World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v16.i11.1314

World J Gastroenterol 2010 March 21; 16(11): 1314-1320
ISSN 1007-9327 (print)

TOPIC HIGHLIGHT

Natalia A Osna, MD, PhD, *Series Editor*

Alcoholic pancreatitis: Lessons from the liver

Dahn L Clemens, Katrina J Mahan

Dahn L Clemens, Katrina J Mahan, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, NE 68198-8090, United States; Research Service, Veterans Administration Medical Center, 4101 Woolworth Avenue, Omaha, NE 68105, United States
Author contributions: Clemens DL and Mahan KJ contributed equally to this work.
Supported by (in part) Grant No. AA016310 to Clemens DL
Correspondence to: Dahn L Clemens, PhD, Research Service, Veterans Administration Medical Center, 4101 Woolworth Avenue, Omaha, NE 68105,
United States. dclemens@unmc.edu
Telephone: +1-402-9953738 Fax: +1-402-4490604
Received: December 21, 2009 Revised: January 28, 2010
Accepted: February 4, 2010
Published online: March 21, 2010

Abstract

The association between alcohol consumption and pancreatitis has been recognized for over 100 years. Despite the fact that this association is well recognized, the mechanisms by which alcohol abuse leads to pancreatic tissue damage are not entirely clear. Alcohol abuse is the major factor associated with pancreatitis in the Western world. Interestingly, although most cases of chronic pancreatitis and many cases of acute pancreatitis are associated with alcohol abuse, only a small percentage of individuals who abuse alcohol develop this disease. This situation is reminiscent of the association between alcohol abuse and the incidence of alcoholic liver disease. The liver and the pancreas are developmentally very closely related. Even though these two organs are quite different, they exhibit a number of general structural and functional similarities. Furthermore, the diseases mediated by alcohol abuse in these organs exhibit some striking similarities. The diseases in both organs are characterized by parenchymal cell damage, activation of stellate cells, aberrant wound healing, and fibrosis. Because of the similarities between the liver and the pancreas, and the alcohol-associated diseases of these organs, we may be able to apply much of the knowledge that we have gained regarding the effects of alcohol on the liver to the pancreas.

Key words: Alcoholic pancreatitis; Alcohol metabolism; Stellate cells; Fibrosis

Peer reviewer: Richard Hu, MD, MSc, Division of Gastroenterology, Department of Medicine, Olive view-UCLA Medical Center, 14445 Olive View Drive, Los Angeles, CA 91342, United States

Clemens DL, Mahan KJ. Alcoholic pancreatitis: Lessons from the liver. *World J Gastroenterol* 2010; 16(11): 1314-1320 Available from: URL: http://www.wjgnet.com/1007-9327/full/v16/i11/1314.htm DOI: http://dx.doi.org/10.3748/wjg.v16.i11.1314

INTRODUCTION

Alcohol abuse is a major cause of morbidity and mortality in the United States; each year it is responsible for more than 100 000 deaths and directly or indirectly costs over 185 billion dollars[1]. Alcohol affects every organ system in the body causing a variety of disorders. Although not the most common alcohol-associated disease, alcoholic pancreatitis is one of the more painful and serious consequences of alcohol abuse.

Alcoholic pancreatitis has been recognized for well over 100 years, yet it remains one of the least understood alcohol-associated diseases. The natural course of alcoholic pancreatitis is not well known. This is, in part, a result of the fact that traditionally pancreatitis has been classified by morphology rather than etiology, as well as the fact that confusing and imprecise criteria have been used to differentiate between different types of pancreatitis. Additionally, there is no good animal model of chronic pancreatitis, and progression of this disease in human beings has been difficult to elucidate.

The mechanism(s) by which alcohol abuse induces alcoholic pancreatitis is not well understood. Although it is evident that alcohol abuse can have an important role in the development of pancreatitis, it does not appear that alcohol abuse alone is responsible for the development of pancreatitis. Rather, it appears that ethanol sensitizes the pancreas to injury and other factors are required to actually develop alcoholic pancreatitis. A number of factors, including cigarette smoking, high-lipid diet, genetics, and infections have been suggested as possible cofactors[2].

There are a number of similarities between alcoholic liver disease and alcoholic pancreatitis; there are also a number of differences. In this review we will attempt to highlight some of the similarities, as well as some of the important differences between alcoholic liver disease and alcoholic pancreatitis. It is hoped that this approach will provide further insight into the pathogenesis of alcoholic pancreatitis.

ALCOHOLIC PANCREATITIS: ACUTE *VS* CHRONIC

Pancreatitis is a necroinflammatory disease that is normally classified as either acute or chronic. In developing countries, alcohol abuse has been reported to be the second most common factor associated with acute pancreatitis. In these countries, alcohol abuse is associated with approximately 35% of the cases[3]. Inappropriate intracellular activation of trypsinogen has long been considered an initiating event in acute pancreatitis, resulting in destruction of pancreas parenchymal cells and inflammation[4]. In most individuals, acute pancreatitis is a mild self-limiting disorder, but in up to 20% of the cases there are severe clinical complications and mortality[3].

Alcoholic chronic pancreatitis is a complex disease normally thought to have an early stage that is associated with recurrent attacks of acute pancreatitis, and a late stage that is characterized by steatorrhea, diabetes, fibrotic scarring, and pancreatic calcification[5]. In the western world, chronic alcohol abuse is the major etiological factor of chronic pancreatitis and accounts for approximately 70% of the reported cases[6]. Although pancreatitis may remain an acute disease, it appears that in many cases alcoholic acute pancreatitis progresses to alcoholic chronic pancreatitis. The progression of alcoholic acute pancreatitis to alcoholic chronic pancreatitis is generally associated with the frequency and severity of acute attacks[7].

ETHANOL METABOLISM

It is generally thought that the liver is a target of the toxic effects of alcohol because of its ability to metabolize alcohol. Like the liver, the pancreas possesses the enzymes responsible for ethanol metabolism. Therefore, it has been proposed that the pancreas is also a target for the toxic effects of ethanol metabolism[8-10].

Alcohol can be metabolized by oxidative, as well as nonoxidative, pathways. The oxidative metabolism of ethanol is primarily carried out by two enzymes, the cytosolic enzyme alcohol dehydrogenase and the microsomal enzyme cytochrome P450 2E1. Metabolism of ethanol by either of these enzymes results in the production of the reactive intermediate acetaldehyde, and the production of reactive oxygen species. Although the pancreas expresses both alcohol dehydrogenase and cytochrome P450 2E1, the capacity for oxidative metabolism by the pancreas is significantly less than that of the liver[11,12].

Nonoxidative metabolism of ethanol is carried out by a number of enzymes, the most important being the fatty acid ethyl ester synthases. Metabolism of ethanol by these enzymes results in the formation of fatty acid ethyl esters (FAEEs). Although the capacity of oxidative metabolism in the pancreas is lower than in the liver, the capacity for nonoxidative metabolism in the pancreas is high because the pancreas has high fatty acid ester synthetic activity[13]. The nonoxidative and oxidative pathways of ethanol metabolism are linked; when the oxidative pathway is low or impaired the nonoxidative pathway is enhanced[9]. Because the oxidative metabolism of ethanol in the pancreas is relatively low, the nonoxidative metabolism of ethanol may be more important and the production of FAEEs and their toxic effects accentuated. It has been shown that infusion of FAEEs into rats causes edema, trypsin activation, and vacuolization of pancreas acinar cells[14]. FAEEs have also been shown to activate the transcriptional activators nuclear factor (NF)-κB and AP-1, which are involved in the activation of proinflammatory cytokines[8]. Additionally, FAEEs have been shown to increase the fragility of lysosomes in pancreatic acinar cells[15]. It has also been shown that FAEEs can inhibit the degradation of extracellular matrix proteins, and therefore may have an involvement in the fibrotic scarring characteristic of alcoholic chronic pancreatitis[16].

Because the expression of alcohol dehydrogenase and cytochrome P450 2E1 are low in the pancreas, the oxidative metabolism of ethanol is also relatively low and is not considered to contribute a major role in many of the biochemical and pathologic changes associated with pancreas acinar cells. That being said, acetaldehyde, a reactive metabolite of the oxidative metabolism of ethanol, has been shown to mediate some detrimental effects in the pancreas. It has been shown that acetaldehyde is involved in the regulation of the transcriptional activators NF-κB and AP-1 in pancreatic acinar cells[8]. Additionally, Masamune *et al*[17-19] demonstrated that acetaldehyde, as well as the fatty acid ethyl ester, palmitic acid ethyl ester, activates the mitogen-activated protein kinases p38, ERK1/2, and JNK/SAPK in isolated pancreatic stellate cells. Furthermore, these authors reported that acetaldehyde activated the transcriptional activator AP-1, but not NF-κB in these cells. In addition, activation of the AP-1 pathway was inhibited by the antioxidant N-acetyl-cysteine (NAC). Because the effects of acetaldehyde were inhibited by inclusion of NAC in the media, the authors concluded

that activation of these signal transduction pathways were mediated by the presence of reactive oxygen species.

Despite the fact that the contribution of the oxidative and nonoxidative pathways of ethanol metabolism differs between the pancreas and the liver, it appears that metabolism of ethanol plays an important role in the disease process in both organs.

CELL DEATH IN PANCREATITIS

Acinar cell death is a major complication of alcoholic pancreatitis and has been linked to the eventual fibrotic scarring associated with this disease. The two major pathways of cell death, apoptosis and necrosis, have both been shown to occur in experimental models of pancreatitis, and it appears that the severity of disease is linked to whether apoptosis or necrosis predominates[20-22].

Cell death as a result of apoptosis is mediated by a group of cysteine proteases known as caspases. Apoptotic cell death generally preserves the integrity of the cell membrane, whereas necrotic cell death generally results in rupture of the cell membrane and release of the cellular contents. Release of the cellular contents can damage neighboring cells and initiate an inflammatory response[23]. It has been shown that the severity of experimental pancreatitis directly correlates with the amount of necrosis, and inversely correlates with the extent of apoptosis[20,22]. Additionally, one of the main indicators of the outcome of pancreatitis in human beings is the extent of necrosis[24]. In experimental animals, it has been shown that alcohol treatment prior to induction of pancreatitis enhances the necrotic response by decreasing the expression of the initiator caspase, caspase-8. This reduces the apoptotic response, and results in more severe pancreatitis[25,26]. Thus, modulating the pathway of cell death during pancreatitis may be a mechanism by which alcohol consumption predisposes the pancreas to more severe damage, or alters the severity of pancreatic injury. This modulation can potentially change a subclinical episode of pancreatitis into a clinical episode.

PANCREATIC STELLATE CELLS

The pancreas, like the liver, possesses stellate cells[27]. Pancreatic stellate cells appear to be morphologically and functionally similar to hepatic stellate cells. In fact, transcriptome analysis of pancreatic and hepatic stellate cells revealed that only 29 of the 23 000 genes analyzed differed in expression[28]. These results indicate that the two populations of cells are very closely related. Stellate cells in the pancreas, as in the liver, are thought to have a major role in extracellular matrix remodeling[29,30]. Thus, pancreatic stellate cells appear to have a major role in fibrotic disorders of the pancreas, such as chronic pancreatitis and pancreatic cancer[31,32]. Whereas hepatic stellate cells normally reside in the space of Disse, pancreatic stellate cells are primarily located in the periacinar space, but are also present in the periductal and perivascular areas of the pancreas[33,34]. Pancreatic stellate cells comprise approximately 4% of all pancreatic cells; in contrast, hepatic stellate cells comprise approximately 8% of all hepatic cells[33]. In the normal pancreas, stellate cells are characterized by the presence of vitamin A-containing lipid droplets in their cytoplasm, and by expression of the cytoskeletal proteins desmin and glial fibrillary protein[33,34]. In response to pancreas injury or acetaldehyde, these cells are activated into a highly proliferative state and are transformed to myofibroblast-like cells[27]. Activated stellate cells are characterized by the absence of lipid droplets, expression of α-smooth muscle actin, and the production of type-1 collagen, as well as other extracellular matrix proteins[30]. Activated pancreatic stellate cells have been shown to be closely associated with areas of pancreatic fibrosis. They are the principal source of type 1 collagen in pancreatic fibrosis, both in humans and experimental animal models[35].

Numerous paracrine factors have been demonstrated to participate in the activation of pancreatic stellate cells. Included in these factors are cytokines such as interleukin (IL)-1, IL-6, IL-8, and tumor necrosis factor α, growth factors such as platelet-derived growth factor (PDGF) and transforming growth factor (TGF)-β_1, angiotensin Ⅱ, acetaldehyde, and reactive oxygen species released by damaged parenchymal cells, or leukocytes recruited in response to tissue injury[36-39]. In turn, the activated stellate cells produce autocrine factors such as PDGF, TGF-β_1, IL-1, and IL-6, which are thought to perpetuate the activation of the pancreatic stellate cells.

It has been demonstrated that both hepatic and pancreatic stellate cells express NADPH oxidase, and it has been proposed that this enzyme has a role in the fibrosis associated with chronic pancreatitis[40,41]. NADPH oxidase is a multicomponent enzyme originally described in phagocytic cells as a source of reactive oxygen species. In phagocytic cells, the activated complex produces extracellular superoxide that has an important role in defense against microbial infection. The NADPH oxidase expressed by stellate cells and the enzyme complex expressed by phagocytic cells exhibit some important differences. One of the most important differences is the fact that in stellate cells NADPH oxidase is constitutively active, producing low levels of reactive oxygen species.

Originally, it was shown that angiotensin Ⅱ mediated its profibrotic action in the liver through NADPH oxidase activity in hepatic stellate cells[40]. *In vivo*, mice lacking NADPH oxidase activity demonstrated attenuated liver fibrosis after bile duct ligation. Investigation of the role of NADPH oxidase in pancreatic stellate cells revealed that PDGF-ββ, IL-1β, and angiotensin Ⅱ induced production of reactive oxygen species in cultured pancreatic stellate cells. The increase in reactive oxygen species and subsequent activation of downstream signaling pathways were abolished by inhibition of NADPH oxidase activity with diphenylene iodonium (DPI)[42].

Additionally, treatment with DPI attenuated the development of pancreatic fibrosis in Wistar Bonn/Kobori rats and in rats with dibutyltin dichloride-induced chronic pancreatitis[42]. In a separate study, it was shown that ethanol enhanced PDGF-mediated activation of pancreatic stellate cells, indicating that NADPH oxidase may have a role in alcoholic pancreatitis[41].

The cascade of pancreatic damage, activation of pancreatic stellate cells, and progression to fibrosis has been termed a necroinflammatory response. It has been suggested that alcohol abuse can result in pancreas damage by a nonnecroinflammatory response as well. Interestingly, pancreatic stellate cells express alcohol dehydrogenase and are able to produce acetaldehyde[27]. Because acetaldehyde has been shown to activate pancreatic stellate cells, it has been suggested that this ability may itself result in the activation of pancreatic stellate cells. In turn, this activation may result in the initiation, as well as the perpetuation of, alcohol induced pancreatitis and pancreatic fibrosis[27].

Tissue repair is a process that is regulated by an intricate balance between the synthesis and degradation of extracellular matrix components[43]. As mentioned above, pancreatic stellate cells are critically important in the remodeling of the extracellular matrix. This remodeling involves not only synthesis of extracellular matrix components but their degradation as well. Pancreatic stellate cells secrete a number of matrix metalloproteinases (MMPs), enzymes that are involved in extracellular matrix degradation[44]. The MMPs are a family of zinc-dependent enzymes secreted by a variety of cells that are able to degrade extracellular matrix components. Thus, pancreatic stellate cells are not only involved in pancreatic damage; they are also critically involved in recovery and repair of pancreatic damage[45].

Specifically, pancreatic stellate cells have been shown to secrete MMP1, MMP2, MMP3, MMP9, and MMP13[39,44,46]. MMPs have different substrate specificities; MMP2 and MMP9 primarily degrade basement membrane collagen (type-4), whereas MMP1 and MMP13 degrade type-1 collagen. The secretion of MMP2 is greatly increased by ethanol and acetaldehyde, and is secreted far in excess of MMP13[44]. This finding led the authors to suggest changes in MMPs secretion as an explanation for the accumulation of fibrotic type 1 collagen in pancreatitis.

Pancreatic stellate cells have also been shown to secrete enzymes that inhibit the activity of MMPs, these enzymes are known as tissue inhibitors of metalloproteinases (TIMPs). TIMP2 is an important inhibitor of MMP2, the matrix metalloproteinase responsible for the degradation of basement membrane collagen. Ethanol and acetaldehyde have been shown to increase the secretion of TIMP2. However, this increase in TIMP2 was significantly less than the increase in MMP2. The overall result was an increase in MMP2 activity[44]. Interestingly, similar findings have been reported in hepatic stellate cells, again indicating the close functional relationship between these two cell types[47].

In a model of acute pancreatitis where the fibrotic damage was resolved, both MMP2 and MMP1 activity were shown to increase, but were regulated in a different temporal fashion. MMP2 activity increased soon after injury, while MMP1 activity increased later[46]. These results indicate different roles for different MMPs in repair and regeneration of the pancreas. They also demonstrate that there is a delicate balance and interplay between different MMPs in the normal recovery of pancreatic injury.

Understanding the factors and mechanisms that maintain stellate cells in a quiescent state or return them to a quiescent state is as important as understanding the factors and mechanisms of stellate cell activation and fibrotic scarring. In both the liver and the pancreas, the nuclear hormone receptor peroxisome proliferator-activated receptor-γ (PPAR-γ) has been implicated as being involved in inhibition of stellate cell activation[18,48,49]. PPAR-γ is a nuclear hormone receptor that is activated by specific ligands and has been shown to inhibit key characteristics of activation, including induction of collagen synthesis in both hepatic and pancreatic stellate cells[18,48,49]. Acetaldehyde has been shown to activate hepatic stellate cells, at least in part, by abrogating PPAR-γ-mediated transcriptional activity in cultured hepatic stellate cells[50]. Additionally, the profibrogenic actions of acetaldehyde were shown to be associated with increased phosphorylation of PPAR-γ at a MAP kinase phosphorylation site. These results demonstrate the involvement of MAP kinases in the inhibition of PPAR-γ-mediated transcriptional activity, and ultimately stellate cell activation[50].

Vitamin A (retinol) also appears to be a major contributor to the maintenance of quiescence in pancreatic stellate cells; its absence in active pancreatic stellate cells may be related to ethanol metabolism[51,52]. In support of this notion, McCarroll *et al*[52] demonstrated that retinol and its metabolites all trans retinoic acid and 9-cis retinoic acid induce quiescence in activated pancreatic stellate cells. Furthermore, quiescence of pancreatic stellate cells was associated with a decrease in the activity of all three classes of MAP kinases. In the presence of ethanol, retinol was not able to fully inhibit activation of pancreatic stellate cells. Because retinol and ethanol can both be metabolized by either alcohol dehydrogenase or by retinol dehydrogenase, the authors suggest that ethanol may act as a competitive inhibitor of normal retinol metabolism, and that this inhibition may, in part, explain the ability of ethanol to activate pancreatic stellate cells[52].

REGENERATION AND REPAIR

The pancreas, like the liver, has a tremendous capacity to regenerate after injury[53,54]. As with all fibrotic diseases, pancreatitis can be considered a result of an aberrant or inappropriate repair process. Thus, it is as important to have a detailed understanding of the mechanisms of pancreas repair and the effects of ethanol on this process, as it is to determine the mechanisms by which alcohol abuse leads to pancreatitis. In animal models of

pancreatits, normal regeneration is characterized by a sequence of events that includes activation and proliferation of pancreatic stellate cells, deposition of extracellular matrix, and proliferation of acinar cells[53,55]. It is now evident that this regenerative process is orchestrated by the temporal and sequential expression of growth factors that act in either an autocrine or paracrine manner to stimulate cells. This coordinated process ultimately results in full structural and functional restitution of the pancreas. Little is known regarding the effects of ethanol on this process.

While investigating the effects of ethanol consumption on regeneration after cerulein-induced pancreatitis, one group, using the Lieber-DeCarli diet, found that ethanol feeding of rats for 2-8 wk significantly decreased amylase content of the pancreas. This finding indicated impaired functional regeneration. This treatment did not affect protein, DNA, or RNA content. Although no histological evaluation was performed, these authors concluded that ethanol had no effect on pancreatic regeneration[56,57]. In contrast, Pap *et al*[58] found that gastric intubation of ethanol over a 2 mo period inhibited the recovery of pancreatic weight and enzyme content in rats that had common bile ducts and main pancreatic ducts occluded to induce pancreatic injury. During this 2 mo period, the animals exposed to ethanol developed chronic calcifying pancreatitis. Cessation of the ethanol treatment resulted in recovery of the pancreas. These results led the authors to suggest that inhibition of pancreatic regeneration by ethanol was required to maintain this chronic pancreatitis. Investigating the role of cholecystokinin (CCK) in pancreatic regeneration, it has been shown that alcohol administration reduced CCK release and prevented pancreas regeneration[59]. Additionally, using a model of virally induced pancreatitis, it has been shown that ethanol administration to mice delays pancreas recovery[60].

The pancreas and the liver are developmentally very closely related. Therefore, it is tempting to speculate that the regenerative process, and the effects of ethanol on this process, may be similar in the pancreas and the liver[61]. In the liver, it has been demonstrated that ethanol abuse impairs regeneration[62,63]. Both the pancreas and the liver contain a population of progenitor cells that are multipotent and able to differentiate into multiple cell types[64,65]. In the liver, these hepatic progenitor cells have been shown to be important in regeneration in alcoholic liver diseases and in other hepatic diseases where oxidative stress has occurred[66,67]. Thus, it may be that repair initiated by pancreatic precursor cells may be impaired by ethanol as well. It is clear that more work is required to determine the effects of ethanol on regeneration and repair of pancreatic damage.

CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

It is obvious that alcoholic pancreatitis is an important health concern and more focus on this disease is warranted. It appears that, as with alcoholic liver disease, the fibrotic scarring associated with chronic pancreatitis is primarily associated with activation of stellate cells. Because of this, it is likely that future research directed at the mechanisms by which ethanol and its metabolites mediate or enhance the activation of these cells will provide targets for therapeutic intervention. Currently, some promising therapeutic candidates include NADPH oxidase and receptors located on the surface of stellate cells.

Future work should strive to understand the mechanisms by which stellate cells remain quiescent. It is clear that balancing the need for activation of stellate cells for repair and wound healing with maintenance of the quiescent state will be challenging. Because similar mechanisms of fibrotic scarring occur in the liver, it will be prudent to monitor progress in this field and apply it to the pancreas.

CONCLUSION

The pancreas and the liver are developmentally closely related and, in a general sense, share certain structural and functional similarities. It is well known by the general public that alcohol abuse can result in liver damage and lead to cirrhosis. It is not as well known that alcohol abuse can also result in pancreatic damage and ultimately in alcoholic chronic pancreatitis. Although there are many differences between the liver and the pancreas, and the alcohol-associated diseases of these organs, there are also many similarities. Because of these similarities, lessons learned regarding the effects of ethanol on the liver may be useful in determining mechanisms by which ethanol damages the pancreas.

Both the liver and the pancreas possess stellate cells. Although some of the biochemical changes that occur as a result of ethanol metabolism in the liver and the pancreas differ, the end result in both organs is the activation of stellate cells. In both organs the activated stellate cells are the major source of fibrotic collagen. Because fibrosis is a characteristic of alcohol-associated damage in both organs, stellate cells are the focus of therapeutic intervention. Among the questions that require further investigation are the mechanisms that will inhibit hyperactivation or inappropriate activation of stellate cells. Paradoxically, activated stellate cells are also involved in the removal of fibrotic collagen. Therefore, determining the mechanisms of appropriate activation, and enhancing the ability of these cells to degrade fibrotic collagen are paramount. Additionally, mechanisms of repair and regeneration must be further delineated. Are progenitor cells involved in repair of alcohol-associated damage in the pancreas, as they are in the liver?

It is clear that although there are differences between the effects of alcohol on the liver and the pancreas, there are also striking similarities. Lessons learned from the liver may be useful in answering questions regarding the pancreas.

REFERENCES

1 **Dufour MC**, Adamson MD. The epidemiology of alcohol-induced pancreatitis. *Pancreas* 2003; **27**: 286-290
2 **Sata N**, Koizumi M, Nagai H. Alcoholic pancreatopathy: a proposed new diagnostic category representing the preclinical stage of alcoholic pancreatic injury. *J Gastroenterol* 2007; **42** Suppl 17: 131-134
3 **Wang GJ**, Gao CF, Wei D, Wang C, Ding SQ. Acute pancreatitis: etiology and common pathogenesis. *World J Gastroenterol* 2009; **15**: 1427-1430
4 **Pandol SJ**. Acute pancreatitis. *Curr Opin Gastroenterol* 2006; **22**: 481-486
5 **Ammann RW**. The natural history of alcoholic chronic pancreatitis. *Intern Med* 2001; **40**: 368-375
6 **Ammann RW**, Heitz PU, Klöppel G. Course of alcoholic chronic pancreatitis: a prospective clinicomorphological long-term study. *Gastroenterology* 1996; **111**: 224-231
7 **Ammann RW**, Muellhaupt B. Progression of alcoholic acute to chronic pancreatitis. *Gut* 1994; **35**: 552-556
8 **Gukovskaya AS**, Mouria M, Gukovsky I, Reyes CN, Kasho VN, Faller LD, Pandol SJ. Ethanol metabolism and transcription factor activation in pancreatic acinar cells in rats. *Gastroenterology* 2002; **122**: 106-118
9 **Werner J**, Saghir M, Fernandez-del Castillo C, Warshaw AL, Laposata M. Linkage of oxidative and nonoxidative ethanol metabolism in the pancreas and toxicity of nonoxidative ethanol metabolites for pancreatic acinar cells. *Surgery* 2001; **129**: 736-744
10 **Werner J**, Saghir M, Warshaw AL, Lewandrowski KB, Laposata M, Iozzo RV, Carter EA, Schatz RJ, Fernández-Del Castillo C. Alcoholic pancreatitis in rats: injury from nonoxidative metabolites of ethanol. *Am J Physiol Gastrointest Liver Physiol* 2002; **283**: G65-G73
11 **Haber PS**, Apte MV, Applegate TL, Norton ID, Korsten MA, Pirola RC, Wilson JS. Metabolism of ethanol by rat pancreatic acinar cells. *J Lab Clin Med* 1998; **132**: 294-302
12 **Norton ID**, Apte MV, Haber PS, McCaughan GW, Pirola RC, Wilson JS. Cytochrome P4502E1 is present in rat pancreas and is induced by chronic ethanol administration. *Gut* 1998; **42**: 426-430
13 **Laposata EA**, Lange LG. Presence of nonoxidative ethanol metabolism in human organs commonly damaged by ethanol abuse. *Science* 1986; **231**: 497-499
14 **Werner J**, Laposata M, Fernández-del Castillo C, Saghir M, Iozzo RV, Lewandrowski KB, Warshaw AL. Pancreatic injury in rats induced by fatty acid ethyl ester, a nonoxidative metabolite of alcohol. *Gastroenterology* 1997; **113**: 286-294
15 **Haber PS**, Wilson JS, Apte MV, Pirola RC. Fatty acid ethyl esters increase rat pancreatic lysosomal fragility. *J Lab Clin Med* 1993; **121**: 759-764
16 **Lugea A**, Gukovsky I, Gukovskaya AS, Pandol SJ. Nonoxidative ethanol metabolites alter extracellular matrix protein content in rat pancreas. *Gastroenterology* 2003; **125**: 1845-1859
17 **Masamune A**, Kikuta K, Satoh M, Satoh A, Shimosegawa T. Alcohol activates activator protein-1 and mitogen-activated protein kinases in rat pancreatic stellate cells. *J Pharmacol Exp Ther* 2002; **302**: 36-42
18 **Masamune A**, Kikuta K, Satoh M, Sakai Y, Satoh A, Shimosegawa T. Ligands of peroxisome proliferator-activated receptor-gamma block activation of pancreatic stellate cells. *J Biol Chem* 2002; **277**: 141-147
19 **Masamune A**, Satoh A, Watanabe T, Kikuta K, Satoh M, Suzuki N, Satoh K, Shimosegawa T. Effects of ethanol and its metabolites on human pancreatic stellate cells. *Dig Dis Sci* 2010; **55**: 204-211
20 **Bhatia M**. Apoptosis versus necrosis in acute pancreatitis. *Am J Physiol Gastrointest Liver Physiol* 2004; **286**: G189-G196
21 **Gukovskaya AS**, Mareninova OA, Odinokova IV, Sung KF, Lugea A, Fischer L, Wang YL, Gukovsky I, Pandol SJ. Cell death in pancreatitis: effects of alcohol. *J Gastroenterol Hepatol* 2006; **21** Suppl 3: S10-S13
22 **Kaiser AM**, Saluja AK, Sengupta A, Saluja M, Steer ML. Relationship between severity, necrosis, and apoptosis in five models of experimental acute pancreatitis. *Am J Physiol* 1995; **269**: C1295-C1304
23 **Edinger AL**, Thompson CB. Death by design: apoptosis, necrosis and autophagy. *Curr Opin Cell Biol* 2004; **16**: 663-669
24 **Topanzian M**, Gorelick FS. Acute pancreatitis. In: Yamada T, Alpers DH, Laine L, Owyang C, Powell DW, editors. Textbook of gastroenterology. Philadelphia: Lippincort Williams & Williams, 2003: 2026-2060
25 **Fortunato F**, Deng X, Gates LK, McClain CJ, Bimmler D, Graf R, Whitcomb DC. Pancreatic response to endotoxin after chronic alcohol exposure: switch from apoptosis to necrosis? *Am J Physiol Gastrointest Liver Physiol* 2006; **290**: G232-G241
26 **Wang YL**, Hu R, Lugea A, Gukovsky I, Smoot D, Gukovskaya AS, Pandol SJ. Ethanol feeding alters death signaling in the pancreas. *Pancreas* 2006; **32**: 351-359
27 **Apte MV**, Phillips PA, Fahmy RG, Darby SJ, Rodgers SC, McCaughan GW, Korsten MA, Pirola RC, Naidoo D, Wilson JS. Does alcohol directly stimulate pancreatic fibrogenesis? Studies with rat pancreatic stellate cells. *Gastroenterology* 2000; **118**: 780-794
28 **Buchholz M**, Kestler HA, Holzmann K, Ellenrieder V, Schneiderhan W, Siech M, Adler G, Bachem MG, Gress TM. Transcriptome analysis of human hepatic and pancreatic stellate cells: organ-specific variations of a common transcriptional phenotype. *J Mol Med* 2005; **83**: 795-805
29 **Friedman SL**. Mechanisms of hepatic fibrogenesis. *Gastroenterology* 2008; **134**: 1655-1669
30 **Omary MB**, Lugea A, Lowe AW, Pandol SJ. The pancreatic stellate cell: a star on the rise in pancreatic diseases. *J Clin Invest* 2007; **117**: 50-59
31 **Longnecker DS**. Pathology and pathogenesis of diseases of the pancreas. *Am J Pathol* 1982; **107**: 99-121
32 **Etemad B**, Whitcomb DC. Chronic pancreatitis: diagnosis, classification, and new genetic developments. *Gastroenterology* 2001; **120**: 682-707
33 **Apte MV**, Haber PS, Applegate TL, Norton ID, McCaughan GW, Korsten MA, Pirola RC, Wilson JS. Periacinar stellate shaped cells in rat pancreas: identification, isolation, and culture. *Gut* 1998; **43**: 128-133
34 **Bachem MG**, Schneider E, Gross H, Weidenbach H, Schmid RM, Menke A, Siech M, Beger H, Grünert A, Adler G. Identification, culture, and characterization of pancreatic stellate cells in rats and humans. *Gastroenterology* 1998; **115**: 421-432
35 **Haber PS**, Keogh GW, Apte MV, Moran CS, Stewart NL, Crawford DH, Pirola RC, McCaughan GW, Ramm GA, Wilson JS. Activation of pancreatic stellate cells in human and experimental pancreatic fibrosis. *Am J Pathol* 1999; **155**: 1087-1095
36 **Apte MV**, Haber PS, Darby SJ, Rodgers SC, McCaughan GW, Korsten MA, Pirola RC, Wilson JS. Pancreatic stellate cells are activated by proinflammatory cytokines: implications for pancreatic fibrogenesis. *Gut* 1999; **44**: 534-541
37 **Mews P**, Phillips P, Fahmy R, Korsten M, Pirola R, Wilson J, Apte M. Pancreatic stellate cells respond to inflammatory cytokines: potential role in chronic pancreatitis. *Gut* 2002; **50**: 535-541
38 **Schneider E**, Schmid-Kotsas A, Zhao J, Weidenbach H, Schmid RM, Menke A, Adler G, Waltenberger J, Grünert A, Bachem MG. Identification of mediators stimulating proliferation and matrix synthesis of rat pancreatic stellate cells. *Am J Physiol Cell Physiol* 2001; **281**: C532-C543
39 **Shek FW**, Benyon RC, Walker FM, McCrudden PR, Pender SL, Williams EJ, Johnson PA, Johnson CD, Bateman AC, Fine DR, Iredale JP. Expression of transforming growth factor-beta 1 by pancreatic stellate cells and its implications for matrix secretion and turnover in chronic pancreatitis. *Am J*

Pathol 2002; **160**: 1787-1798
40 **Bataller R**, Schwabe RF, Choi YH, Yang L, Paik YH, Lindquist J, Qian T, Schoonhoven R, Hagedorn CH, Lemasters JJ, Brenner DA. NADPH oxidase signal transduces angiotensin II in hepatic stellate cells and is critical in hepatic fibrosis. *J Clin Invest* 2003; **112**: 1383-1394
41 **Hu R**, Wang YL, Edderkaoui M, Lugea A, Apte MV, Pandol SJ. Ethanol augments PDGF-induced NADPH oxidase activity and proliferation in rat pancreatic stellate cells. *Pancreatology* 2007; **7**: 332-340
42 **Masamune A**, Watanabe T, Kikuta K, Satoh K, Shimosegawa T. NADPH oxidase plays a crucial role in the activation of pancreatic stellate cells. *Am J Physiol Gastrointest Liver Physiol* 2008; **294**: G99-G108
43 **Bentrem DJ**, Joehl RJ. Pancreas: healing response in critical illness. *Crit Care Med* 2003; **31**: S582-S589
44 **Phillips PA**, McCarroll JA, Park S, Wu MJ, Pirola R, Korsten M, Wilson JS, Apte MV. Rat pancreatic stellate cells secrete matrix metalloproteinases: implications for extracellular matrix turnover. *Gut* 2003; **52**: 275-282
45 **Jaster R**. Molecular regulation of pancreatic stellate cell function. *Mol Cancer* 2004; **3**: 26
46 **Yokota T**, Denham W, Murayama K, Pelham C, Joehl R, Bell RH Jr. Pancreatic stellate cell activation and MMP production in experimental pancreatic fibrosis. *J Surg Res* 2002; **104**: 106-111
47 **Knittel T**, Mehde M, Kobold D, Saile B, Dinter C, Ramadori G. Expression patterns of matrix metalloproteinases and their inhibitors in parenchymal and non-parenchymal cells of rat liver: regulation by TNF-alpha and TGF-beta1. *J Hepatol* 1999; **30**: 48-60
48 **Galli A**, Crabb D, Price D, Ceni E, Salzano R, Surrenti C, Casini A. Peroxisome proliferator-activated receptor gamma transcriptional regulation is involved in platelet-derived growth factor-induced proliferation of human hepatic stellate cells. *Hepatology* 2000; **31**: 101-108
49 **Shimizu K**, Shiratori K, Hayashi N, Kobayashi M, Fujiwara T, Horikoshi H. Thiazolidinedione derivatives as novel therapeutic agents to prevent the development of chronic pancreatitis. *Pancreas* 2002; **24**: 184-190
50 **Ceni E**, Crabb DW, Foschi M, Mello T, Tarocchi M, Patussi V, Moraldi L, Moretti R, Milani S, Surrenti C, Galli A. Acetaldehyde inhibits PPARgamma via H2O2-mediated c-Abl activation in human hepatic stellate cells. *Gastroenterology* 2006; **131**: 1235-1252
51 **Jaster R**, Hilgendorf I, Fitzner B, Brock P, Sparmann G, Emmrich J, Liebe S. Regulation of pancreatic stellate cell function in vitro: biological and molecular effects of all-trans retinoic acid. *Biochem Pharmacol* 2003; **66**: 633-641
52 **McCarroll JA**, Phillips PA, Santucci N, Pirola RC, Wilson JS, Apte MV. Vitamin A inhibits pancreatic stellate cell activation: implications for treatment of pancreatic fibrosis. *Gut* 2006; **55**: 79-89
53 **Elsässer HP**, Adler G, Kern HF. Time course and cellular source of pancreatic regeneration following acute pancreatitis in the rat. *Pancreas* 1986; **1**: 421-429
54 **Menke A**, Lutz PM, Ludwig CU, Gress TM, Adler G. Regeneration of acute pancreatitis: influence of peptide growth factors. In: Büchler MW, Uhl W, Friess H, Malfertheiner P, editors. Acute pancreatitis: novel concepts in biology and therapy. Berlin: Blackwel Sceince, 1999: 129-141
55 **Elsässer HP**, Adler G, Kern HF. Fibroblast structure and function during regeneration from hormone-induced acute pancreatitis in the rat. *Pancreas* 1989; **4**: 169-178
56 **Rydzewska G**, Jurkowska G, Wróblewski E, Faszczewska A, Gabryelewicz A. Pancreatic regeneration after chronic ethanol feeding in rats. *J Physiol Pharmacol* 1999; **50**: 227-241
57 **Rydzewska G**, Jurkowska G, Dziecioł J, Faszczewska A, Wróblewski E, Gabryelewicz A. Does chronic ethanol administration have influence on pancreatic regeneration in the course of caerulein induced acute pancreatitis in rats. *J Physiol Pharmacol* 2001; **52**: 835-849
58 **Pap A**, Boros L. Alcohol-induced chronic pancreatitis in rats after temporary occlusion of biliopancreatic ducts with Ethibloc. *Pancreas* 1989; **4**: 249-255
59 **Pap A**, Boros L, Hajnal F. Essential role of cholecystokinin in pancreatic regeneration after 60% distal resection in rats. *Pancreas* 1991; **6**: 412-418
60 **Clemens DL**, Jerrells TR. Ethanol consumption potentiates viral pancreatitis and may inhibit pancreas regeneration: preliminary findings. *Alcohol* 2004; **33**: 183-189
61 **Slack JM**. Developmental biology of the pancreas. *Development* 1995; **121**: 1569-1580
62 **Koteish A**, Yang S, Lin H, Huang J, Diehl AM. Ethanol induces redox-sensitive cell-cycle inhibitors and inhibits liver regeneration after partial hepatectomy. *Alcohol Clin Exp Res* 2002; **26**: 1710-1718
63 **Yang SQ**, Lin HZ, Yin M, Albrecht JH, Diehl AM. Effects of chronic ethanol consumption on cytokine regulation of liver regeneration. *Am J Physiol* 1998; **275**: G696-G704
64 **Fausto N**. Liver regeneration and repair: hepatocytes, progenitor cells, and stem cells. *Hepatology* 2004; **39**: 1477-1487
65 **Zulewski H**, Abraham EJ, Gerlach MJ, Daniel PB, Moritz W, Müller B, Vallejo M, Thomas MK, Habener JF. Multipotential nestin-positive stem cells isolated from adult pancreatic islets differentiate ex vivo into pancreatic endocrine, exocrine, and hepatic phenotypes. *Diabetes* 2001; **50**: 521-533
66 **Roskams T**, Yang SQ, Koteish A, Durnez A, DeVos R, Huang X, Achten R, Verslype C, Diehl AM. Oxidative stress and oval cell accumulation in mice and humans with alcoholic and nonalcoholic fatty liver disease. *Am J Pathol* 2003; **163**: 1301-1311
67 **Yang S**, Koteish A, Lin H, Huang J, Roskams T, Dawson V, Diehl AM. Oval cells compensate for damage and replicative senescence of mature hepatocytes in mice with fatty liver disease. *Hepatology* 2004; **39**: 403-411

S- Editor Tian L **L- Editor** O'Neill M **E- Editor** Zheng XM