played by the activated pancreatic stellate cells in the development of pancreatic fibrosis and inflammation is well-demonstrated by the study of Masamune *et al*. [3]; these researchers demonstrated that pancreatic stellate cells express NADPH oxidase to generate reactive oxygen species which mediate key cell functions and the activation of pancreatic stellate cells. Finally, the close relationship between inflammation and pain (the main symptom of the initial phases of chronic pancreatitis) has been investigated by Michalski *et al*. [4]. They found that the responsiveness of peripheral blood mononuclear cells to the neuropeptide pituitary adenylate cyclase-activating polypeptide is altered in chronic pancreatitis patients. In fact, the nociceptive status of chronic pancreatitis patients correlated with pancreatic pituitary adenylate cyclase-activating polypeptide levels and with IL-10 bias of pituitary adenylate cyclase-activating polypeptide-exposed peripheral blood mononuclear cells of chronic pancreatitis patients. Thus, the ability of peripheral blood mononuclear cells to produce and to respond to

pituitary adenylate cyclase-activating polypeptide might influence the neuroimmune interactions which regulate pain and inflammation in chronic pancreatitis.

The role of substances initiating chronic pancreatitis in humans is further complicated by genetic factors. Currently, it has been reported alterations of three genes causing or associated with or protecting against chronic pancreatitis: those encoding cationic trypsinogen (PRSS1; OMIM 276000), anionic trypsinogen (PRSS2; OMIM 601564) and the pancreatic secretory trypsin inhibitor (SPINK1; OMIM 167790). Rosendahl *et al*. have analyzed alterations of an additional gene encoding the trypsin-degrading enzyme chymotrypsin C (CTRC) in German subjects with idiopathic or hereditary chronic pancreatitis [5]. Two alterations in this gene, p.R254W and p.K247_R254del, were significantly overrepresented in the pancreatitis group, being present in 3.3% of the affected individuals but in only 0.7% of the controls (P<0.001). A replication study identified these two variants in 2.9% of individuals with alcoholic chronic pancreatitis but in only 0.7% of subjects with alcoholic liver disease (P=0.02). CTRC variants were also found in 14.1% of Indian subjects with tropical pancreatitis but in only 1.2% of healthy controls (P=0.003). The authors also assessed the functional analysis of the CTRC variants and found impaired activity and/or reduced secretion. These results indicate that loss-of-function alterations in CTRC predispose to pancreatitis by diminishing its protective trypsin-degrading activity.

Studies on the initial and developmental factors responsible for chronic pancreatitis in experimental animals demonstrate once again the difficulties of relating these results to humans without considering that genetic alterations may constitute an important predisposing factor for chronic pancreatitis in our species.

Keywords Alcohol Drinking; Genes; Inflammation Mediators; Pancreatitis, Chronic

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