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CHRONIC PANCREATITIS: AN UPDATE

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ABSTRACT

In Western societies, the commonest association of chronic pancreatitis (CP) is alcohol abuse. Our understanding of the pathogenesis of CP has improved in recent years, though important advances that have been made with respect to delineating the mechanisms responsible for the development of pancreatic fibrosis (a constant feature of CP) following repeated acute attacks of pancreatic necroinflammation (the necrosisfibrosis concept). The pancreatic stellate cells (PSCs) are now established as key cells in fibrogenesis, particularly when activated either directly by toxic factors associated with pancreatitis (such as ethanol, its metabolites or oxidant stress) or by cytokines released during pancreatic necroinflammation. In recent years, research effort has also focused on the genetic abnormalities that may predispose to CP. Genes regulating trypsinogen activation/inactivation and cystic fibrosis transmembrane conductance regulator (CFTR) function have received particular attention. Mutations in these genes are now increasingly recognized for their potential 'disease modifier' role in distinct forms of CP including alcoholic, tropical, and idiopathic pancreatitis. Treatment of uncomplicated CP is usally conservative with the major aim being to effectively alleviate pain, maldigestion and diabetes, and consequently, to improve the patient's quality of life. Surgical and endoscopic interventions are reserved for complications such as pseudocysts, abscess, and malignancy.

Keywords: Pancreatitis, Pathogenesis, Diagnosis, Therapy

1.0 INTRODUCTION

Chronic pancreatitis (CP) is a condition characterized by progressive and irreversible damage to both exocrine and endocrine components of the pancreas, eventually resulting in significant exocrine insufficiency (maldigestion) and diabetes.[1] As such, this update is a natural extension of published report. They reported incidence of CP in industrialized countries ranges from 3.5 to 10 per 100,000 population. Alcohol abuse is the major cause of CP in Western countries, but other factors such as genetic mutations, pancreatic duct obstruction caused by strictures, hypertriglyceridemia, hypercalcemia, and autoimmunity also have been implicated.[1–3] Another distinct, non–alcohol-related form of CP has received increasing attention in recent times is tropical pancreatitis. The pathogenesis of this condition is unknown, although an association with a mutation in a serine protease inhibitor gene (SPINK1) has been proposed.[4] In a minority of cases of CP, no identifiable cause was found and a diagnosis of idiopathic pancreatitis is made.[5] However, it is anticipated that with increasing identification of putative genetic/environmental factors, the numbers of true idiopathic cases of CP will diminish further.

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The key histopathologic features of CP (regardless of etiology) are pancreatic fibrosis, acinar atrophy, chronic inflammation, and distorted and blocked ducts.[1,6] Additional distinctive histologic features have been described in some forms of CP, such as extensive pancreatic calcification in tropical pancreatitis[4] and a prominent lymphocytic and plasma cell infiltrate in autoimmune pancreatitis.[7, 8]

2.0 Clinical Features

The 3 major clinical features of CP are Pain, Maldigestion, and Diabetes.

2.1 Pain

Abdominal pain is the most vexing clinical problem and the most common indication for surgical intervention in patients with CP. Severe pain decreases appetite, thereby contributing to malnutrition and weight loss. The pain is usually epigastric in location although more diffuse pain in the upper abdomen can occur and may radiate to the back. Although recurrent (type A) or continuous (type B) pain is considered to be the hallmark of CP. A subgroup of patients may have no pain at all, presenting instead with symptoms of pancreatic insufficiency. While the course of pain in CP can be unpredictable. In general it is reported pain is improve or resolve with time in the majority of patients. Whether the alleviation of pain coincides with the onset of exocrine insufficiency (according to burn-out hypothesis) is still a matter of debate.[9,10] In patients with known CP, pain also may result from an acute attack of pancreatitis, from a pancreatic pseudocyst, portal, splenic vein thrombosis, or bile duct obstruction (associated with jaundice). Associated gastric or duodenal ulcers also may be the cause of pain in these patients.

2.2 Maldigestion and Diabetes

Steatorrhea and weight loss are further important features of CP. Steatorrhea is a symptom of advanced disease and does not occur until pancreatic lipase secretion is reduced to less than 10% of normal. Maldigestion of lipids occurs earlier than that of other nutrients (proteins and carbohydrates) since lipase secretion decreases more rapidly than protease or amylase secretion. In addition to exocrine insufficiency, diabetes mellitus may develop in the long-term course of the disease. The diabetes is classified as type IIIc according to the American Diabetes Association[11] and is characterized by destruction of both insulin- and glucagon-producing cells. The diabetic state often is fragile because the co-existing deficiency of glucagon synthesis aggravates hypoglycemic situations.

3.0 Classification

Chronic pancreatitis may be separated into 4 different stages:

I. A pre-clinical stage with absent or uncharacteristic symptoms
II. Recurrent acute episodes of pancreatitis without definite signs of CP
III. Further recurrent episodes with intermittent or constant pain in between and signs of CP such as duct dilatation and pancreatic calcification on imaging
IV. A final stage, mostly without acute flares and absence or decreased frequency of pain, possibly associated with evidence of endocrine and exocrine insufficiency (burnout, see below)

Single stages may be skipped, eg, some patients initially may present with a painless stage IV chronic pancreatitis, showing maldigestion, steatorrhea, or diabetes.

4.0 Natural History

The natural history of CP has been difficult to characterize because of the variability in presentation of the disease and the relative inaccessibility of the pancreas to histologic assessment. However, several studies involving large series of medical and surgical cases have provided some important insights in this area.[5 ,9,10, 12– 14]

Alcohol-induced CP usually develops after a prolonged period (5–15 year) of heavy alcohol consumption and does not develop after an isolated bout of heavy drinking. In a recent report analyzed a series of 343 patients with CP included 265 patients with alcoholic CP, 57 with idiopathic CP, and 11 with hereditary pancreatitis. They reported that the median age at onset of alcoholic pancreatitis is 36 years, whereas that of hereditary pancreatitis was as early as 10 years. Idiopathic CP has 2 forms of clinical presentation: an early onset (juvenile) form with a median age at onset of 23 years, and a late-onset (senile) form with a median age at onset of 62 years[10]. Tropical pancreatitis is characterized by an early onset (mean age, 22 years), rapid progression, and severe pancreatic damage in the

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absence of a history of alcohol abuse or biliary disease.[4] On the other hand, autoimmune pancreatitis is reported to occur at a later age, with a mean age at onset of 59.4 years.[8]

The median time to the development of pancreatic insufficiency after disease onset, depends on the type of pancreatitis which is still under consideration. In alcoholic and lateonset idiopathic pancreatitis, exocrine insufficiency develops earlier than in early onset idiopathic pancreatitis[9,10,15]; in alcoholic CP, pancreatic insufficiency can develop as early as 6 years after the onset of disease.[10] Similarly, endocrine insufficiency occurs earlier in alcoholic pancreatitis with a median time of 8 years, compared with 27 years in early onset idiopathic pancreatitis. In tropical pancreatitis, both exocrine and endocrine insufficiency is reported to be evident at very early stages, often at the time of presentation in the majority (70%) of patients.[4]

With respect to the progression of pancreatic insufficiency over time, there are conflicting data, described no change or even slight improvements in pancreatic function over time in patients with CP. In contrast, reported a progressive deterioration of pancreatic function during a median follow-up period of 16 years in patients with alcoholic pancreatitis[10,12,16-18.] The reasons for these discrepant findings are unclear, but may reflect the differences in study design, duration of follow-up evaluation, or differences in the sensitivities of the tests used to assess pancreatic function.

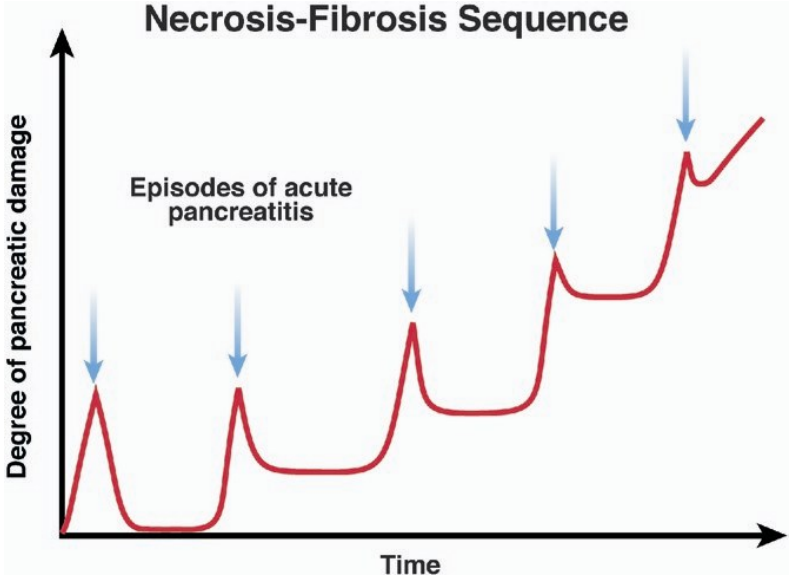

Figure 1. Necrosis-fibrosis concept of progressive pancreatic injury. Repeated attacks of acute pancreatic necroinflammation result in increasing residual damage to the pancreas, eventually resulting in irreversible damage to the gland, characterized by acinar atrophy and fibrosis.

The course of the pain of CP is unpredictable in individual patients. However, in general, pain is reported to improve or resolve with time in the majority of patients with CP. In this regard, it was reported that 240 of 251 patients (95.6%) with alcoholic pancreatitis achieved pain relief after a median time of 10 years (range, 0–30 years) and that, in the majority of patients, this pain relief coincided with the onset of exocrine and endocrine pancreatic insufficiency (pancreatic "burnout")[10]. However, others earlier studies reported no correlation of pain relief with pancreatic insufficiency.[9,12] Abstinence from alcohol is another important factor influencing pancreatic dysfunction and pain in patients with alcoholic CP. Abstainers have a slower rate of deterioration of pancreatic function and a better response to pain therapy than nonabstainers.[10,15,19,20]

The risk of developing pancreatic cancer is significantly higher in patients with CP than in the general population.[21] Alcoholic CP and tropical pancreatitis are associated with a 15-fold and a 5-fold increased risk of pancreatic cancer, respectively,[21,22]whereas the cumulative lifetime risk of cancer in patients with hereditary pancreatitis is reported to be as high as 40%.[21]

Mortality in CP, particularly alcoholic pancreatitis, is approximately one-third higher than that in an age- and sex-matched general population.[23] However, only one fifth of this excess mortality can be attributed directly to pancreatitis itself. Most of the deaths in CP are caused by the effects of alcohol and/or smoking on the liver, lungs, and digestive system. In their recently reported series of alcoholic and idiopathic CP patients, Mullhauptet al[10] reported that the 3 major causes of death were cardiovascular disease, severe infection, and malignancy.

5.0 Pathogenesis of Chronic Pancreatitis

Research into the pathogenesis of CP was initially focused on large and small pancreatic ducts and then on the pancreatic parenchymal and nonparenchymal cells. In more recent times, the genetics of CP has attracted considerable attention and has revolutionized our knowledge of the possible mechanisms mediating pancreatic injury (this topic is discussed in more detail later in the section titled "Genetics of Chronic Pancreatitis"). The majority of studies related to the pathogenesis of CP have focused on alcohol-induced CP. (The focus on alcohol in this article reflects the large amount of available scientific literature on the topic. Relatively little is known about the pathogenesis of acute episodes in tropical or autoimmune pancreatitis, although there is a growing body of literature dealing with autodigestive injury in hereditary acute pancreatitis.) This is not surprising, given that alcohol abuse is the most common

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association of CP. Traditionally, alcoholic pancreatitis has been thought of as a form of CP from the start, punctuated during its course by acute exacerbations. This notion was based on studies showing that histologic and radiologic evidence of CP was evident in the pancreas of many patients at the time of their first attack of pancreatitis.[24,25] Furthermore, autopsy studies had reported evidence of pancreatic fibrosis in alcoholics with no clinical history of pancreatitis.[26] However, this concept has been challenged in recent years, with current opinion favoring the necrosis-fibrosis hypothesis that alcoholic pancreatitis begins as an acute process that progresses to chronic irreversible damage as a result of repeated acute attacks (Figure 1).

The necrosis-fibrosis concept is supported by both clinical and experimental data. A large prospective study has reported that clinical manifestations of CP (exocrine and endocrine dysfunction) were more likely to occur in alcoholics with frequent clinical recurrent acute attacks.[10,15] In addition, a postmortem study of patients with fatal acute alcoholic pancreatitis has shown that in 53% of patients there was no evidence of chronic changes in the pancreas.[27]

Experimental evidence in support of the necrosis-fibrosis hypothesis has accumulated rapidly in recent years and suggests that this concept is applicable not only to alcoholic CP but also to non–alcohol-related pancreatitis (such as hereditary and tropical pancreatitis), in which the clinical course is punctuated with recurrent attacks of pancreatic necroinflammation. Animal models of pancreatic fibrosis have now been developed by inducing repeated episodes of acute necroinflammation in the pancreas using an inhibitor of superoxide dismutase[28] or by administration of supraphysiologic doses of ceruleinwith or without other measures such as ethanol administration or pancreatic duct obstruction.[29,30] Most recently, Vonlaufen et al[31] have demonstrated that repeated pancreatic necroinflammation induced by endotoxin administration in alcohol-fed animals leads to the changes of CP within the gland. The molecular mechanisms responsible for pancreatic fibrosis after necroinflammatory episodes now are understood better, largely due to the characterization of the cells that play a critical role in the fibrogenic process, namely, the pancreatic stellate cells (PSCs; see below).

6.0 Alcohol-Induced Pancreatic Injury

Studies in the field of alcoholic pancreatitis often have been hampered by the lack of suitable animal models of the disease and the difficulty in obtaining human pancreatic tissue for analysis. Nonetheless, significant advances have been made in recent years, particularly with respect to the direct toxic effects of alcohol on the pancreatic acinar cell, which may predispose the gland to necroinflammation and the role of PSCs in the production of pancreatic fibrosis.

Investigations into the pathogenesis of alcoholic pancreatitis usually have followed 1 of 2 approaches, based on 2 fundamental clinical observations. One observation is that the incidence of alcoholic pancreatitis is proportional to the level of alcohol consumption, suggesting the presence of dose-related effects of alcohol on the pancreas.[32–34] The other observation is that only a minority of alcoholics develop pancreatitis, suggesting that an additional cofactor or susceptibility factor is required to trigger overt disease.[35,36]

7.0 Constant Effects of Alcohol on the Pancreas

7.1 Effect of alcohol on large ducts.

Early research efforts in this area (inspired by Opie's[37] observations regarding the mechanism responsible for gallstone pancreatitis) were focused on the effects of alcohol on large ducts and, in particular, the sphincter of Oddi (SO). The large-duct theories (biliary-pancreatic reflux, duodenopancreatic reflux, and the stimulation-obstruction theory) postulated that altered motility of the SO in response to alcohol administration played a central role in the development of the disease. However, unresolved controversy about the effects of alcohol on SO function and pancreatic secretion means that these theories remain of doubtful relevance to the pathogenesis of alcoholic pancreatitis (see review by Apteet al[38]).

7.2 Effect of alcohol on small ducts.

In the 1970s, researchers shifted their focus from large to small pancreatic ducts, mainly as a result of the work of Sarles,[39,40]who proposed that alcoholic pancreatitis was caused by the precipitation of secreted pancreatic proteins within small pancreatic ducts, leading to acinar atrophy and fibrosis. The protein plug theory often has been questioned because of the lack of clear evidence that protein precipitation within pancreatic ducts precedes acinar damage. However, recent reports of an association between mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene (which affect duct cell function) and the risk of developing idiopathic CP have revived interest in the possible role of ductular dysfunction in pancreatic injury.[41,42] The association between CFTR mutations and alcoholic pancreatitis is at present uncertain. Nonetheless, the possibility that the duct cell (in addition to the acinar cell) is an important site of alcohol-induced injury cannot be discounted. In this regard, it is of interest to note that as early as in 1965, Sarleset al[43] had reported that patients with alcoholic pancreatitis manifested increased levels of sweat electrolytes (chloride and sodium), suggesting CFTR dysfunction in this disease.

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There is some evidence to suggest that chronic alcohol consumption facilitates protein plug formation within pancreatic ducts. This includes: (i) increased total protein concentration of pancreatic juice in alcoholics[44]; (ii) an increased capacity of acinar cells to synthesize lithostathine on alcohol exposure[45] (lithostathine is a known constituent of protein plugs with a propensity for precipitation); and (iii) an alcohol-induced decrease in acinar content of glycoprotein GP2[46] (possibly because of increased secretion into pancreatic juice); this glycoprotein has unique self-aggregating properties and is an important constituent of protein plugs. Thus, it is possible that blockage of small intralobular ducts by protein precipitates hinders acinar cell secretion, thereby blocking the exit of digestive enzymes and predisposing the cell to acute autodigestive injury (see below).

7.3 Effect of alcohol on pancreatic acinar cells.

Over the past 3 decades, the focus of research in alcoholic pancreatitis has shifted from pancreatic ducts to the pancreatic acinar cell itself. This focus is understandable given that the cells produce large amounts of digestive enzymes (6–20 g/day), with the potential to cause considerable tissue damage. The acinar cell is normally protected from digesting itself by synthesizing most zymogens as inactive precursors, by segregating zymogens into membrane-bound organelles, and by intracellular antiproteases. Disruption of these normal protective mechanisms results in premature intracellular activation of digestive enzymes, leading to autodigestive injury. Trypsinogen can be autoactivated or activated by the lysosomal enzyme cathepsin B.[47] Active trypsin, in turn, can activate other pro-enzymes and trigger a digestive enzyme activation cascade within the cell.

Evidence to support a role for digestive enzymes in pancreatitis comes from several in vitro and in vivo studies (see Apteet al[48] for a review), but perhaps the most compelling evidence to date in support of this theory has been provided by the identification of mutations in the cationic trypsinogen gene in patients with hereditary pancreatitis. As detailed later in the section on Genetics of Chronic Pancreatitis, 2 mutations in particular (R122H and N29I) are known to be gain-of-function mutations, resulting in the synthesis of an altered form of trypsin that is resistant to inactivation.[2,3,49]A role for digestive enzymes also has been invoked for pancreatitis related to hypercalcemia (via trypsinogen activation and trypsin stabilization) and tobacco smoking (via reduced trypsin inhibitory capacity).[3]

7.4 Effect of Alcohol on Pancreatic Enzymes

Several studies have indicated that chronic alcohol administration produces changes in the acinar cell, which may favor premature activation of digestive enzymes. Apte et al[50] have shown that messenger RNA (mRNA) levels and protein content of the digestive enzymes trypsinogen, chymotrypsinogen, and lipase, as well as the lysosomal enzyme cathepsin B, is increased in the pancreas of alcohol-fed rats. This increase in enzyme content is accompanied by an increase in the fragility of the organelles that contain these enzymes (zymogen granules and lysosomes, respectively).[51,52]The effect of alcohol on lysosomal fragility is thought to be mediated by cholesteryl esters and fatty-acid ethyl esters[53,54] (substances known to accumulate in the pancreas after chronic alcohol consumption[55,56]). The mechanism responsible for the alcohol-induced increase in zymogen granule fragility is unclear, but a study by Apteet al[46] suggests that it may be a consequence of reduced GP2 levels in zymogen granule membranes since this glycoprotein is known to determine the shape and stability of zymogen granules. Alcohol-induced oxidant stress may be another factor that plays a role in lysosomal and zymogen granule membrane destabilization (see below). The net effect of the alcohol-induced increase in digestive and lysosomal enzyme content in the presence of decreased stability of the corresponding organelles would be an increased likelihood of contact between lysosomal and digestive enzymes, thereby leading to premature intracellular activation of digestive enzymes and autodigestive injury to the gland.

7.5 Alcohol Metabolism by Pancreatic Acinar Cells

Taking their cues from studies of ethanol-induced liver toxicity, researchers postulated that ethanol may be metabolized by the pancreatic acinar cell to generate toxic metabolites that may mediate the changes in the subcellular organelles described above. Indeed, in vitro studies with cultured acinar cells and isolated acini have now shown convincingly that the pancreas metabolizes ethanol via both the oxidative and nonoxidative pathways, generating the metabolites acetaldehyde and fatty acid ethyl esters (FAEEs), respectively (see review by Wilson and Apte[57]). Enzymes catalyzing ethanol oxidation (alcohol dehydrogenase, cytochrome P4502E1, and catalase) and nonoxidative ethanol metabolism (FAEE synthase) have been identified in the pancreas. Furthermore, oxidant stress has been shown to occur in both human and rat pancreas after ethanol exposure, most likely because of increased production of reactive oxygen species (known by-products of ethanol oxidation) and decreased antioxidant defenses.

7.6 Effect of Toxic Metabolites of Ethanol

Acetaldehyde, FAEEs, and reactive oxygen species all have been shown to cause deleterious effects on the pancreatic acinar cell (see review by Apteet al[38]). Acetaldehyde causes morphologic damage to both rat and dog pancreas and also has been reported to inhibit stimulated secretion from isolated pancreatic acini. Oxidant stress may contribute to the destabilization of zymogen granules and

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lysosomes observed in ethanol-fed rats (noted earlier). FAEEs also have been shown to damage the pancreas and its subcellular organelles. As reviewed comprehensively by Apte et al,[58]infusion of FAEEs in rats leads to pancreatic edema, acinar vacuolization, and trypsinogen activation, and to increased extracellular matrix protein levels (a finding that may have relevance to the development of alcohol-induced pancreatic fibrosis). Some of the intracellular signaling molecules that may play a role in ethanol-induced acinar cell toxicity have now been identified. Gukovskaya et al[59] have shown that ethanol, acetaldehyde, and FAEEs modulate the levels of transcription factors nuclear factor B and activator protein-1 in parenchymal (acinar) cells, which in turn regulate the expression of cytokines that mediate pancreatic necroinflammation. More recently, FAEEs also have been shown to cause a sustained increase in the second messenger Cawithin acinar cells, an effect that is thought to result in mitochondrial depolarization and cell death.[60]

7.7 Effect of Alcohol on Pancreatic Microcirculation

An aspect of pancreatic physiology that until recently largely had been ignored with respect to the pathogenesis of alcoholic pancreatitis is the microcirculation of the gland. However, 2 recent studies have shown that acute on chronic ethanol administration to rats significantly decreased pancreatic perfusion.[61,62]This effect was associated with an increase in leukocyte adhesion and increased expression of adhesion molecules and cytokines in the pancreas. These studies suggest that ethanolinduced disturbances in pancreatic microcirculation may contribute to the processes of pancreatic injury, but further work is required to confirm and characterize these effects.

8.0 Individual Susceptibility to Alcoholic Pancreatitis

As seen from the preceding discussion, it is clear that alcohol exerts direct, constant, and toxic effects on the pancreas that predispose the gland to autodigestion and necroinflammation. This is most likely the case in all persons who drink heavily. However, as alluded to earlier, it also is clear that only a minority of heavy drinkers develop acute pancreatitis, indicating that an additional insult or second hit is required to precipitate a clinical attack of pancreatitis. The search for this trigger factor/ cofactor/susceptibility factor has prompted numerous studies over the past 2 decades, with a number of possible candidate factors scrutinized. These have included diet, amount and type of alcohol consumed, the pattern of alcohol consumption, hyperlipidemia, and smoking (see Haber et al[63] for review). As discussed in a recent review, the role of smoking in alcoholic pancreatitis is particularly controversial.[64] Several inherited factors have also been studied (as discussed later in the section on Genetics of Chronic Pancreatitis). Therefore, it is somewhat disappointing that despite the extensive search, the factor(s) that unequivocally confer(s) increased susceptibility to alcoholic pancreatitis remain(s) unknown. There remain candidate factors that have not yet been examined fully, including polymorphisms of proteins relevant to cellular antioxidant defenses and polymorphisms of alcohol-metabolizing enzymes, particularly FAEE synthases, minor CF mutations, and environmental factors such as bacterial endotoxin.

Experimentally, putative triggers that have been examined for alcoholic pancreatitis include the secretagogue cholecystokinin (CCK) and bacterial endotoxin. There is some evidence that prior alcohol administration sensitizes rodent pancreas to injury by supraphysiologic levels of CCK,[30,65]but the clinical relevance of CCK as a trigger factor has to be questioned. In human beings CCK is released only in picomolar quantities after meals, therefore it is difficult to envisage a situation in which abnormally high levels of CCK would be released into the circulation to trigger pancreatitis in alcoholics.

In contrast to CCK, endotoxin represents a more plausible, physiologically relevant, trigger factor for alcoholic pancreatitis. This is because: (i) increased gut permeability with translocation of gram-negative bacteria (such as *Escherichia coli*) across the mucosal barrier is known to occur after chronic alcohol intake in both human beings and experimental animals[66,67]; (ii) plasma lipopolysaccharide (LPS, an endotoxin that is a component of bacterial cell walls) levels have been shown to be significantly higher in drinkers (either after chronic alcohol intake or a single binge) compared with nondrinkers[68]; and (iii) endotoxemia is known to be predictive of the severity of acute pancreatitis (regardless of cause). It is of interest, therefore, that a recent study by Vonlaufenet al[31] showed significant pancreatic necroinflammation in alcohol-fed rats injected with 1 dose of LPS, and more importantly, the development of progressive injury as evidenced by pancreatic fibrosis in alcohol-fed rats challenged with repeated doses of LPS.

9.0 Progression of Acute Pancreatitis to Chronic Pancreatitis

As noted earlier, it now is generally accepted that the development of CP is the result of progressive (accrued) pancreatic damage after recurrent episodes of pancreatic necroinflammation. A few years ago, Schneider and Whitcomb[69] proposed the sentinel acute pancreatitis event hypothesis to explain the progression to CP. They postulated that the “sentinel” event in this disease is a bout of acute pancreatic injury, which makes the gland particularly vulnerable, in the recovery phase, to additional insults such as alcohol, metabolic stress, and oxidative stress.

Research efforts toward elucidating the molecular mechanisms of CP, particularly pancreatic fibrosis, were given significant impetus with the identification, isolation, and characterization of stellate cells in the pancreas (reviewed by Apte et al[38,70]). PSCs are similar

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morphologically to hepatic stellate cells, the principal effector cells in liver fibrosis.[71] It is now established that activated PSCs play a key role in the fibrogenic process in CP via their ability to regulate both the synthesis and degradation of the extracellular matrix proteins that comprise fibrous tissue.[38 , 70]

Evidence from both clinical and experimental studies indicates a role for PSCs in ethanol-induced pancreatic fibrosis (see Apteet al[38] for review). In vivo studies of tissue from human beings with alcoholic pancreatitis and from animals with experimental pancreatic fibrosis have shown the presence of activated PSCs in areas of fibrosis. In vitro studies have established that PSCs are activated directly by ethanol and acetaldehyde as assessed by increased extracellular matrix (ECM) protein production by the cells. Of particular interest is the observation that rat PSCs show alcohol dehydrogenase activity, indicating that, apart from parenchymal (acinar) cells, ethanol also can be metabolized by nonparenchymal cells in the pancreas. Activation of PSCs by ethanol can be completely inhibited by the alcohol dehydrogenase (ADH) inhibitor 4-methylpyrazole, indicating that ethanol-induced PSC activation likely is mediated by its oxidative metabolite, acetaldehyde. Furthermore, both ethanol and acetaldehyde cause oxidant stress within cultured PSCs and, importantly, incubation of PSCs with ethanol or acetaldehyde in the presence of the antioxidant vitamin E prevents the activation of PSCs by the 2 compounds. These findings suggest that ethanol-induced PSC activation is most likely mediated by its metabolism (via ADH) to acetaldehyde, and the subsequent generation of oxidant stress within the cells. Interestingly, the observations by Vonlaufenet al[31] of pancreatic fibrosis in alcohol-fed rats challenged with LPS are strongly supported by the in vitro findings of a synergistic effect of alcohol and LPS on PSC activation.

During prolonged heavy alcohol intake, PSCs could be exposed not only to ethanol and its metabolites and LPS, but also to proinflammatory cytokines released during episodes of ethanol-induced pancreatic necroinflammation. Cytokines such as tumor necrosis factor , interleukins 1 and 6, monocyte chemotactic protein, transforming growth factor , platelet-derived growth factor (known to be up-regulated during acute pancreatitis) each have been reported to activate PSCs in vitro.[38] Of particular note is that PSCs are themselves capable of synthesizing cytokines, and endogenous cytokine production by the cells is stimulated by factors such as ethanol, acetaldehyde, and other cytokines.[72,73] These observations suggest that, in addition to paracrine pathways of activation, PSCs also may be activated in an autocrine manner (via endogenous cytokines), which could cause perpetuation of cell activation, even when the initial trigger factors are no longer present. Such persistent PSC activation may potentiate ECM production by the cells, eventually causing pancreatic fibrosis.

From the above, it is apparent that during chronic alcohol consumption, PSCs are likely to be activated by 2 pathways operative in vivo—the necroinflammatory pathway (via cytokines) and the nonnecroinflammatory pathway (direct effects of ethanol and its metabolites and oxidant stress). The identification of a nonnecroinflammatory pathway of stellate cell activation implies that tissue necrosis or inflammation may not be an absolute prerequisite for the stimulation of fibrogenesis in the pancreas during alcohol abuse.

10.0 Pathogenesis of Autoimmune Pancreatitis

Autoimmune pancreatitis (AIP) is a relatively uncommon, non–alcohol-related form of CP that has received increasing attention in recent years. Only about 150 cases worldwide have been reported to date (the majority being from Japan).[7] Autoimmune pancreatitis is characterized by the presence of (i) increased serum gammaglobulin levels (particularly IgG4); (ii) the presence of autoantibodies (antinuclear antibodies, antilactoferrin antibodies, anticarbonic anhydrase antibodies, and rheumatoid factor); (iii) pancreatic fibrosis with lymphocytic infiltration and an absence of pancreatic calcification; (iv) an association with other autoimmune diseases; and (v) response to steroid therapy. The majority view of pancreatologists is that AIP does not present as acute attacks. However, Takayamaet al[74] reported that a third of AIP patients on prednisolone therapy in their series suffered from recurrent attacks of acute pancreatitis over a median follow-up period of 54.5 months. The pathogenesis of this disease remains largely unknown but from clinical and experimental studies it is postulated that aberrant HLA-DR expression (in AIP HLA-DR expression has been found on pancreatic ductal and acinar cells) leads to the presentation of autoantigens to lymphocytes, resulting in an autoimmune response.

11.0 Genetics of Chronic Pancreatitis

More than 50 years ago, it was recognized for the first time that CP may cluster in selected families, suggesting an inherited disease in these patients.[75] The underlying genetic defect, however, remained obscure for more than 4 decades. As stated in this first report on inherited pancreatitis, “hereditary chronic relapsing pancreatitis does not present earmarks which distinguish it from nonhereditary chronic relapsing pancreatitis.”[75] In 10%–30% of patients suffering from CP, no apparent underlying cause, including heredity, can be identified. Recent research indicates that a significant percentage of these patients with so-called *idiopathic CP* may also have a genetic basis for their condition. The section below delineates the different genes involved in the pathogenesis of hereditary or idiopathic pancreatitis, the impact of these genetic discoveries on other types of CP such as alcohol-related CP and tropical calcific pancreatitis, and the implications for disease pathogenesis.

11.1 Cationic Trypsinogen(PRSS 1)

In 1896, Chiari[76] postulated that pancreatitis results from autodigestion of the gland. An inappropriate conversion of pancreatic zymogens to active enzymes within the pancreatic parenchyma was proposed to initiate the inflammatory process. A key role has been attributed to the activation of trypsinogen to trypsin, converting all proteolyticproenzymes to their active form. Three different trypsinogens have been described in human pancreatic juice and have been designated, according to their electrophoretic mobility, as cationic trypsinogen (PRSS1), anionic trypsinogen (PRSS2), and mesotrypsinogen (PRSS3). Compared with the anionic isoenzyme, the cationic trypsinogenautoactivates more easily and is more resistant to autolysis.

By linkage analysis, several groups located a gene for hereditary pancreatitis on the long arm of chromosome 7 (7q35). Subsequently, a mutation in the cationic trypsinogen gene, also referred to as *serine protease 1* (*PRSS1*) (OMIM 276000), was identified as 1 of several possible underlying defects. In 5 families, a c.365GA transition leading to a substitution of arginine by histidine at residue 122 (p.R122H) segregated with the disease. [77] R122H appears to be the most common *PRSS1* mutation observed worldwide. Subsequent studies have reported other *PRSS1* alterations including p.A16V, p.N29I, p.N29T, p.R116C, and p.R122C, as well as several others, in families with suspected hereditary pancreatitis or in patients without a family history (for detailed information of the different variants see: www.uni-leipzig. de/pancreasmutation). The functional relevance of PRSS1 mutations has been examined by studies using recombinant cationic trypsinogen subjected to site-directed mutagenesis. Mutations such as N29I and R122H enhance trypsinogenautoactivation; R122H also inhibits autolysis of the active enzyme.[78,79]Thus, gain-of-function mutations leading to enhanced intrapancreatictrypsinogen activation may be the common initiating step of pancreatitis caused by *PRSS1* mutations, whereas stabilization of trypsin may be an accessory mechanism.

Two *PRSS1* variants, p.E79K and p.A16V, display unique features: E79K trypsinogen does not alter catalytic activity or autolysis of trypsin, nor does it influence inhibition of its activity by the trypsin inhibitor SPINK1. However, it activates anionic trypsinogen, PRSS2, at least 2-fold better than wild-type cationic trypsin. Thus, E79K can lead to increased trypsinogen activation by transactivation of PRSS2 instead of autoactivation,[80]but its pathogenic relevance remains to be elucidated because this variant also has been found in healthy controls. Recombinant A16V also has no effect on trypsinogen activation. Instead, it increases (by 4-fold) the rate of activation peptide processing mediated by chymotrypsin C, resulting in accelerated trypsinogen activation in vitro.[81] In contrast to R122H and N29I, which display a penetrance of 70%–80%, A16V is found almost exclusively in patients without a family history of pancreatitis.[82] Recently, a triplication of an approximately 605-kb segment containing *PRSS1* and *PRSS2* was reported in 5 families with hereditary pancreatitis.[83] Thus, besides point mutations, a gain of trypsin through a gene-dosage effect also may contribute to the disease pathogenesis. The importance of *PRSS1* mutations as pathogenic mediators in hereditary pancreatitis is supported by a recent study using a transgenic mouse model expressing mutant R122H mouse trypsinogen. The pancreas of these mice displayed early onset acinar injury, inflammatory cell infiltration, and enhanced response to cerulein-induced pancreatitis. With progressing age, pancreatic fibrosis and acinar cell dedifferentiation developed.[84]

11.2 Anionic Trypsinogen (PRSS2)

Because increased proteolytic activity caused by mutated *PRSS1* enhances the risk for CP, it was thought that mutations in the anionic isoenzyme*PRSS2* (OMIM 601564) also may predispose to disease. Notably, however, a recent study indicated that the PRSS2 mutation may be a protective factor against CP. A recent study reported a c.571GA transition resulting in substitution of glycine by arginine at codon 191 (p.G191R), which was found in 220 of 6459 (3.4%) controls but only in 32 of 2466 (1.3%) patients (odds ratio, 0.37; P 1.110^{-8}).[85] Further analyses showed that patients (with hereditary, idiopathic, and alcoholic pancreatitis) with G191R were of an older age than those without the protective variant. In vitro studies showed that recombinant G191R protein, on activation by enterokinase or trypsin, showed a complete loss of trypsin activity due to the introduction of a novel tryptic cleavage site that renders the enzyme hypersensitive to autocatalytic proteolysis. Thus, it appears that the G191R PRSS2 variant mitigates intrapancreatic trypsin activity, thereby playing a protective role against CP. Although the overall contribution of G191R to disease pathogenesis is low, the functional characterization of G191R provides the first example in pancreatitis for a disease-protective genetic variant.

11.3 Serine Protease Inhibitor, Kazal Type 1 (SPINK 1)

The serine protease inhibitor, Kazal type 1 (*SPINK1*) (OMIM 167790), also known as *pancreatic secretory trypsin inhibitor*, is thought to be a potent inhibitor of intrapancreatic trypsin activity. SPINK1 was first isolated in the bovine pancreas by Kazal et al in 1948.[86] It possesses a reactive site that serves as a specific target for trypsin. However, trypsin inhibition by SPINK1 is only temporary because the trypsin-SPINK1 complex itself serves as a substrate for trypsin, resulting in the subsequent degradation of the inhibitor molecule and restoration of the original trypsin activity.[87]

The focus on SPINK1 mutations as possible pathogenetic factors in pancreatitis was the result of the knowledge that a significant number of hereditary pancreatitis patients do not show a *PRSS1* mutation, indicating that defects in other genes might be involved in disease pathogenesis. It was hypothesized that, in addition to gain-offunction mutations in *PRSS1* as a cause of pancreatitis, CP also

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may be a result of "loss-of-function" mutations in pancreatic trypsin inhibitors. A mutation in the *SPINK1* gene (a c.101AG transition leading to substitution of asparagine by serine at codon 34 [p.N34S]) has been found in 18 of 96 unrelated pediatric pancreatitis patients; 6 patients were homozygous for this mutation.[88] No phenotypic differences between heterozygous and homozygous N34S patients were detected. This association between N34S and CP has now been confirmed by several other studies.

N34S is found mostly in patients without a family history of CP: 15%–40% of patients with so-called *idiopathic CP* carry N34S on 1 allele or on both alleles. Data from 8 large studies in Europe and the United States indicate that 12.6% of patients with CP are heterozygous and 3.6% are homozygous for N34S, whereas only 1.9% of controls are heterozygous for this variant. Interestingly, the N34S mutation also has been reported in about half the patients with tropical calcific pancreatitis from India.[89] The pathogenic action of N34S, however, remains elusive. Recombinant N34S mutated human SPINK1 does not show any altered trypsin inhibitor capacity.[90] It is worth noting that N34S is in complete linkage disequilibrium (LD) with 4 other intronic sequence variants: c.56-37TC, c.87268AG, c.195-604GA, and c19566_-65insTTTT.[88] Thus, it may be speculated that it is one of these intronic alterations and not N34S itself that is the pathogenic relevant mutation.

The second most common *SPINK1* mutation, c.1942TC, affects position 2 of the splice donor site in the third intron, which is highly conserved in eukaryotes. Analysis of mutated mRNA shows a truncated *SPINK1* because exon 3 is skipped.[91] Several other *SPINK1* alterations have been described in recent years, mainly in single patients or families only (for detailed information of the different variants see: www.unileipzig.de/pancreasmutation). With the exception of a few mutations that strongly suggest a loss of function by destruction of the ATG initiation codon (c.2TC) or by shift of reading frame with premature termination (c.27delC, c.98dupA), the functional consequences of most variants are unknown. Recently, expression studies of 2 dominant inherited mutations affecting the signal peptide, c.41TC (p.L14P) and c.41TG (p.L14R), reported a rapid intracellular degradation of the mutant inhibitor molecules leading to abolished SPINK1 secretion.[92] Similar to and perhaps even more pronounced than for *PRSS1*, *SPINK1* mutations display a marked variability of penetrance and inheritance pattern. Some variants that are likely to lead to complete functional loss of the mutated allele such as c.2TC, c.27delC, or codon 14 mutations, appear to follow a dominant trait, whereas the N34S variant appears to be a recessive or complex trait.
The role of SPINK1 in pancreatitis has been evaluated recently in 2 genetically engineered animal models. Transgenic expression of rat *Spink1* in mice, which leads to an increased endogenous trypsin inhibitor capacity by 190%, significantly reduced the severity of cerulein-induced pancreatitis,[93]while targeted disruption of *Spink3* (the murine homologue of human *SPINK1*) resulted in autophagic degeneration of acinar cells, impaired regeneration, and death within 2 weeks after birth.[94] In the latter model, enhanced tryptic activity was detected in pancreatic acini prepared 1 day after birth.[95]

11.4 Cystic Fibrosis Transmembrane Conductance Regulator (CFTR)

Cystic fibrosis transmembrane conductance regulator (CFTR) is an apical membrane chloride channel critical for fluid and electrolyte secretion in the respiratory and digestive tracts. In the pancreas, CFTR is localized to centroacinar and proximal ducts and regulates ductal bicarbonate secretion. Abnormal CFTR function as a result of CFTR gene mutations is associated with CF, an autosomal-recessive disease characterized by pulmonary dysfunction and pancreatic insufficiency. A minority of CF patients suffer from recurrent pancreatitis. In 1998, 2 studies described an association between idiopathic CP and mutations in the *CFTR* gene (OMIM 602421).[96,97] One study tested 134 patients with CP, including 60 patients with idiopathic and 71 patients with alcoholinduced disease, for 22 mutations.[97] Eighteen patients (13.4%), including 12 with idiopathic CP (20%), were heterozygous for a *CFTR* mutation. The frequency of *CFTR* mutations in alcohol-related CP was twice what was expected and in idiopathic CP it was 4 times as expected. In the other study, 17 *CFTR* mutations in 27 patients with idiopathic CP were investigated.[41] Seven patients (25.9%) had at least 1 *CFTR* mutation and 1 patient was compound heterozygous. The frequency of *CFTR* mutations in idiopathic CP was 6 times higher than expected. However, both these studies only investigated the most common of the approximately 1000 *CFTR* mutations that now have been described. Subsequent studies analyzing the complete *CFTR* coding sequence as well as *PRSS1* and *SPINK1* in idiopathic CP patients found that 25%–30% of patients carried at least 1 *CFTR* mutation, but that only a few patients were compound heterozygous.[98,99]Thus, idiopathic CP actually may represent "atypical" cystic fibrosis caused by the combination of 2 mild or of 1 mild and 1 severe *CFTR* mutation. Several CP patients, however, were transheterozygous for a *CFTR* alteration and a *SPINK1* or *PRSS1* variant, illuminating the significance of the combination of mutations in different genes in disease pathogenesis.[98 , 99]

12.0 Alcoholic Pancreatitis

The association between alcohol abuse and pancreatitis is well established, but individual susceptibility to alcohol varies widely and only a minority of heavy drinkers develop CP. Increasing evidence portends that additional environmental or genetic cofactors are necessary, which are mostly unknown. Several studies investigating *PRSS1*, pancreatitis associated protein, $_1$-antitrypsin, *CFTR*, cytokeratin 8, major histocompatibility complex antigens, and alcohol metabolizing or detoxifying enzymes have yielded negative or conflicting results.

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Since xenobiotic-mediated cellular injury is thought to play a role in the pathogenesis of alcoholic CP, genetic variations reducing the activity of detoxifying biotransformation enzymes have also been examined. Recently, a low detoxification activity allele of the UDP-glucuronosyltransferase 1A7, *UGT1A7*3*, was linked to pancreatic cancer and alcoholic CP.[100] However, a subsequent study could not confirm these findings.[101]

In a large multicenter study, an association between mutated *SPINK1* and alcoholic CP was described: the N34S mutation was found in 16 of 274 (5.8%) patients with alcoholic CP, but only in 4 of 540 (0.8%) healthy control individuals and 1 of 98 (1.0%) alcoholic controls without CP.[102] Subsequent studies have reported an N34S frequency in alcohol-related CP of around 6 %. Most recently, the protective *PRSS2* variant, G191R (see below), was reported to be significantly less common in patients with alcoholic CP compared with healthy controls (5 of 609 [0.8%] vs 220 of 6459 [3.4%]; *P* .0001).[85]

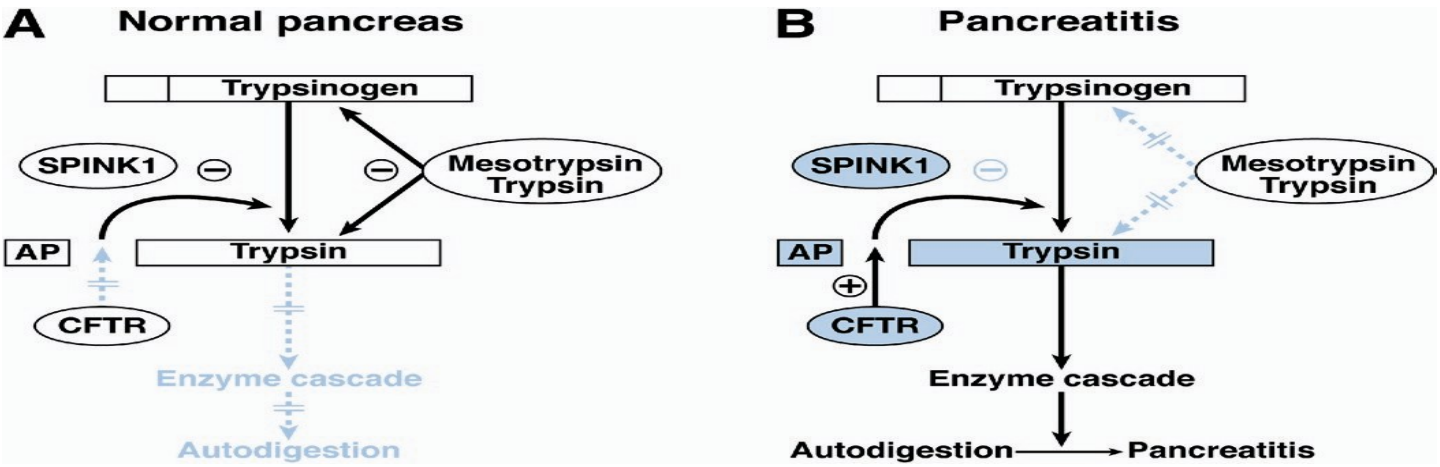

Figure 2. Role of digestive enzymes in pancreatitis. (*A*) Normal pancreas. Trypsin resulting from autoactivation of trypsinogen within the pancreatic parenchyma is inhibited by SPINK1 and also by mesotrypsin or trypsin (as a second-line defense). This defense mechanism prevents the pancreas from activating the pancreatic enzyme cascade and autodigestion. (*B*) Pancreatitis. Mutations in *PRSS1* or in *SPINK1* lead to an imbalance of proteases and their inhibitors within the pancreatic parenchyma, resulting in an inappropriate activation of pancreatic zymogens with subsequent autodigestion and inflammation. Mutations in *CFTR* also may disturb the delicate balance between proteases and antiproteases, by intrapancreatic acidification or by defective apical trafficking of zymogen granules, thereby facilitating the intrapancreatic activation of digestive enzymes. *Dark boxes* represent products of mutated genes. AP, activation peptide. Modified from Witt et al.[85]

For a long time, hereditary pancreatitis was thought to be a rare disorder. However, the findings of *PRSS1*, *SPINK1*, and *CFTR* mutations in patients with so-called *idiopathic CP* indicate that cases of inherited CP are much more common than originally envisioned. These data challenge the differentiation between “hereditary” and “idiopathic” pancreatitis. Different mutations in different genes might lead to different phenotypic presentations and inheritance patterns, and even the same mutation in the same gene might have different consequences depending on the individual’s genetic background and environmental factors. The discovery of *SPINK1* mutations in other types of CP such as tropical calcific pancreatitis and alcohol-induced CP further blurs the borders between the particular CP subtypes. It is anticipated that the identification of other genes involved in the pathogenesis of inherited CP will also enhance our knowledge about more common types of CP such as alcoholic or tropical CP. Future research most likely will reveal a very complex interaction between various environmental and genetic factors, with flowing transitions among these subtypes (Figure 3).

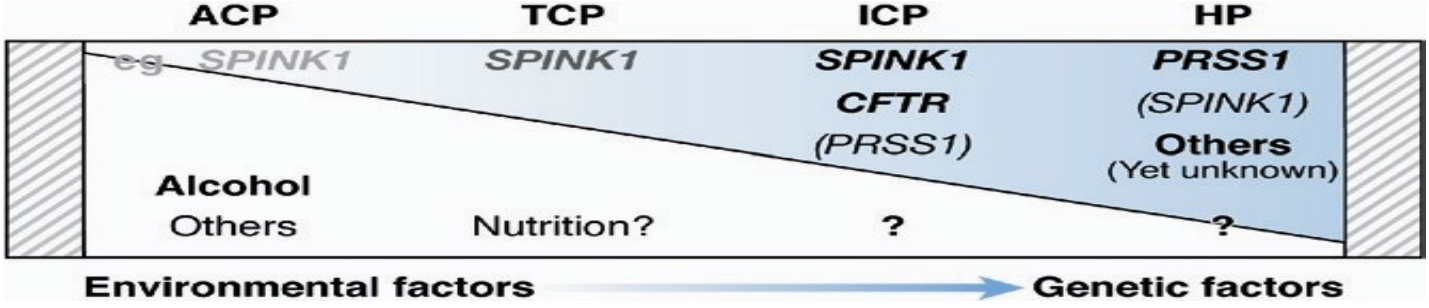

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Figure 3. Influence of different environmental and genetic factors on the pathogenesis of chronic pancreatitis. ACP, alcoholic chronic pancreatitis; TCP, tropical calcific pancreatitis; ICP, idiopathic pancreatitis; HP, hereditary pancreatitis.

13.0 Current Concept of the Pathogenesis of Chronic Pancreatitis

The clinical and experimental evidence (largely based on alcohol-related studies) has led to the following concept for the pathogenesis of CP (Figure 4).

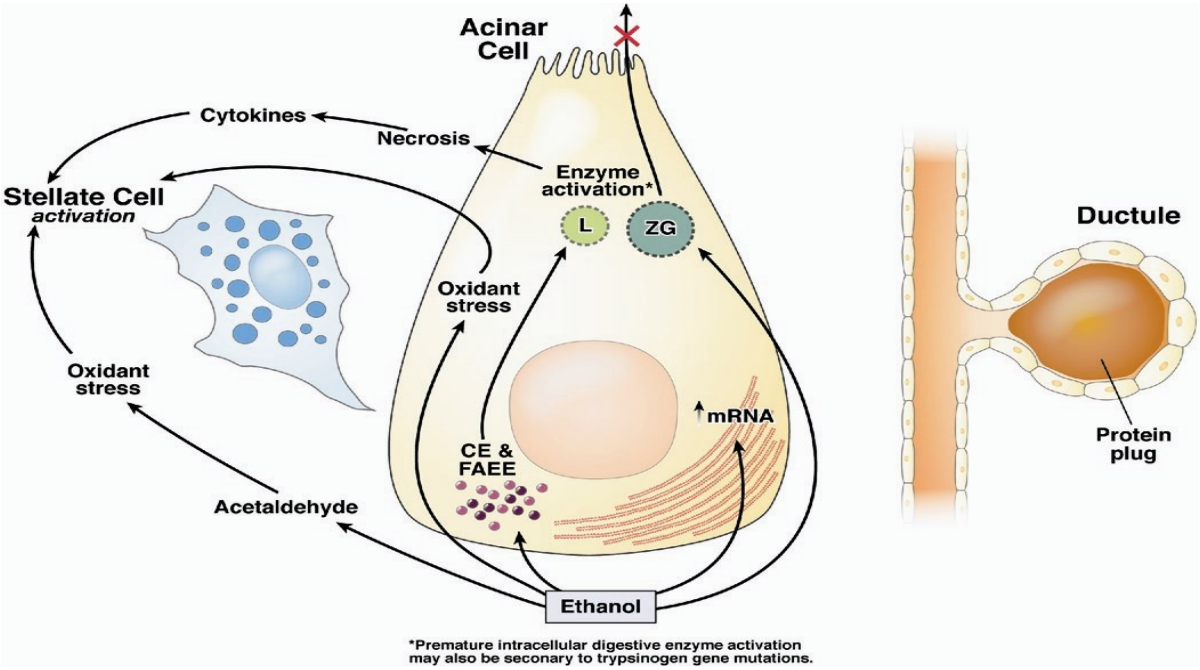

Figure 4. Current concept of the pathogenesis of chronic pancreatitis. Three major elements of the pancreas are implicated in the development of irreversible pancreatic damage. (1) An acinar cell that is susceptible to autodigestive injury for the following reasons (depending on cause): (a) the effects of ethanol and its metabolites on subcellular organelles including increased digestive and lysosomal enzyme content (secondary to increased synthesis [increased mRNA] and impaired secretion) and destabilization of lysosomes and zymogen granules; (b) impairment of trypsinogen activation/deactivation processes. In the presence of an appropriate trigger factor, overt acinar cell injury is initiated. (2) A pancreatic stellate cell that is activated by cytokines released during pancreatic necroinflammation or by direct effects of ethanol, its metabolites, and oxidant stress, leading to excessive extracellular matrix protein production. (3) A pancreatic ductule blocked by protein precipitation, which may further facilitate disease progression. AC, acetaldehyde; CE, cholesteryl esters; L, lysosome; ZG, zymogen granule.

The pancreas may be rendered susceptible to autodigestive injury, either because of abnormal trypsin activation/inactivation mechanisms (as in hereditary, metabolic, and tropical pancreatitis) or because of the effects of toxins such as ethanol (via its metabolites and its metabolic by-products) on digestive and lysosomal enzyme content within the acinar cell and on the stability of the organelles that contain these enzymes. An appropriate trigger factor (environmental or genetic) then stimulates overt pancreatic necrosis. Repeated episodes of acute necroinflammation (regardless of etiology) and the release of proinflammatory cytokines leads to the activation of pancreatic stellate cells (PSCs). PSCs also are activated directly by ethanol (via its metabolite acetaldehyde and the subsequent generation of oxidant stress). Persistent activation of PSCs leads to an imbalance between extracellular matrix protein synthesis and degradation, eventually resulting in pancreatic fibrosis, a cardinal feature of CP.

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14.0 Diagnosis of Chronic Pancreatitis

The diagnosis of CP relies on relevant symptoms, imaging modalities to assess pancreatic structure, and assessment of pancreatic function. The diagnostic gold standard of early stage disease would be an adequate surgical biopsy, which is rarely available. However, because the primary lesions of early stage CP are usually focal, fine-needle biopsy examinations may

yield false-negative results. In the absence of definite signs of CP, it often is difficult to differentiate early stage disease from recurrent acute pancreatitis. For a definitive diagnosis, a careful history and follow-up may be necessary. It is important that the assessment of a patient with painful CP includes upper gastrointestinal endoscopy, abdominal ultrasonography, and endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography (MRCP) in order to detect a potentially reversible cause of pain (eg, peptic ulcer, pseudocyst, common bile duct stricture).

The correlation between structural and functional impairment of the pancreas in CP is often poor.[103] Patients with severe exocrine insufficiency may have a largely normal pancreatic structure and vice versa. In general, advanced stages of CP may be diagnosed easily by imaging procedures such as ultrasound, computerized tomography (CT), magnetic resonance tomography, and magnetic resonance cholangiopancreatography (MRCP). In contrast, the diagnosis of early disease presents a considerable challenge.

The biochemical, structural, and functional parameters used to assist in the diagnosis of CP are discussed below:

14.1 Serum Parameters

IIn patients presenting with pain, levels of pancreatic enzymes (mainly lipase) are determined in order to identify an acute episode of the disease. In patients without acute attacks, reduced serum trypsinogen, lipase, or amylase levels may be found; however, the sensitivities of these tests are less than 60%, so none of them per se are helpful in diagnosing CP.[104]

14.2 Imaging Procedures

Several imaging procedures are available for the evaluation of CP. Transabdominal ultrasound and computerized tomography are the most commonly used techniques, whereas endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasonography (EUS), and MRCP usually are restricted to specialized centers.

14.3 Abdominal X-ray

Plain abdominal x-ray has lost its place in the modern diagnostic imaging paradigm. Nonetheless, in some cases, calcification on an abdominal x-ray when associated with steatorrhea can clinch the diagnosis and obviate the need for a further, more extensive, work-up.

14.4 Transabdominal Ultrasonography

Transabdominal ultrasonography is an inexpensive technique representing the first procedure usually performed in patients with suspected CP. Duct alterations, calcification, and cysts and are detected with high sensitivity by this modality. Other complications of pancreatitis such as duodenal or gastric distention and bile duct dilatation also may be demonstrated. In patients with excessive abdominal gas or acute pancreatitis associated with ileus, the view is often limited, making the procedure highly related to the investigator’s skills. Nevertheless, sonography is a simple technique and, in the hands of experienced investigators, remains a useful method for rapid and reliable diagnosis.

14.5 Endoscopic Retrograde Cholangiopancreatography (ERCP)

ERCP is regarded as the gold standard for the detection of CP. Typical alterations of pancreatic ducts observed on ERCP are dilatations, stenoses, and abnormalities of the side branches. The duct structure also may be used to stage the disease according to the Cambridge classification.[105] However, Cambridge stage I is often questioned as a reliable finding indicating CP. The most important role of ERCP is the identification of structural abnormalities such as duct stenosis, stones, or cysts that may be amenable to interventional treatment and, the exclusion, if possible, of pancreatic cancer. It is to be noted that ERCP eventually may be superseded by a noninvasive alternative, namely MRCP, for the diagnosis of CP.

14.6 Endoscopic Ultrasonography (EUS) and Magnetic Resonance Cholangiopancreaticography (MRCP)

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The role of endosonography for diagnosing early stage CP is not well defined. The technique is regarded as the most sensitive procedure to detect the disease. Thirteen criteria, such as reduced or increased echogenicity, increased lobulation, and alteration of small and large ducts, have been described.[106] It is accepted that the absence of these criteria reliably rules out CP, whereas the presence of 5 or 6 criteria strongly indicates the diagnosis.[107] The significance of less than 5 criteria, however, is unclear. Apart from interobserver variability, one has to take into account the fact that a nonhomogeneous echo structure is not a specific sign for CP but also can be seen in the normal pancreas, especially in the elderly.[108] There have been 2 follow-up studies of patients with suspected CP with a normal ERCP, but with alterations on EUS. One study showed no alterations on ERCP during a follow-up period of 12–38 months,[109]whereas the other suggested a rapid progression of disease because ductal changes were observed on ERCP after a mean follow-up period of 18 months in 22 of 38 patients.[110] The latter finding indicates a surprisingly rapid progression to CP.

At present, it is still unclear what criteria may be used to diagnose mild CP reliably in patients with a normal ERCP. MRCP is regarded as useful in patients at high risk of developing post-ERCP pancreatitis, with a low probability of ductal alterations, or inaccessibility of the pancreatic duct as a result of pancreatic or gastric surgery.[111]

15.0 Diagnosis of Pancreatic Cancer in Chronic Pancreatitis

As noted earlier, patients with CP have an increased risk of developing pancreatic cancer.[21] Currently, no imaging procedure can reliably detect a malignant tumor reliably in patients with CP. A recent study reported that 2-(18)F)-fluoro-2-deoxy-D-glucose positron emission tomography can differentiate between neoplastic and inflammatory pancreatic tumors at a sensitivity of 91% and a specificity of 87%.[112] However, whether 2-(18)F)-fluoro-2-deoxy-D-glucose positron emission tomography is superior to traditional imaging techniques such as CT or magnetic resonance imaging (MRI) is questionable because the latter also have been reported to classify CP and pancreatic cancer correctly in 90% of patients.

16.0 Functional Studies

The secretin-cerulein test is regarded as the “gold standard” for the detection of exocrine pancreatic insufficiency. [113] However, the procedure is only available in a few specialized centers and its protocol as well as its evaluation is not well standardized. In addition, the test is time consuming and uncomfortable for the patient. Therefore, less invasive alternatives have been developed including fecal elastase, lipase, or chymotrypsin; the pancreolauryl test; the bentiromide test; and a variety of breath tests using radiolabeled pancreatic substrates, usually triolein. However, none of these tests have been able to meet clinical needs unequivocally. In mild or moderate pancreatic insufficiency, the sensitivity of these tests is inadequate. It is only in severe disease that pancreatic function tests show a high sensitivity[114]; however, the diagnosis of severe CP is usually obvious by other means, making a pancreatic function test unnecessary. In patients with mild or moderate disease, pancreatic function tests only achieve sensitivities of 50% and 65 %–75%, respectively, and hence they are not very helpful in the diagnostic work-up of patients with recurrent pain of unclear origin. Other MRI–derived tests have been described, but the majority of these studies did not assess patients with mild or moderate CP.[115,116]

17.0 Treatment of Chronic Pancreatitis

The treatment of CP is mainly symptomatic and is directed toward the cardinal features of pain, and exocrine and endocrine insufficiency. A diagnosis of CP does not necessarily require treatment because patients may be asymptomatic. However, if a precipitating factor such as an anatomic anomaly or a metabolic disease can be identified, it may be treated by surgical or medical intervention. In general, the therapeutic strategies for CP include abstinence from alcohol and cigarette consumption, pain relief, correction of exocrine and endocrine insufficiency, nutritional support, and endoscopic or surgical intervention.

In alcoholic patients, the major goals of treatment are sustained abstinence from alcohol and smoking, the improvement of compliance, and social re-integration. Most alcoholic patients are heavy smokers and, clinically, it can be difficult to achieve abstinence from both alcohol and tobacco. In a practical sense, the treating physician may have to concede continued smoking as a trade-off for alcohol abstinence. Although the role of alcohol abstinence in the reduction of pancreatic pain is somewhat unclear, there is evidence to indicate that deterioration of pancreatic function is slower in abstainers than in nonabstainers,[9,20]and that abstainers have a better response to pain therapy than nonabstainers. The role of smoking as an causative factor in CP is controversial.[64,117,118] Nonetheless, cigarette consumption contributes to the excess mortality associated with the condition.

17.0 Pain

In CP, abdominal pain is a serious clinical problem leading to a markedly compromised quality of life and, potentially, narcotic addiction. Treatment of pain should be started with conventional analgesics such as acetaminophen. If pain relief is not achieved,

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additional prescription of opiates may be necessary. However, it is important to be mindful of the well-known side effects of opioids such as central nervous system depression, alterations of gastrointestinal motility, and induction of dependence. Other, as yet unproven, strategies of pain relief include inhibition of pancreatic enzyme secretion using pancreatic enzyme therapy and the use of antioxidants. Invasive approaches such as celiac plexus block, endoscopic procedures, and surgical drainage and resection also have been used as therapy for the pain of CP, but none of these procedures has ever been the subject of controlled trials either in comparison with medical therapy or with no therapy.

17.2 Treatment of Exocrine Insufficiency

In theory, pancreatic enzymes are indicated in patients with steatorrhea (fecal fat 7 g/day) and weight loss. In clinical practice, however, measurement of fecal fat rarely is performed, so that the decision for enzyme replacement is based on an assessment of the patient's clinical state. The dose of pancreatic enzymes given should be high enough to treat steatorrhea, but a significant increase of body weight is rarely achieved. These enzymes should be taken with meals in acid-protected (enteric-coated) formulations (except in patients after gastric surgery, ie, Kausch–Whipple resection). Approximately 25,000–50,000 U lipase/meal are recommended, but a higher dose or combination with a proton pump inhibitor may be required.

17.3 Treatment of Diabetes

Diabetes in CP is classified as type IIIc.[11] However, the treatment is not different from patients with type I diabetes. Due to the co-existing deficiency of glucagon, patients with CP have an increased risk of hypoglycemic events. This is a particular problem in patients with poor compliance and/or continued alcohol consumption or autonomic neuropathy. In these patients, the therapeutic goal should be to avoid hypoglycemia by a simple insulin regimen. As indicated earlier, the survival of patients with alcoholic CP is limited. Approximately 50% of patients will not live longer than 10 years after the initial diagnosis and therefore will not benefit from aggressive insulin therapy. A more intensive insulin regimen is indicated only in patients with good compliance and cessation of alcohol. Acarbose and insulin sensitizers are ineffective.

17.4 Nutrition

There is no such thing as a specific pancreatic diet. Abstinence from alcohol and the intake of smaller but more frequent meals is recommended. Restriction of fat intake is not advised if the pancreatic exocrine insufficiency is largely compensated by enzyme-replacement therapy. Restriction of dietary fat and administration of medium-chain triglycerides (MCTs) is indicated only in cases of severe maldigestion refractory to treatment since MCTs may worsen diarrhea in many patients. Deficiencies of fat-soluble vitamins are found mainly in patients who continue to drink; in these cases vitamin supplementation can be instituted

.

17.5 Interventional Treatment of Complications

There is a long-standing controversy concerning the indication(s) for interventional (mainly endoscopic) therapy of complications of CP such as duct stones, pancreatic or biliary tract stenosis, or pseudocysts. There has been a profound lack of randomized controlled studies, resulting in therapeutic decisions largely being made on the basis of technical skills available rather than scientific evidence. Many centers perform interventional therapy only in symptomatic patients with recurrent pain or acute attacks, associated with ductal dilatation proximal to the stenosis or an obstructive stone. Some evidence exists that stenting a biliary stenosis is inferior to surgery; transitional stenting has been shown to be effective only in patients with a mass in the head of the pancreas obstructing the pancreatic duct.[119] Interventional therapy is obligatory in patients with cyst-associated pain, gastric compression, or biliary obstruction when alternatives are absent (eg, if surgery is refused by the patient or the surgeon).

17.6 Surgery

Indications for surgery include complications such as common bile duct or duodenal obstruction, failure of endoscopic therapy in a patient with intractable pain, or a suspected pancreatic cancer.[120] Like endoscopic therapy, surgical procedures for pain in CP have never been subjected to randomized controlled trials comparing them with medical therapy or no therapy. In patients with pain and an inflammatory tumor of the head of the pancreas, a duodenum-preserving resection of the head is the method of choice in many centers.[121] As an alternative procedure, a longitudinal prancreaticojejunostomy may be considered if the main pancreatic duct is dilated to 7 mm or more.[122]

18. Conclusion

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In summary, CP is characterized by progressive and ultimately irreversible pancreatic injury that manifests clinically as maldigestion and diabetes. Alcohol abuse is the most common association of CP in the Western world. Important advances have been made in recent years with respect to our understanding of the pathogenesis of this disease, particularly related to the mechanisms responsible for the development of pancreatic fibrosis (a cardinal feature of CP) after repeated acute attacks of pancreatic necroinflammation (the necrosisfibrosis concept). The pancreatic stellate cell is now established as playing a central role in fibrogenesis, particularly when activated either directly by toxic factors associated with pancreatitis (such as ethanol, its metabolites, or oxidant stress) or by cytokines released during pancreatic necroinflammation. Considerable research effort also has been directed toward the genetic abnormalities that may predispose to CP. Mutations of several candidate genes related to trypsinogen activation/inactivation and to CFTR function increasingly are being recognized for their potential disease-modifier role in distinct forms of CP including alcoholic, tropical, and idiopathic pancreatitis. Treatment of uncomplicated CP is usually conservative, with the major aim being to effectively alleviate pain, maldigestion, and diabetes, and, consequently, to improve the patient's quality of life. Surgical and endoscopic interventions are reserved for complications such as pseudocysts, abscesses, and malignancies.

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