Recent Advances in Alcoholic Liver Disease
II. Minireview: molecular mechanisms of alcoholic fatty liver

Min You and David W. Crabb
Departments of Medicine, Indiana University School of Medicine and Richard Roudebush Veteran’s Affairs Medical Center, Indianapolis, Indiana 46202

You, Min, and David W. Crabb. Recent Advances in Alcoholic Liver Disease. II. Minireview: molecular mechanisms of alcoholic fatty liver. Am J Physiol Gastrointest Liver Physiol 287: G1–G6, 2004; 10.1152/ajpgi.00056.2004.—Alcohol has long been thought to cause fatty liver by way of altered NADH/NAD+ redox potential in the liver, which, in turn, inhibits fatty acid oxidation and the activity of tricarboxylic acid cycle reactions. More recent studies indicate that additional effects of ethanol both impair fat oxidation and stimulate lipogenesis. Ethanol interferes with DNA binding and transcription-activating properties of peroxisome proliferator-activated receptor-α (PPARα), as demonstrated with cultured cells and in ethanol-fed mice. Treatment of ethanol-fed mice with a PPARα agonist can reverse fatty liver even in the face of continued ethanol consumption. Ethanol also activated sterol regulatory element binding protein 1, inducing a battery of lipogenic enzymes. These effects may be due in part to inhibition of AMP-dependent protein kinase, reduction in plasma adiponectin, or increased levels of TNF-α in the liver. The understanding of these ethanol effects provides new therapeutic targets to reverse alcoholic fatty liver.

The understanding of the control of lipid metabolism in the liver and other tissues has undergone a revolution in the past decade. The control of levels of the enzymes involved in fatty acid oxidation and synthesis are predominantly controlled by two regulatory molecules, peroxisome proliferator-activated receptor-α (PPARα) and sterol regulatory element binding protein 1 (SREBP-1), respectively (Fig. 1). PPARα is a member of the nuclear hormone receptor superfamily, which, when dimerized with retinoid X receptors (RXR), controls transcription of a set of genes containing peroxisome proliferator response elements (PPREs), which are involved in free fatty acid (FFA) transport and oxidation. These include membrane transporters such as carnitine palmitoyl-transferase I (CPT I), apolipoprotein genes, and several components of the mitochondrial and peroxisomal fatty acid oxidation pathways. In addition, an enzyme that is critical to the control of malonyl-CoA levels, malonyl-CoA decarboxylase (MCD), was recently shown to be regulated by PPARα (12). The transcriptional activity of PPARα is activated on binding of FFA as well as a number of drugs such as nonsteroidal anti-inflammatory drugs and fibrates. This provides a feedback loop that increases the capacity of the liver to dispose of fatty acids when the intracellular concentration of the fatty acids rises. Fasted PPARα-null mice have severe impairment in their ability to oxidize FFA in the liver, resulting in hypoglycemia, hypothermia, hypoketonemia, elevated plasma levels of FFAs, and fatty liver (1). PPARα is not required for expression of constitutive levels of peroxisomal β-oxidation enzymes; however, the receptor is required for induction of this system by peroxisome proliferators (1). PPARα knockout animals develop fatty liver and obesity as they age (5) or are fed a high-fat diet (10). They are particularly sensitive to the development of steatohepatitis when fed a methionine- and choline-deficient diet (8). This may relate to the inability of the liver to export fat in the form of lipoproteins when methionine and choline are deficient.

Fatty acid levels are markedly increased in the liver after alcohol consumption; therefore, one would predict that the PPARα-controlled battery of fat-metabolizing enzymes should be induced by alcohol consumption. Whereas a subset of PPARα-responsive genes has been reported to be induced by ethanol, for example, cytochrome P-450 4A1 (lauryl ω-hydroxylase) and liver fatty acid binding protein, many others did not change or even decreased; for example, medium-chain acyl-CoA dehydrogenase activity and mRNA levels were decreased by ethanol feeding. The physiological result of the increased generation of dicarboxylic fatty acids by enhanced lauryl ω-hydroxylase activity and the failure of ethanol to induce acyl-CoA oxidase, the first step in peroxisomal ω-oxidation, is increased excretion of urinary dicarboxylic fatty acids in alcohol-fed rats and in alcoholic men. Thus it would appear that the failure of full induction of fatty acid-metabolizing genes in alcohol-fed animals might contribute to the development of fatty liver.

The rate of synthesis of fat is also increased by ethanol. This is accompanied by increased levels of a number of lipogenic enzymes, which are now known to be regulated by the transcription factor SREBP. SREBP belong to a family of transcription factors containing basic helix-loop-helix-leucine zipper motifs and regulate enzymes responsible for cholesterol, fatty acid, and triglyceride synthesis in liver and other tissues. Three SREBP isoforms, designated SREBP-1a, SREBP-1c, and SREBP-2, have been identified. SREBP-1a is mainly expressed in cultured cells, providing both cholesterol and fatty acids that are required for cell membrane synthesis. In liver, SREBP-1c is involved in fatty acid synthesis, whereas SREBP-2 plays a major role in the regulation of cholesterol synthesis. SREBP s are synthesized as 125-kDa precursors and are attached to the nuclear envelope and endoplasmic reticulum. On activation, the NH2-terminal domain of each SREBP (68 kDa, referred as mature protein) is released proteolytically from the membrane into the nucleus, where it binds to and activates promoters containing sterol response elements (SREs). The role of SREBP-1 in fatty liver development has been firmly established by animal models, including transgenic and knockout mice. Transgenic mice overexpressing SREBP-1a or -1c have massive

Address for reprint requests and other correspondence: D. W. Crabb, Emerson Hall Rm. 317, 545 Barnhill Dr., Indianapolis IN 46202 (dcrabb @iupui.edu).

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fatty livers due to increased accumulation of cholesteryl esters and triglycerides, and the fatty liver of obese (ob/ob) mice is caused by elevated SREBP-1c levels, thereby increasing lipogenic gene expression, enhancing fatty acid oxidation pathways, and increase the concentration of malonyl-CoA. Malonyl-CoA inhibits the entry of free fatty acid (FFA) into the mitochondria and blocks fatty acid oxidation in the mitochondrion. CPT I, carnitine palmitoyl-transferase; ACC, acetyl-CoA carboxylase; AdipoR2, adiponectin receptor 2; TNF-α R1, TNF-α receptor 1.

Fatty livers due to increased accumulation of cholesteryl esters and triglycerides, and the fatty liver of obese (ob/ob) mice is caused by elevated SREBP-1c levels, thereby increasing lipogenic gene expression, enhancing fatty acid synthesis, and accelerating triglyceride accumulation in the liver. Recent work has shown that ethanol feeding or exposure of cultured cells to ethanol leads to increased levels of the mature form of SREBP-1 and induction of the mRNAs of many members of the lipogenic enzyme set.

Perhaps the most important questions remaining are: what mediates effects of ethanol on these transcription factors? Does ethanol affect a central regulatory system that is responsible for both the reduction in PPARγ/H9251 and the increase in SREBP-1 activity, or are these the results of independent actions of ethanol? Would prevention of fatty liver, even with continued alcohol consumption, prevent the more severe complications of alcoholic liver injury? Several new leads that may answer these questions have appeared recently. Ethanol is reported to reduce the blood level of adiponectin, a hormone made in the adipose tissue, which is reported to activate PPARα and AMP-dependent protein kinase (AMPK), and inhibit SREBP-1. Furthermore, AMPK has been reported to reduce the expression of SREBP-1 and inhibit acetyl-CoA carboxylase (ACC). The latter effect will reduce the level of malonyl-CoA and increase the rate of entry of fatty acyl-CoA into the mitochondrion. This review will explore the interactions of ethanol with these regulators of hepatic fat metabolism and the possibility of controlling fatty liver by pharmacological intervention.

**EFFECTS OF ETHANOL ON PPARα FUNCTION IN CULTURED CELLS**

Ethanol inhibited the transcriptional activating and DNA-binding ability of the PPARα, and its response to ligands (clofibrate, WY14,643), in hepatoma cells or primary cultures of hepatocytes, cells with the capability of oxidizing ethanol (7). This effect was not seen in cells that lack alcohol dehydrogenase (ADH), suggesting that metabolism of ethanol was required for this effect. Further support for this hypothesis was provided by showing that the effect of ethanol was abolished by the ADH inhibitor 4-methylpyrazole and augmented by the aldehyde dehydrogenase (ALDH) inhibitor cyanamide. Incubation of cells with acetaldehyde (50–200 μM) also reduced the ability of PPARα in nuclear extracts to bind DNA. Thus acetaldehyde was likely responsible for the effect of ethanol.

The activity of several other nuclear receptors (hepatocyte nuclear factor 4, apolipoprotein AI regulatory protein-1, and chicken ovalbumin upstream promotor-transcription factor) was not affected by ethanol (7), suggesting that this is neither nonspecific toxicity of acetaldehyde nor an effect on downstream signaling pathways shared by the nuclear receptors.

**EFFECTS OF ETHANOL ON PPARα FUNCTION IN VIVO**

To determine whether this effect of ethanol also occurs in vivo, chronic ethanol feeding studies were performed (6). Four weeks of ethanol feeding resulted in histological and biochemical fat accumulation. PPARα protein levels were relatively unchanged, whereas RXRα levels were substantially reduced. This may reflect the effect of increased portal vein endotoxin, because reduced hepatic RXRα in response to endotoxin has been reported (3). PPARα/RXR binding to its consensus sequence was also reduced significantly (6). Of the PPAR-controlled gene battery, the mRNA for medium-chain acyl-CoA dehydrogenase was decreased by 40%, but those encoding acyl-CoA oxidase, CPT I, very-long-chain acyl-CoA synthetase, and very-long-chain acyl-CoA dehydrogenase were unchanged by the ethanol feeding protocol. As reported by
others, liver fatty acid binding protein was induced by ethanol feeding.

Treatment of the animals with the PPARα agonist WY14,643 alone for the last 2 wk of the experiment resulted in induction of PPARα protein ~1.5-fold, no change in RXRα levels, a threefold increase in the binding of PPARα/RXR to its consensus DNA sequence, and mRNA levels of many PPARα target genes (long-chain acyl-CoA dehydrogenase, medium-chain acyl-CoA dehydrogenase, acyl-coA oxidase, very-long-chain acyl-CoA synthetase, and fatty acid binding protein) significantly higher than in ethanol-treated mice.

WY14,643 treatment of animals during the last 2 wk of ethanol feeding increased the level of PPARα protein and its ability to bind DNA. It also induced mRNA levels of PPARα target genes, and this was associated with a higher rate of fatty acid β-oxidation, normalization of serum FFA and triglyceride levels, and reversal of fat accumulation in the livers. Clearly, incomplete activation of the PPARα battery of enzymes during ethanol consumption contributes to the development of alcohol-induced fatty liver (6).

Fatty acid oxidation is not solely controlled by the activity of enzymes of β-oxidation. The entry of fatty acyl-CoA into the mitochondrion is controlled by the level of malonyl-CoA, which is an allosteric regulator of CPT I. Malonyl-CoA is synthesized by ACC and is degraded by MCD. The role of PPARα in regulating the expression and activity of the enzymes involved in controlling malonyl-CoA levels has received attention recently. Reduced rates of fatty acid oxidation in the hearts of PPARα (−/−) mice were associated with higher concentrations of malonyl-CoA and the reduced expression and activity of MCD, suggesting that PPARα could transcriptionally regulate expression of MCD (4). PPARα activation (by WY14,643), but not PPARγ activation (by troglitazone), increased MCD mRNA expression and activity in cardiac and skeletal muscle (24). Further studies demonstrated that the promoter of MCD was activated 17-fold in cells cotransfected with PPARα/RXRα expression plasmids, and MCD mRNA levels in hepatoma cells and in the liver of fenofibrate-fed rats were increased as well (12). Thus the inhibition of PPARα function by ethanol would likely also lead to increased malonyl-CoA and inhibition of fatty acid entry into the mitochondrion.

**EFFECTS OF ETHANOL ON SREBP FUNCTION IN CULTURED CELLS**

The role of SREBPs in alcoholic fatty liver was first investigated by our group examining the effect of ethanol on transcription of an SRE-containing promoter in cultured hepatoma cells (23). Two rat hepatoma cell lines, H4IIEC3 and McA-RH7777, were transfected with the reporter pSyn SRE-luciferase and treated with various concentrations of ethanol, then they were harvested for assay of reporter enzymes. Ethanol treatment significantly increased pSyn SRE reporter activities up to sixfold in these hepatoma cells. However, the same effect was not observed in CV-1 cells, again suggesting that acetaldehyde generated from ethanol metabolism might be required. This was again confirmed by the use of inhibitors of ethanol metabolism, 4-Methylpyrazole nearly abolished the effect of ethanol on pSyn SRE-luciferase expression, whereas cyanamide, the ALDH inhibitor, augmented the effect markedly. Furthermore, the amount of mature SREBP-1 increased ~2.5-fold after H4IIEC3 cells were exposed to either ethanol (50 mM) or acetaldehyde (200 μM). In agreement with our findings, a recent work showed that acetaldehyde treatment enhanced the levels of the precursor and mature forms of SREBP-1 in HepG2 cells in a dose-dependent manner, and the enhancing effect increased over time, peaking at 24 and 48 h of the exposure to acetaldehyde (13).

**EFFECTS OF ETHANOL ON SREBP FUNCTION IN VIVO**

We further investigated the effect of ethanol on SREBP-1 in vivo by using the standard liquid diet, pair-feeding protocol. Feeding mice a low-fat diet (4% safflower oil, 6% cocoa butter, and 72% high carbohydrate) with ethanol (27.5% of total calories) for 4 wk led to fatty liver development. A substantial increase in the amount of mature SREBP-1 protein was found in the livers of ethanol-fed mice. Moreover, ethanol feeding increased mRNA expression of several known SREBP-1 target hepatic lipogenic genes including fatty acid synthase (FAS), sterol-CoA desaturase, malic enzyme, ATP citrate lyase, and ACC, indicating that ethanol-mediated induction of SREBP-1 maturation may be associated with the increase in expression of these genes (23). Consistent with our finding, Ji and Kaplowitz (9) reported that feeding mice a high-fat diet (15.7% carbohydrate, 25% protein, 35% corn oil) with ethanol (24.3%) for 6 wk using the intragastric infusion model approximately doubled SREBP-1 mRNA over 6 wk and increased the mature form of SREBP-1 protein. Taken together, these studies suggest that products of ethanol metabolism may increase hepatic lipogenesis through activating hepatic SREBP-1.

**INVOLVEMENT OF AMPK IN ETHANOL EFFECTS**

AMPK is emerging as a “metabolic master switch” regulating pathways of hepatic triglyceride and cholesterol synthesis. It phosphorylates and inhibits enzymes involved in lipid metabolism such as 3-hydroxy-3-methyl glutamate-CoA reductase and ACC. ACC is generally regarded as the rate-limiting enzyme in fatty acid biosynthesis, and as discussed, its product, malonyl-CoA, is a potent inhibitor of CPT I. AMPK is the major kinase responsible for the inactivation of ACC, and recently, the activation of MCD by AMPK was reported (15). Therefore, activation of AMPK is expected to reduce malonyl-CoA levels, increasing fatty acid oxidation.

More interestingly, it has been firmly established that SREBP-1 can be both transcriptionally and posttranscriptionally regulated by AMPK. Several studies demonstrate that reduced SREBP-1 mRNA and protein expression in rat hepatocytes and liver result from AMPK activation. Activation of AMPK decreased the stability of mature SREBP-1 protein in hepatocytes by acceleration of its proteasomal degradation (15, 16). Therefore, we tested the hypothesis that AMPK may play a role in mediating the effects of ethanol on SREBP-1. We found that metformin or aminomimidazole-4-carboxamide ribonucleotide, two known AMPK activators, partially blocked the ethanol-mediated induction of SREBP-dependent promoter activity in hepatoma cells. It was further observed that chronic ethanol feeding inhibited hepatic AMPK activity and enhanced activity of its target protein ACC. Therefore, our findings suggest that AMPK may play a role in regulating the effects of ethanol on hepatic SREBP-1 activation, fatty acid metabolism,
and the development of alcoholic fatty liver. The potential role of AMPK in the development of alcoholic fatty liver was further suggested by a recent report that the fat-derived hormone adiponectin, a known activator of AMPK, alleviated alcoholic fatty liver disease (20).

**ROLES OF TNF-α AND ADIPONECTIN IN ALCOHOLIC FATTY LIVER**

The cytokine TNF-α has been suggested to play a pivotal role in the development of alcoholic liver injury. The evidence for this comes largely from the intragastric alcohol feeding model. Depletion of Kupffer cells with gadolinium prevented alcoholic liver injury; similarly, administration of neutralizing antibody against TNF-α blocked liver injury (necrosis and inflammation), with less effect on steatosis. The blockade of TNF-α effects was not complete in this model, as evidenced by elevation of transaminases in the ethanol-fed, antibody-treated animals. In an effort to more definitively demonstrate the role of TNF-α, TNF receptor knockout animals [lacking either TNF receptor (TNFR1) (p55) or TNFR1 (p75)] were fed ethanol by the intragastric lavage technique. The animals lacking TNFR1 (p55) had normal transaminases, negligible necrosis and inflammation, and nearly absent steatosis (22). In addition, administration of TNF-α to mice results in the development of fatty liver and has been linked to increased rates of fatty acid synthesis and esterification and activation of SREBP (11). In the systemic inflammatory state induced with endotoxin, PPARα expression is reported to be markedly reduced (18). Thus it is interesting to speculate that the effects of ethanol on both PPARα and SREBP-1 might be mediated by increased portal endotoxin and Kupffer cell-generated TNF-α. However, an additional hormone, adiponectin, may participate in the effects of ethanol.

Adiponectin, also referred to as 30-kDa adipocyte complement-related protein (Acrp30), is a hormone secreted by adipocytes. Full-length adiponectin undergoes proteolytic processing, and a small amount of globular adiponectin (gAd) circulates in plasma. Two adiponectin receptors, AdipoR1 and AdipoR2, were identified last year (21). AdipoR1 is a high-affinity receptor for globular adiponectin and a low-affinity receptor for the full-length ligand, whereas AdipoR2 is an intermediate-affinity receptor for both forms of adiponectin. AdipoR1 is abundantly expressed in skeletal muscle, whereas AdipoR2 is predominantly expressed in the liver; therefore, only full-length adiponectin is active in the liver. A large body of work has shown that decreased levels of circulating adiponectin are associated with obesity, insulin resistance, Type 2 diabetes, and atherosclerosis, and administration of adiponectin diminished the abnormalities associated with the metabolic syndrome. Further studies revealed that the effect of adiponectin is largely mediated by an increase in fatty acid oxidation associated with activation of AMPK and PPARα pathways downstream of the adiponectin receptors, both in vitro and in animals (16, 21).

The potential role of adiponectin in alcoholic fatty liver was first suggested by a recent study (20). Chronic consumption of a high-fat, ethanol-containing diet significantly decreased circulating concentrations of adiponectin by 30–40% after 3–4 wk and reduced adiponectin correlated closely with the development of liver injury. Delivery of recombinant adiponectin into these mice dramatically alleviated hepateomegaly, fatty liver, and liver inflammation. Whereas chronic ethanol feeding significantly decreased the rate of hepatic fatty acid oxidation and reduced the activities of CPT I, ACC, and FAS, adiponectin treatment restored all these activities (20). Thus it is possible that reduction of hepatic fatty acid oxidation during ethanol consumption results from the suppression of adiponectin levels by ethanol. Ethanol could suppress adiponectin through its activation of TNF-α. Indeed, both hepatic expression and circulating levels of TNF-α increased with ethanol feeding, and adiponectin treatment markedly suppressed TNF-α production in these mice (20). This could partly explain the protective role of adiponectin against alcoholic fatty liver. It is well known that adiponectin and TNF-α regulate each other’s production and antagonize each other’s biological effects in their target tissues. The role of TNF-α in alcoholic liver injury has been described above. Chronic ethanol consumption led to increased circulating and local concentrations of TNF-α in adipose tissue and liver. However, it remains unclear whether increased TNF-α resulting from ethanol feeding causes adiponectin reduction or whether suppression of adiponectin production by ethanol leads to TNF-α induction. This issue is complex. A recent study (17) showed that moderate alcohol consumption significantly increased plasma adiponectin levels both in healthy and relatively insulin-resistant middle-aged men without affecting their plasma TNF-α levels. Therefore, effects of ethanol on adiponectin expression appear to depend on the amount of alcohol consumed and the dietary context.

**DISCUSSION**

The original biochemical explanation for alcoholic fatty liver centered on the ability of ethanol metabolism to shift the redox state of the liver and inhibit fatty acid oxidation. Subsequent studies found repression of some enzymes involved in fatty acid oxidation and induction of lipogenic enzymes in ethanol-fed animals, but there has been no unifying hypothesis to explain these effects. We suggest that the effects of ethanol on lipid metabolism result from inhibition of PPARα and stimulation of SREBP-1, in effect resulting in metabolic remodeling of the liver toward a fat-storing, rather than fat-oxidizing, organ. These effects may, in turn, result from effects of ethanol on AMPK. It is attractive to view AMPK as a central modulator of hepatic fat metabolism, especially because AMPK activity is subject to effects of ethanol on adiponectin and possibly TNF-α (Fig. 1).

We suggest that proximal effects of ethanol include increasing portal vein endotoxin, adipose and Kupffer cell TNF-α production, and a reduction in circulating adiponectin. Exactly how ethanol affects the adipose tissue is uncertain. At the hepatocyte, lower adiponectin would result in reduced activity of PPARα and AMPK. The signal cascades between AdipoR2 and these mediators are unknown. TNF-α is known to reduce the expression of PPARα in liver. The effects of TNF-α on AMPK are not known and are a current area of interest in our laboratory.

Inhibition of AMPK by ethanol feeding results in an increase in SREBP-1 activity. As a result, target genes for SREBP-1 are upregulated, contributing to increased hepatic lipid synthesis. AMPK inhibition also results in increased activity of ACC and
decreased activity of MCD by way of changes in the phosphorylation state of these enzymes and thus would reduce the rate of fatty acid oxidation via increased malonyl-CoA concentrations. AMPK may also affect the activity of PPARα. PPARα is activated in heart by p38 MAP kinase (2), and the activity of p38 might be reduced by inhibition of AMPK activity (19). Reduced PPARα activity will lead to reduced capacity for fatty acid oxidation and reduced expression of MCD.

Whereas this sequence is attractive as an explanation for ethanol effects in the intact animals, alternative actions of ethanol need to be kept in mind, particularly in light of the ability of ethanol to inhibit PPARα and activate SREBP-1 in cultured cells. Adiponectin cannot be playing a role in these experimental findings. Ethanol and acetaldehyde treatment are reported to increase TNF-α production by many cells, including hepatoma cells, so paracrine effects of TNF-α on AMPK, PPARα, and SREBP-1 need to be further explored. Additional possibilities include formation of acetaldehyde-protein adducts with PPARα or modulation of the function of PPARα by activation of yet other kinase cascades (for example, p42/44 MAPK, protein kinase A, p38 MAPK, protein kinase B/Akt, and Stat5b have been reported to alter PPARα activity in various tissues). Ethanol might affect one of these pathways and thereby reduce the transcriptional activity PPARα. The increased level of mature SREBP-1 might be stimulated by effects of ethanol on the steroids that regulate activity of SREBP cleavage activating protein (SCAP), the membrane milieu within which SCAP functions, the activity of the processing proteases S1P or S2P, or the rate of degradation of mature SREBP-1, which is believed to be a proteasomal process.

The ability of compounds that activate PPARα to reverse the development of fatty liver is conceptually important, because in other models (e.g., feeding of saturated fat or medium-chain triglycerides, blocking the effect of TNF-α with antibodies), prevention of fatty liver was correlated with reduced overall injury to the liver. Exactly how these drugs effect this change is uncertain. The increased DNA binding activity of PPARα that was seen in WY14,643-treated animals was associated with increased levels of mRNAs for a number of fat-metabolizing enzymes, increased fatty acid oxidation capacity in liver homogenates, lowered plasma triglyceride and FFA levels, and increased plasma ketone body levels (6). These effects were observed even with ethanol in the diet. In our model, the activity of ACC is central to the development of alcoholic fatty liver. The enzyme was induced by ethanol, possibly via SREBP-1 activation, and WY14,643 reduced its activity. Although ACC is not known to have a PPRE in its promoter, there is evidence that this enzyme is negatively regulated by PPARα agonists (14), possibly via activation of AMPK. It is thus uncertain whether the ability of fibrates to reverse fatty liver depends mainly on inhibition of ACC and activation of MCD or whether induction of fatty acid-oxidizing enzymes is also required. Furthermore, the effect of fibrates on adiponectin and TNF-α needs to be evaluated.

These studies on the genetics of fatty liver in alcohol-fed animals lay the foundation for further clinical investigation. Modulation of these signaling pathways may provide novel and effective therapies for alcoholic fatty liver and possibly prevent the inflammatory and fibrotic responses of the liver to ethanol.

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