Risk Factors of Chronic Pancreatitis

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Chronic pancreatitis (CP), an inflammatory disease characterized by fibrosis leading to the destruction of pancreatic exocrine and endocrine tissue, still remains a challenging clinical problem with many controversial issues regarding pathogenesis, outcome, and treatment [1, 2]. Various predisposing factors have been identified over the last decades, but their impact on etiology and the natural disease course is still a matter of debate. In the Western world the disease is commonly associated with excessive consumption of alcohol. The etiological role of alcohol was strongly supported by epidemiological features rather than experimental data; nevertheless, excessive consumption of alcohol was thought to be the most common cause, accounting for 70–80% of all cases. About 20% of cases were considered idiopathic pancreatitis, while the remaining 10% included cases associated with duct obstruction, trauma, pancreas divisum, cystic dystrophy of the duodenal wall, hyperparathyroidism, hypertriglyceridemia, autoimmune pancreatitis, tropical pancreatitis and hereditary pancreatitis [3]. Other important epidemiological aspects emerging in the recent years are the role of cigarette smoking on CP evolution, the recognition that alcohol alone seldom causes CP and the discovery of pancreatitis-associated gene mutations [4]. In many studies, smoking has been found to be an additional risk factor in alcohol-induced or other types of CP, and experimental and clinical observations showed that smoking can damage the pancreas [5]. In
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non-alcoholic idiopathic CP, smoking is associated with progression of the disease through an anticipation of pancreatic calcifications in the late-onset patients group [6]. In addition, smoking may increase the severity of alcoholic CP as verified by the occurrence of an earlier clinical diagnosis and a significant increase of the risk of pancreatic calcifications [7]. Recent knowledge clearly prompts us to consider that excessive alcohol consumption alone does not cause CP in animals or humans. It is observed that only a minority (3–7%) of heavy drinkers ultimately develop CP; therefore, alcohol should be considered a cofactor associated with pancreatitis only in conjunction with a specific trigger or other additional yet-to-be identified predisposing genetic or environmental factors [4]. Some genes and various gene polymorphisms (table 1) are able to increase susceptibility to develop CP in alcoholics through an increase of pancreatic progressive damage [8]. Such studies can help us to understand the reasons of the different epidemiologic results concerning the different degree of pancreatic damage in different populations with equal intake of alcohol or to understand why, within the same population, we can observe more frequently alcoholic liver disease rather than pancreatic disease [9].

**Search for a Model of Multiple Risk Factors Interaction**

CP represents a complex multi-step disease without a single etiology, even if the end-stage histology from all etiologies has identical phenotype features. The pancreatic injury may occur through different mechanisms with transition between an acute pancreatitis condition to recurrent pancreatitis and, finally, to CP [10]. Most patients have multiple risk factors and the overall risk is a product of all risk factors in an additive or multiplicative fashion. Recently, a three-domain model of CP was introduced in order to consider the interaction of multiple risk factors that had similar effects [11]. The **metabolic and environmental domain** comprises stressors as alcohol, smoking and other conditions able to give hyperstimulation of the pancreas (hypercalcemia, hyperlipidemia, renal failure and recurrent injuries). Factors in this domain may occur in patients who present mutations of PRSS1, SPINK1 and CFTR genes and who represent the main actors of the **inadequate injury protection domain**. This domain also encompasses some conditions which limit pancreatic duct flushing such as ductal obstruction, pancreas divisum, Oddi’s sphincter stenosis/dysfunction. The area of overlap between these two domains identifies the group of patients who will develop recurrent acute pancreatitis. The third domain is the **altered immune response domain**, which comprises other gene mutations inducing overexpression of cytokines and growth factors and environmental factors such as alcohol, smoking and, more rarely, medications. The pathologic process linked to this domain is mainly oriented to development of pancreatic fibrosis by means of the activation of pancreatic stellate cells. In a normal condition, pancreatic stellate cells, localized at the basal acinar level, are quiescent; factors like oxidative stress, alcohol, cytokines, pancreatic necrosis and others activate these cells with subsequent proliferation and transformation in myofibroblast-like cells, through a complex intracellular pathway involving the kinase system and growth factors [12]. The final product is the synthesis and secretion of type II collagen, leading to an irreversible and spreading pancreatic fibrosis. Development of CP requires an area of overlap of the three domains: metabolic and environmental stresses plus inadequate injury protection plus altered immune response. In other terms, it seems necessary that CP develops a complex interaction between genetic, environmental and immunologic factors. Risk assessment based upon this interpretation may help identify individuals who are likely to develop CP early in the disease course, and pursue a targeted policy to slow or prevent this illness in the future.

**Table 1. Genes able to increase susceptibility to develop CP in alcoholics**

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<th>Gene</th>
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<tr>
<td>α₁-Antitrypsin</td>
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<td>Alcohol dehydrogenase</td>
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<tr>
<td>Cytochrome P&lt;sub&gt;450&lt;/sub&gt;-2E1</td>
</tr>
<tr>
<td>Glutathione S-transferase</td>
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<tr>
<td>Aldehyde dehydrogenase</td>
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<tr>
<td>HLA (human leukocyte antigen)</td>
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**Genetic polymorphism**

N-Acetyltransferase-2 → slow acetylator phenotype

Susceptibility genes involved in the:

a) Intra-acinar protection system against activation of trypsinogen and trypsin-related damage
b) Regulation of immune response
c) Regulation of inflammatory response
References