Molecular Mechanisms of Alcoholic Pancreatitis

M.V. Apte  R.C. Pirola  J.S. Wilson
Pancreatic Research Group, University of New South Wales, Sydney, Australia

Key Words
Alcohol · Alcoholic pancreatitis · Autodigestion · Pancreatic fibrosis

Abstract
Alcoholic pancreatitis is a major complication of alcohol abuse. Since only a minority of alcoholics develop pancreatitis, there has been a keen interest in identifying the factors that may confer individual susceptibility to the disease. Numerous possibilities have been evaluated including diet, drinking patterns and a range of inherited factors. However, at the present time, no susceptibility factor has been unequivocally identified. In contrast, considerable progress has been made with respect to the constant effects of alcohol on the pancreas. The molecular mechanisms of alcohol-induced pancreatic injury are being increasingly defined with an emphasis, in recent years, on the acinar cell itself as the principal site on ethanol-related damage. It has now been established that the acinar cell is capable of metabolizing alcohol and that the direct toxic effects of alcohol and/or its metabolites on acinar cells may predispose the gland to autodigestive injury in the presence of an appropriate triggering factor. A significant recent development relates to the characterization of pancreatic stellate cells, increasingly implicated in alcoholic pancreatic fibrosis. Here the current concepts regarding the mechanisms/pathways mediating alcohol-induced pancreatic injury are outlined.

Introduction
The heavy medical and social burdens imposed by alcoholic pancreatitis have prompted research into the pathogenesis of this disease. Studies have been hampered by the lack of suitable animal models of alcoholic pancreatitis and the difficulty in obtaining human pancreatic tissue for analysis. Nonetheless, considerable progress has 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 necro-inflammation) and the characterization of pancreatic stellate cells (PSCs) as key effector cells in alcohol-induced pancreatic fibrosis. Here the research findings that influence current thinking regarding the molecular mechanisms responsible for alcoholic-induced pancreatic injury are discussed. Investigations into the pathogenesis of alcoholic pancreatitis have usually followed one of two approaches, based on two fundamental clinical observations. The first is that only a minority of alcoholics develop pancreatitis, indicating that certain individuals have an increased susceptibility to the disease [1, 2]. The second is that the risk of developing alcoholic pancreatitis increases with increasing alcohol consumption, suggesting a dose-related effect of alcohol on the pancreas [3–5].

Factors Influencing Individual Susceptibility

Over the past two decades, a number of candidate factors that may confer susceptibility to alcoholic pancreatitis have been examined. These include diet [6], amount
and type of alcohol consumed [6, 7], the pattern of alcohol consumption [6], lipid intolerance [8] and smoking [9, 10]. Inherited factors have also been studied. These are detailed elsewhere in this book and therefore not individually referenced here. They include blood group antigens, HLA serotypes, α1-antitrypsin phenotypes, cystic fibrosis genotype, genotypes of cytokines (tumor necrosis factor-α (TNF-α), transforming growth factor-β (TGF-β), interleukin-10), genotypes of alcohol-metabolizing enzymes (alcohol dehydrogenase (ADH), cytochrome P4502E1 (CYP2E1)), genotypes of enzymes that detoxify metabolites of alcohol (such as glutathione S transferases), and mutations of genes related to pancreatic proteins that may play an important role in autodigestive injury to the gland (these include digestive enzymes and proteins that can inactivate digestive enzymes such as pancreatic secretory trypsin inhibitor, mesotrypsin and enzyme Y). Generally speaking, these studies into individual susceptibility have failed to provide a uniform explanation for the majority of cases of alcoholic pancreatitis. Most recently, a positive association has been reported between the risk of developing alcoholic pancreatitis and a polymorphism of the carboxyl ester lipase (CEL) gene [11]. CEL, a digestive enzyme secreted by the exocrine pancreas, catalyses the synthesis of fatty acid ethyl esters (FAEEs) from fatty acids and ethanol. As discussed in detail below, FAEEs are non-oxidative metabolites of ethanol that are thought to play a significant role in pancreatic acinar cell injury. While the reported association of a CEL gene polymorphism and alcoholic pancreatitis is of considerable interest, it must be noted that the functional significance of the polymorphism is yet to be elucidated. Thus, the search for individual susceptibility factors continues.

Constant Effects of Alcohol on the Pancreas

The remainder of this article will be confined to the constant effects of alcohol on the pancreas. Over the past 30 years, the focus of research in this area has shifted from the sphincter of Oddi to small pancreatic ducts and subsequently to the pancreatic acinar cell itself. The role of the sphincter of Oddi in alcoholic pancreatitis remains unclear principally due to a lack of consensus about the effects of alcohol on sphincter activity. In humans, both decreased [12, 13] and increased [14] sphincter of Oddi activity in response to alcohol have been reported. Studies with experimental animals support the latter finding, i.e. a ‘spasmogenic’ effect of alcohol on the sphincter [15].

In this regard, a recent study has reported a significant reduction in transspincteric flow in possums treated with intravenous ethanol [16]. Thus, alcohol-induced sphincter of Oddi spasm may be one of the mechanisms responsible for the decrease in pancreatic secretion observed after acute alcohol administration in humans [17].

In the early 1970s, the focus of attention moved to small pancreatic ducts. Sarles [18, 19] proposed that alcoholic pancreatitis is caused by the blockage of small ducts by protein plugs (formed by the precipitation of secreted pancreatic proteins) leading to acinar atrophy and fibrosis. The main reservation regarding the protein plug theory is the lack of clear evidence that protein precipitation within pancreatic ducts precedes acinar damage. This has made it difficult to determine whether protein plugs are a cause or an effect of pancreatic injury. However, the possibility that acinar and ductal changes occur simultaneously in alcoholic pancreatitis and play a synergistic role in the development and progression of the disease cannot be ruled out. As early as in 1965, Sarles et al. [20] reported that patients with alcoholic pancreatitis manifest increased levels of sweat electrolytes (chloride and sodium), suggesting cystic fibrosis transmembrane regulator dysfunction in this disease. On the other hand, alcohol has been shown to induce changes in acinar cell function that may potentiate the formation of protein plugs via increased synthesis of proteins known to have a tendency to precipitate in pancreatic juice, such as lithostathine and glycoprotein 2 (GP2).

Over the past few years, researchers have turned their attention to the pancreatic acinar cell itself as a possible initial site of injury in alcoholic pancreatitis. This focus is understandable given that the cell produces large amounts of digestive enzymes with the potential to cause considerable tissue damage. Taking their cues from studies of ethanol toxicity in the liver [21], investigators have postulated that ethanol metabolism by the pancreatic acinar cell and the resulting molecular alterations in the cell predispose the cell to significant injury. The findings that support this concept are detailed below.

Ethanol Metabolism by Pancreatic Acinar Cells

It is now established that the pancreas has the capacity to metabolize ethanol. Previous studies in the liver have shown that there are two major pathways of ethanol metabolism, oxidative and non-oxidative. These generate
the metabolites acetaldehyde and FAEEs, respectively [22–24]. Oxidative ethanol metabolism involves the conversion of ethanol to acetaldehyde, a reaction that is catalyzed by ADH with contributions from CYP2E1 and possibly also catalase. Non-oxidative metabolism of ethanol involves its conversion to FAEEs via FAEE synthases.

**Oxidative Pathway**

**ADH**

In cultured pancreatic acinar cells, Haber et al. [22] used ion exchange chromatography to demonstrate oxidation of $^{14}$C-ethanol to its oxidative product $^{14}$C-acetate. The rate of ethanol oxidation (particularly at high concentrations of 50 mM) was comparable to that observed in hepatocytes cultured under the same conditions. These investigators also provided evidence (via studies on the kinetics of ethanol oxidation and the use of specific ADH inhibitors) that the observed ethanol oxidation is mediated by the class III isotype of ADH. A subsequent study by Gukovskaya et al. [23] using isolated pancreatic acini has corroborated the above findings. Gukovskaya et al. have demonstrated that pancreatic ADH has a high $K_m$ for ethanol and is not inhibited by 4-methylpyrazole (an ADH class I and II inhibitor), supporting the conclusion that the ADH isoform in pancreatic acinar cells is most likely ADH III.

**CYP2E1**

As noted earlier, another enzyme that plays a role in ethanol oxidation, particularly at high ethanol concentrations and after chronic ethanol consumption, is CYP2E1. The presence of CYP2E1 has been demonstrated in rat pancreas [25] as well as in human pancreas [26] by immunoblotting and immunohistochemical techniques, respectively. Moreover, chronic ethanol administration has been shown to induce the expression of CYP2E1 in the rat pancreas [25], an effect similar to that described in the liver [27]. Despite this, CYP2E1 has not been found to contribute appreciably to pancreatic ethanol oxidation (based on enzyme inhibitor studies) in cultured pancreatic acinar cells [22]; however, it must be noted that this was an acute study examining the effect of ethanol on acinar cells isolated from chow-fed animals. In order to fully delineate the role of CYP2E1 in the pancreas, it would be necessary to examine ethanol oxidation in acinar cells isolated from rat pancreas where CYP2E1 has been induced by chronic ethanol administration.

**Non-Oxidative Pathway**

**FAEEs**

With regard to the non-oxidative pathway of ethanol metabolism, there is evidence that FAEEs accumulate in both the human [28] and rat pancreas [29] after ethanol consumption. It is likely that this accumulation is due to the generation of the compounds within the pancreas itself. This notion is supported by studies showing the formation of FAEEs in isolated pancreatic acini incubated with ethanol [23, 24] and the demonstrated presence of FAEE synthase activity in the pancreas [23, 30]. Candidate FAEE synthase enzymes in the pancreas are CEL and triglyceride lipase. Pancreatic CEL has been shown to exhibit FAEE synthetic activity and can therefore be confirmed as a FAEE synthase [31]. However, the FAEE synthetic activity of triglyceride lipase has not yet been fully characterized.

**Relative Contributions of Pathways of Pancreatic Ethanol Metabolism**

The established ability of the pancreas to metabolize ethanol via both oxidative and non-oxidative pathways, has prompted investigators to examine (i) the relative contribution of the two pathways to pancreatic ethanol metabolism, and (ii) the possible metabolic link between the pathways (i.e. whether inhibition of one of the pathways causes an increase in the flux of ethanol metabolism through the other). The rate of oxidative metabolism of ethanol in the pancreas has been found to be consistently higher than that of non-oxidative metabolism of ethanol [23, 24]. However, this finding does not necessarily diminish the significance of non-oxidative metabolism of ethanol within the pancreas, because tissue levels of the products (FAEEs) generated by this pathway have been shown to be sufficient to cause injury to subcellular organelles within the gland (vide infra) [32].

The possibility of a metabolic link between the two pathways of ethanol metabolism has been examined by Werner et al. by both in vitro [30] and in vivo [33] studies. The authors report that, in rat pancreatic homogenates incubated with ethanol in the presence of inhibitors of oxidative metabolism, the formation of FAEEs was increased compared to that in the absence of the inhibitors. However, inhibition of oxidative metabolism per se and/or inhibition of relevant enzymes (particularly ADH) was not measured in this experimental setting, preventing a firm conclusion as to the existence of a metabolic link between the two pathways. More recently, Werner et al. [33] have reported an in vivo study where acute infusion of ethanol and inhibitors of oxidative metabolism led to...
Evidence that Ethanol Administration Induces Pancreatic Injury

Animal models of both acute and chronic ethanol administration have been employed to study alcohol-related morphological and metabolic changes in the pancreas. These are discussed in detail elsewhere and therefore only a summary of the salient findings is provided here. Acute in vivo infusion of ethanol to rats has been reported to cause dose-dependent injury to the pancreas characterized by pancreatic edema, acinar vacuolization and activation of trypsinogen [33]. Chronic (continuous) intragastric infusion of ethanol with high dietary fat for 4 weeks has also been reported to cause pancreatic edema and focal changes including inflammatory cell infiltration and acinar necrosis [34]. However, the 'unphysiological' nature of ethanol administration in this model is a drawback. The Lieber-DeCarli pair-feeding model represents a more physiological method of chronic ethanol feeding than the intragastric model, since it allows ad libitum intake of an ethanol-containing liquid diet [35]. This method of ethanol administration does not produce overt pancreatic injury, but has been shown to induce a number of metabolic changes within the cell [36]. These include a significant increase in the content of digestive enzymes and lysosomal enzymes within the acinar cell, accompanied by a significant decrease in the stability of the organelles that contain these enzymes (zymogen granules and lysosomes, respectively). Basal pancreatic (acinar cell) secretion has recently been reported to be inhibited in ethanol-fed rats [37]. Inhibition of pancreatic secretion due to ethanol may occur at several levels including the sphincter of Oddi (spasm) [14, 15], pancreatic ducts (protein plug formation) [5] and acinar cells (disturbances in exocytosis possibly due to acetaldehyde-induced microtubular dysfunction [38] or to ethanol-induced reorganization of F-actin in the apical cytoskeleton of acinar cells as has been described in a recent in vitro study using isolated acini [39]). A decrease in acinar secretion may further increase the content of digestive enzymes in the cells. This increase in enzyme content together with the increased potential for contact between lysosomal enzymes (particularly cathepsin B, known to be capable of activating trypsinogen [40, 41]) and digestive enzymes could result in premature intracellular activation of digestive enzymes and, in the presence of an (as yet unknown) triggering agent, an overt attack of pancreatitis.

One of the candidate trigger factors that has been investigated is cholecystokinin (CCK). Early studies with CCK have provided conflicting results with chronic ethanol administration reported to either intensify [42] or have no effect [43] on the severity of CCK-induced pancreatitis in rats. A later report indicates that chronic ethanol administration via gastrostomy catheters sensitizes the rat pancreas to the development of CCK-induced pancreatitis [44]. This effect has been recently confirmed by Perides et al. [45] in mice using the more physiological Lieber-DeCarli model of chronic ethanol administration. Viral infection has recently been postulated as another triggering factor for alcoholic pancreatitis. In this regard, Clemens and Jerrells [46] have reported that mice receiving the Lieber-DeCarli ethanol diet demonstrated increased pancreatic injury upon infection with Coxsackie B virus compared to pair-fed controls.

In addition to the alterations in pancreatic digestive enzymes, chronic ethanol feeding has also been reported to induce changes in two 'non-digestive' pancreatic proteins (lithostathine and GP2) that may be relevant to protein plug formation within pancreatic ductules. Chronic ethanol administration increases the capacity of the pancreas to synthesize lithostathine [47]. As noted earlier, lithostathine is a major component of protein plugs. It is postulated that the increased synthesis of lithostathine may lead to increased concentrations of the protein in pancreatic juice. Hydrolysis of native lithostathine in pancreatic juice by proteases such as trypsin is known to generate lithostathine S1 – a form of lithostathine that polymerizes at neutral pH forming a nucleation site/nidus for further protein deposits. Chronic ethanol administration has also been shown to decrease the content of GP2 in pancreatic homogenates [48]. One of the mechanisms responsible for the reduction in pancreatic GP2 content is increased secretion into pancreatic juice. GP2 is known to form fibrillar aggregates within the juice that may form a nidus for protein and calcium precipitation.
Thus alcohol-induced alterations in acinar cell secretion of lithostathine and GP2 may potentiate protein plug formation within pancreatic ducts.

**How Does Ethanol Metabolism Cause Pancreatic Injury by Acinar Cells?**

Ethanol metabolism within the pancreas has the potential to contribute significantly to the ethanol-related pancreatic damage via direct effects of the metabolites acetaldehyde and FAEEs, and/or via metabolic alterations induced within the cells such as changes in the intracellular redox state and the generation of oxidant stress.

Acetaldehyde (albeit at high concentrations) has been shown to cause morphological damage to both the rat and dog pancreas [49, 50]. It has also been reported to inhibit stimulated secretion from isolated pancreatic acini [38, 51]. This inhibition is thought to be secondary to interference with the binding of secretagogues to their receptors [51] and possibly, microtubular dysfunction affecting exocytosis from the acinar cell [38]. During the oxidation of ethanol to acetaldehyde, and subsequently acetate, hydrogen ions (reducing equivalents) are released [21, 52]. This alters the intracellular redox state of the cell (as indicated by a reduced [NAD]/[NADH] ratio and increased [lactate]/[pyruvate] ratio) leading to a number of metabolic alterations that could contribute to acinar injury [21].

Oxidant stress is another important consequence of ethanol oxidation that may play a role in pancreatic injury. Both acute and chronic ethanol exposures are known to cause oxidant stress in the rat pancreas [53, 54]. Evidence of oxidant stress has also been reported in the pancreas of patients with alcoholic chronic pancreatitis [55, 56]. In general, oxidant stress results from an imbalance between the production of free radicals or reactive oxygen species (highly reactive molecules with the potential to damage lipid membranes, intracellular proteins and DNA) and the antioxidant defense mechanisms within the cell (including glutathione, the enzymes glutathione peroxidase, superoxide dismutase and catalase and their co-factors such as vitamin C, vitamin E, zinc and selenium). The mechanisms responsible for oxidant stress secondary to ethanol exposure include acetaldehyde-induced depletion of reduced glutathione [57, 58] and the increased generation of free radicals during the metabolism of ethanol via CYP2E1 [59].

FAEEs, products of non-oxidative ethanol metabolism, have been shown to induce pancreatic injury in vivo [60] as well as in vitro [32]. Werner et al. [60] have reported that infusion of FAEEs into rats leads to pancreatic edema, acinar vacuolization and activation of trypsinogen, while Haber et al. [32] have shown that FAEEs destabilize lysosomes within pancreatic acinar cells. FAEE toxicity may be mediated by (i) direct interaction of the compounds with cellular membranes [61], (ii) release of free fatty acids by hydrolysis of FAEEs (a process thought to contribute to FAEE-induced mitochondrial damage) [62], and (iii) promotion of the synthesis of cholesterol esters (compounds that are known to accumulate in the rat pancreas after chronic ethanol administration [63] and to destabilize lysosomal membranes in vitro [32]).

In summary, evidence from in vivo and in vitro studies indicates that ethanol influences acinar cell function in a way that predisposes the cell to autodigestive injury. Chronic ethanol exposure (i) increases the content of digestive and lysosomal enzymes within the acinar cell via an increase in synthesis and a decrease in secretion (secondary to inhibition of exocytosis due to microtubular dysfunction and/or F-actin reorganization within the cell); (ii) decreases the stability of the organelles that contain digestive enzymes and lysosomes (possibly mediated via FAEE, cholesteryl esters and/or oxidant stress), and (iii) potentiates protein plug formation within ductules (which could further block acinar secretion and cause local and upstream effects). Taken together, these effects may facilitate the activation of digestive enzymes by lysosomal enzymes within the acinar cell and, in the presence of an appropriate trigger factor, initiate autodigestion.

**Progression of Alcoholic Acute Pancreatitis to Chronic Pancreatitis**

The histopathological spectrum of alcoholic pancreatitis ranges from acute pancreatitis (acinar necrosis and inflammation) to chronic changes involving the loss of acinar cells and fibrosis [64]. Alcoholic pancreatitis has been traditionally thought of as a form of chronic pancreatitis from the start, punctuated during its course by acute exacerbations. This notion was based on studies showing that histological and radiological evidence of chronic pancreatitis was apparent in the pancreas of many patients at the time of their first attack of pancreatitis [65, 66]. Furthermore, autopsy studies had reported evidence of pancreatic fibrosis in alcoholics with no clinical history of pancreatitis [67].
The above concept has been challenged in recent years, with current opinion favoring the ‘necrosis-fibrosis’ hypothesis that alcoholic pancreatitis begins as an acute process which progresses to chronic irreversible damage as a result of repeated acute attacks. This hypothesis is supported by both clinical and experimental data. A large prospective study has reported that clinical manifestations of chronic pancreatitis (exocrine and endocrine dysfunction) were more likely to occur in alcoholics with clinical recurrent acute infl ammations [68]. In addition, a postmortem study of patients with fatal alcoholic pancreatitis has demonstrated that in 53% of the patients there was no evidence of chronic changes in the pancreas [69]. Experimental evidence in support of the necrosis-fibrosis hypothesis has accumulated rapidly in recent years – animal models of pancreatic fibrosis have now been developed by inducing repeated episodes of acute necro-infl ammation in the pancreas using an inhibitor of superoxide dismutase inhibitor [70] or administration of supraphysiological doses of cerulein with or without other measures such as ethanol administration or pancreatic duct obstruction [44, 45, 71, 72].

Pathogenesis of Alcoholic Pancreatic Fibrosis

Research efforts in elucidating the mechanisms of alcoholic pancreatic fibrosis were given significant impetus with the identification, isolation and characterization of stellate cells in the pancreas [73–75]. PSCs are morphologically similar to hepatic stellate cells, the principal effector cells in liver fi brosis [76]. It is now established that activated PSCs play a key role in the fi brogenic process via their ability to regulate both the synthesis and degradation of extracellular matrix proteins that comprise fi brous tissue [77].

There is evidence from both clinical and experimental studies indicating a role for PSCs in ethanol-induced pancreatic fi brosis. In vivo studies of tissue from humans with alcoholic pancreatitis and from animals with experimental pancreatic fi brosis have demonstrated the presence of activated PSCs in areas of fi brosis [36, 78, 79]. In vitro studies have established that PSCs are activated directly by ethanol and acetaldehyde as assessed by increased extracellular matrix protein production by the cells [80]. Of particular interest is the observation that rat PSCs exhibit ADH activity [80], indicating that, apart from parenchymal (acinar) cells, ethanolic metabolism can also be metabolized by non-parenchymal cells in the pancreas. Initial studies using the ADH inhibitor 4-methylpyrazole have indicated that the isotype of ADH in PSCs is ADH I (in contrast to the ADH III isotype reported in acinar cells). Further work to characterize the kinetics of ADH activity in PSCs and to examine the non-oxidative pathway of ethanol metabolism in these cells is needed.

Activation of PSCs by ethanol can be completely inhibited by the ADH inhibitor 4-methylpyrazole, indicating that ethanol-induced PSC activation is likely mediated by its oxidative metabolite, acetaldehyde. Both ethanol and acetaldehyde have been shown to cause oxidant stress within cultured PSCs, as indicated by increased formation of the lipid peroxidation product malondialdehyde [80]. Incubation of PSCs with ethanol or acetaldehyde in the presence of the antioxidant vitamin E has been shown to prevent the activation of PSCs by the two compounds [80]. 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.

During prolonged heavy alcohol intake, PSCs could be exposed not only to ethanol and its metabolites but also to pro-infl ammatory cytokines released during episodes of ethanol-induced pancreatic necro-infl ammation. Cytokines such as TGF-β, platelet-derived growth factor, TNF-α, interleukins 1 and 6 and monocyte chemotactic protein are known to be upregulated during acute pancreatitis and each of these has been reported to activate PSCs in vitro [81, 82].

In view of the above, two fi brogenic pathways (acting in parallel) may be proposed to explain the development of alcohol-related pancreatic fi brosis: the necro-infl ammatory pathway (activation of PSCs by cytokines released during ethanol-induced acinar cell necrosis), and the non-necro-infl ammatory pathway (direct activation of PSCs by ethanol via acetaldehyde and/or oxidant stress). The identification of a non-necro-infl ammatory pathway of stellate cell activation implies that tissue necrosis or inflammation may not be an absolute prerequisite for the stimulation of fi brogenesis in the pancreas during alcohol abuse. This concept is supported by a recent study which describes activation of hepatic stellate cells in the absence of hepatitis in liver biopsies from alcoholic patients [83].

Signal Transduction Mechanisms in Alcoholic Pancreatitis

In view of the injurious effects of ethanol and its metabolites on parenchymal and non-parenchymal pancreatic cells, attention has recently focused on the cell signal-
ing pathways that may be responsible for mediating the observed changes. In this regard, Gukovskaya et al. [23, 84] have shown that ethanol and its metabolites acetaldehyde and FAEEs regulate the transcription factors NF-κB and AP-1 in parenchymal (acinar) cells, which in turn, regulate pancreatic cytokine expression. With respect to non-parenchymal cells (PSCs), two recent studies have described induction of the mitogen-activated protein kinase pathway (a major pathway regulating protein synthesis in mammalian cells), by ethanol and acetaldehyde [85, 86]. Additional signaling molecules that have been recently implicated in ethanol-induced PSC activation include PI3 kinase and protein kinase C [87, 88]. It is envisaged that identification of relevant signaling molecules may enable specific pathways to be therapeutically targeted so as to prevent/reduce the deleterious effects of ethanol on the pancreas.

**Current Concept of the Molecular Mechanisms of Alcoholic Pancreatitis**

The findings of clinical and experimental studies related to alcohol and the pancreas form the basis of our concept of the drinker’s pancreas (fig. 1). This may be defined as a gland that is predisposed to autodigestive injury due to the effects of ethanol (via its metabolites and its metabolic byproducts) on digestive and lysosomal enzyme content within the acinar cell and on the stability of the organelles that contain these enzymes. In the presence of an appropriate trigger, the above ethanol-induced metabolic changes result in overt pancreatic necrosis. Repeated episodes of acute necro-inflammation and the release of pro-inflammatory cytokines leads to activation of PSCs. PSCs are also 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.


8 Haber PS, Wilson JS, Apte MV, Hall W, Goumas K, Pirola RC: Lipid intolerance does not account for susceptibility to alcoholic and gallstone pancreatitis. Gastroenterology 1994; 106:742–748.


