

Adipose tissue-liver axis in alcoholic liver disease

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Abstract

Alcoholic liver disease (ALD) remains an important health problem worldwide. The disease spectrum is featured by early steatosis, steatohepatitis (steatosis with inflammatory cells infiltration and necrosis), with some individuals ultimately progressing to fibrosis/cirrhosis. Although the disease progression is well characterized, no effective therapies are currently available for the treatment in humans. The mechanisms underlying the initiation and progression of ALD are multifactorial and complex. Emerging evidence supports that adipose tissue dysfunction contributes to the pathogenesis of ALD. In the first part of this review, we discuss the mechanisms whereby chronic alcohol exposure contributed to adipose tissue dysfunction, including cell death, inflammation and insulin resistance. It has been long known that aberrant hepatic methionine metabolism is a major metabolic abnormality induced by chronic alcohol exposure and plays an etiological role in the pathogenesis of ALD. The recent studies in our group documented the similar metabolic effect of chronic alcohol drinking on methionine in adipose tissue. In the second part of this review, we also briefly discuss the recent research progress in the field with a focus on how abnormal methionine metabolism in adipose tissue contributes to adipose tissue dysfunction and liver damage.

Key words: Alcohol; Lipolysis; Adipose; Methylation; Methionine; Liver

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Core tip: Alcoholic liver disease (ALD) remains an important health problem worldwide. The disease spectrum is

featured by early steatosis, steatohepatitis (steatosis with inflammatory cells infiltration and necrosis), with some individuals ultimately progressing to fibrosis/cirrhosis. Although the disease progression is well characterized, no effective therapies are currently available for the treatment in humans. The mechanisms underlying the initiation and progression of ALD are multifactorial and complex. Emerging evidence supports that adipose tissue dysfunction contributes to the pathogenesis of ALD. In this review, we discuss the mechanisms whereby chronic alcohol exposure contributed to adipose tissue dysfunction, as well as their contribution to ALD.

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ALCOHOLIC LIVER DISEASE

Sustained and excessive alcohol consumption is often accompanied with pathological changes in the liver, termed alcoholic liver disease (ALD). The spectrum of ALD encompasses steatosis, steatohepatitis (steatosis with inflammatory cells infiltration and hepatocyte necrosis), with some individuals ultimately progressing to fibrosis/cirrhosis, leading to increased risk of hepatocellular carcinoma^[1-3]. The early-stage ALD, including steatosis and early steatohepatitis, is clinically reversible after termination of alcohol drinking, although the latter takes longer time for the recovery. The pathomechanism implicated in the development of ALD is complex and believed to involve multiple pathogenic factors. Although much progress has been made over last three decades of research on the mechanisms underlying the disease, ALD remains an important health problem worldwide. It ranks among the major causes of morbidity and mortality in the world, and affects millions of patients worldwide each year and there is currently no Food and Drug Administration-approved therapy available to halt or reverse this process in humans.

PATHOGENESIS OF ALD

Steatosis

Hepatic steatosis, characterized by the excessive accumulation of fat in hepatocytes, is the most common and earliest response of the liver to chronic alcohol consumption. Although "pure" steatosis is clinically considered to be a benign condition, excessive fat accumulation makes hepatocytes vulnerable to the attack of "the second hit", such as proinflammatory cytokines and oxidative stress, leading to the progression to steatohepatitis^[4,5]. The mechanisms involved in the development of alcohol-induced hepatic steatosis are multifactorial and remain to be fully elucidated.

Sterol regulatory element binding proteins (SREBP)-1c, a master transcription factor controlling *de novo* lipogenesis, is upregulated in the liver of mice chronically exposed to ethanol-containing diet^[6]. Importantly, liver-specific knockout of SREBP-1c protected mice against alcohol-induced fatty liver and liver damage^[7], supporting the notion that enhanced hepatic *de novo* lipogenic process plays a pivotal role in alcohol-triggered fat accumulation in the liver. Moreover, chronic alcohol exposure is associated with impaired fatty acid β -oxidation, contributing to fat accumulation in hepatocytes. Suppressions of both adenosine monophosphate-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor- α (PPAR- α), two regulatory proteins of fatty acids oxidation, are mechanistically involved in this process^[8,9]. Furthermore, long-term alcohol consumption is reported to enhance uptakes of free fatty acids (FFAs) and triglyceride-rich lipoproteins by hepatocytes^[10,11] and impair hepatic very-low-density lipoprotein secretion *via* suppressing microsomal triglyceride transfer protein activity^[12], thereby contributing to fatty liver after chronic alcohol exposure.

Steatohepatitis

Steatohepatitis is characterized by fatty liver, hepatic neutrophil infiltration, and hepatocyte cell death. The stage is a prerequisite for progression to fibrosis and cirrhosis^[13]. The molecular mechanism for the progression from steatosis to steatohepatitis involve complicated interactions between the direct effects of toxic ethanol metabolites on different cell types in the liver, overproduction of reactive oxygen species (ROS), and overactivated inflammatory responses^[14-21]. Acetaldehyde, the major product of ethanol metabolism in the liver, plays an important role in the development of alcoholic steatohepatitis. Acetaldehyde is a reactive compound and highly toxic to hepatocytes. It binds to both proteins and DNA, leading to not only their functional changes but also activation of adaptive immune system and immune cell infiltration to the damaged liver^[22,23]. Moreover, acetaldehyde also impair mitochondrial integrity and function, leading to oxidative stress and cell death^[24-26]. Oxidative stress, derived from an imbalance between ROS production and cellular antioxidant capability, is believed to play a critical role in the transition from simple steatosis to steatohepatitis^[27]. Many pathways have been suggested to contribute to the occurrence of oxidative stress in response to chronic ethanol exposure. In hepatocytes, the cytochrome P450 2E1 (CYP2E1) activation and mitochondria dysfunction seem to play central roles in inducing cellular oxidative stress state. CYP2E1 is highly inducible and has high catalytic activity for ethanol. During its catalytic circle, CYP2E1 generate significant amount of ROS, which can subsequently leads to cellular injury, lipid peroxidation, and mitochondrial damage^[28-31]. Chronic alcohol consumption is associated with increased CYP2E1 expression

and activity^[32], partially resulting from increased protein stability due to decreased proteasomal degradation^[33,34]. CYP2E1 activity correlates with ethanol-induced liver injury and lipid peroxidation, which was reduced by the inhibition of CYP2E1 using either chemical inhibitors or genetic knockout of *CYP2E1* gene^[35-38]. The detrimental effects of chronic alcohol consumption on liver mitochondria have been well documented. Long-term alcohol exposure is associated with reduced activity of key enzymes in mitochondrial respiratory chain and decreased mitochondria oxygen utilization^[39,40]. Alcohol also leads to disruption between complex I and complex III of the mitochondrial electron transport chain, leading to elevated superoxide anion production^[41]. Furthermore, chronic alcohol drinking is associated with damaged mitochondrial membrane integrity, possibly due to acetaldehyde accumulation, leading to defective mitochondrial GSH uptake, which sensitizes hepatocytes to TNF- α -induced cell death^[42,43]. In addition to hepatocytes, accumulated evidence identified Kupffer cells (KCs) activation to be a central element in the development of steatohepatitis. Chronic alcohol exposure not only results in intestinal gram-negative bacterial overgrowth but also increases gut permeability, leading to the translocation of bacteria-derived LPS from the gut lumen to the blood^[44-46]. The increased circulating LPS induces inflammatory actions in KCs in the liver *via* interacting with toll-like receptor (TLR)-4, resulting in production of oxidative stress and proinflammatory cytokines, including TNF- α , which plays a pivotal role in alcohol-induced hepatocyte cell death^[47-50].

Fibrosis

Liver fibrogenesis is a wound-healing response to chronic liver injury. It is featured by excessive extracellular deposition of collagen and other extracellular matrix proteins, mainly derived from activated hepatic stellate cells (HSCs)^[51-53]. The major stimuli for HSCs activation during chronic alcohol consumption include acetaldehyde^[54,55], the main ethanol metabolite, and proinflammatory cytokines produced by KCs in response to gut-derived products *via* LPS-TLR4 interactions^[56,57].

ADIPOSE TISSUE REGULATES WHOLE BODY LIPID HOMEOSTASIS

Adipose tissue plays a central role in regulating whole body lipid and energy homeostasis. The modern concept viewed adipose tissue as a complex, essential, and highly active metabolic and endocrine organ, not only as a reservoir for energy storage^[58,59]. Adipose tissue communicates with other tissues and organs, including the liver, to integrate total body lipid homeostasis *via* both controlling circulating FFAs levels and synthesizing and releasing a host of secreted molecules, collectively designated as adipokines, including leptin, adiponectin, resistin, to name a few^[58,60]. Adipose tissue stores excess energy in the form of triglycerides (TGs) and re-

leases it in the form of FFAs, a process called lipolysis, to meet other tissues or organs' energy requirements^[61]. Under physiological conditions, lipid storage and release are both coordinated and tightly regulated so that lipid fuels are stored during postprandial periods and released during fasting states. When the regulation of TG storage and FFAs release by adipose tissue is perturbed, particularly when release of FA becomes dissociated from energy requirements in extra-adipose tissues, plasma FA levels are elevated and excessive storage of TGs in these tissues, such as the liver, ensues, leading to hepatic steatosis (fatty liver). The critical role of adipose tissue in regulating hepatic lipid homeostasis can be best manifested by the facts that both long-term fasting and lipodystrophy (adipose tissue deficiency) results in fatty liver^[62-64]. Insulin plays a dominant role in suppressing adipose tissue lipolysis during postprandial periods^[65,66]. Therefore, adipose tissue insulin resistance is associated with elevated circulating FFAs levels due to uncontrolled lipolysis.

ADIPOSE TISSUE DYSFUNCTION IN ALD

Although it has been well-established that chronic alcohol consumption exerts a detrimental effect on hepatic fat synthesis and disposal, leading to the development of hepatic steatosis, emerging evidence supports that adipose tissue dysfunction also plays an important role in the pathogenesis of ALD. In the clinic setting, it has been reported that visceral fat accumulation is positively related to the onset of alcoholic liver damage and body mass index represents an independent risk factor for fibrosis in alcoholic patients^[67-70]. Moreover, adipose tissue inflammation is correlated with the severity of pathological features in the liver of patients with ALD^[69]. Experimentally, long-term alcohol consumption is associated with adipose tissue oxidative stress, insulin resistance, inflammation, adipocyte cell death, and adiponectin decline^[71-75]. Chronic alcohol feeding results in hyper-lipolysis (degradation of TGs) in adipose tissue, leading to elevated circulation FFAs concentrations and a significant loss of white adipose tissue^[10]. A recent study demonstrated that moderate obesity and alcohol synergistically induced steatohepatitis^[76], further supporting the critical role of adipose tissue (dys)/function in the development of ALD. Importantly, both rosiglitazone (a PPAR- γ agonist mainly targeting adipocytes)^[77] and recombinant adiponectin (an adipokine exclusively secreted by adipocytes)^[78] improved ALD, suggesting that improving adipose tissue function represents a potential therapeutic approach for ALD.

EFFECTS OF CHRONIC ALCOHOL CONSUMPTION ON ADIPOSE TISSUE FUNCTION

Oxidative stress, cell death, and inflammation

Although the liver is the major organ for ethanol me-

tabolism, accumulated evidence supports that chronic alcohol feeding is also associated with increased oxidative stress, cell death, and inflammatory response in adipose tissue. Upregulation of CYP2E1 seems to play an important role in these events. Chronic ethanol feeding of rats causes increased expression and enzymatic activity of CYP2E1 in adipocytes/adipose tissue^[72,79], leading to oxidative stress induction, which is evidenced by elevated 4-HNE production and protein carbonyls. When fully-differentiated 3T3-L1 adipocytes with CYP2E1 overexpression were exposed to ethanol-containing medium, increased oxidative stress was observed^[72]. In contrast, overexpression of antisense CYP2E1 in adipocytes prevented ethanol-triggered oxidative stress^[72]. Adipocyte cell death plays a pivotal role in triggering adipose tissue inflammatory responses^[80,81]. Chronic alcohol consumption results in CYP2E1/Bid cascade-dependent adipocyte cell death in adipose tissue of rats, which contributes to adipose tissue inflammation in response to chronic alcohol exposure in that both *Cyp2e1* and *Bid* knockout mice are protected from adipose tissue inflammation^[72]. Interestingly, C1q, a component of the classical pathway of complement, seems to represent a critical link between cell death and inflammation in the setting of chronic alcohol consumption^[72].

Adipokines

Alcohol consumption is known to disrupt adipokine release from adipose tissue^[82,83]. Adiponectin and leptin are key adipokines that modulate hepatic lipid homeostasis. Reduced circulating leptin and adiponectin levels are observed in chronic alcohol exposed rodents, which contribute to the development of ALD^[72,84-86]. *Via* binding with adiponectin receptor on hepatocytes, adiponectin activates AMPK pathway to stimulate FA oxidation, leading to reduced fat accumulation in the liver^[87,88]. Indeed, either exogenous adiponectin administration or endogenously stimulating adiponectin production attenuate alcohol induced fatty liver in mice^[78,84,89,90]. Mechanisms underlying alcohol-triggered adiponectin decline are multifactorial, including oxidative stress^[79,91], hyperhomocysteinemia (HHcy)^[84], and heme-oxygenase-1 dependent pathway^[92]. Other than adiponectin, leptin is another adipokine reported to be affected by chronic alcohol consumption and contribute to ALD. Animal studies showed that chronic alcohol consumption decreases circulating leptin levels^[80,93,94], which is associated with adipose tissue mass reduction. Importantly, exogenous leptin administration restored plasma leptin reduction triggered by chronic alcohol feeding and alleviated hepatic steatosis^[95]. It is noteworthy here that clinical investigations support that moderate alcohol consumption is associated with increased adiponectin levels^[95,96].

Lipolysis

Uncontrolled adipose tissue lipolysis, mainly due to insulin resistance, plays an etiological role in the

development of obesity-related non-alcoholic fatty liver disease^[97-100]. Insulin signaling in adipocytes plays a central role in controlling FFAs release by adipose tissue *via* lipolysis^[65,66]. Peripheral insulin resistance derived from obesity compromises the suppressive effect of insulin on lipolysis, leading to increased exposure of the liver to circulating FFAs with subsequent development of fatty liver. The effect of chronic alcohol consumption on adipose tissue insulin sensitivity remains to be fully characterized; however, existing evidence supports that chronic alcohol consumption is associated with adipose tissue insulin resistance. In rats, chronic ethanol feeding results in impaired insulin-stimulated glucose transport in adipocytes, which is associated with a disruption of insulin-mediated Cbl/TC10 signaling and actin polymerization^[97]. Moreover, chronic ethanol feeding compromises the suppression of the anti-lipolytic effects of insulin in adipocytes in both rats and mice, leading to enhanced triglyceride degradation in adipose tissue^[10,73]. Interestingly, in comparison to subcutaneous fat, visceral white adipose tissue seems to be more susceptible to alcohol-induced lipolysis enhancement, which may involve increased acetaldehyde production^[100]. In contrast to adipose tissue insulin resistance in obese animals which is associated with an increase in body weight and adipocyte size, chronic alcohol consumption leads to reduced adipose tissue mass and adipocyte size^[10], indicating that distinct mechanism(s) are involved in the initiation of adipose tissue insulin resistance. Adipose triglyceride lipase and hormone sensitive lipase (HSL) are two critical enzymes catalyzing fatty acids release from the adipose tissue. Both enzymes are found to be activated in mice chronically fed with alcohol. Interestingly, chronic alcohol feeding has no effect on plasma catecholamine and insulin levels, while PTEN and SOC3, two negative regulators of insulin signaling pathway, are up-regulated, leading to insulin resistance^[10].

ABERRANT METHIONINE METABOLISM AND ALCOHOL-INDUCED ADIPOSE TISSUE DYSFUNCTION

Methionine metabolism abnormality in ALD: Aberrant hepatic methionine metabolism is a major metabolic abnormality induced by chronic alcohol exposure and plays an etiological role in the pathogenesis of ALD^[101-104]. As illustrated in Figure 1, intracellular methionine metabolism involves two major pathways, transmethylation reaction and transsulfuration reaction. The first step in methionine metabolism is the formation of S-adenosylmethionine (SAM) in a reaction catalyzed by methionine adenosyltransferase. Under physiological conditions, most of the SAM generated per day is used in transmethylation reactions in which methyl groups are added to a vast number of molecules, including DNA, RNA, phospholipids, histones, and other proteins, *via* specific methyltransferases. In this process, SAM is

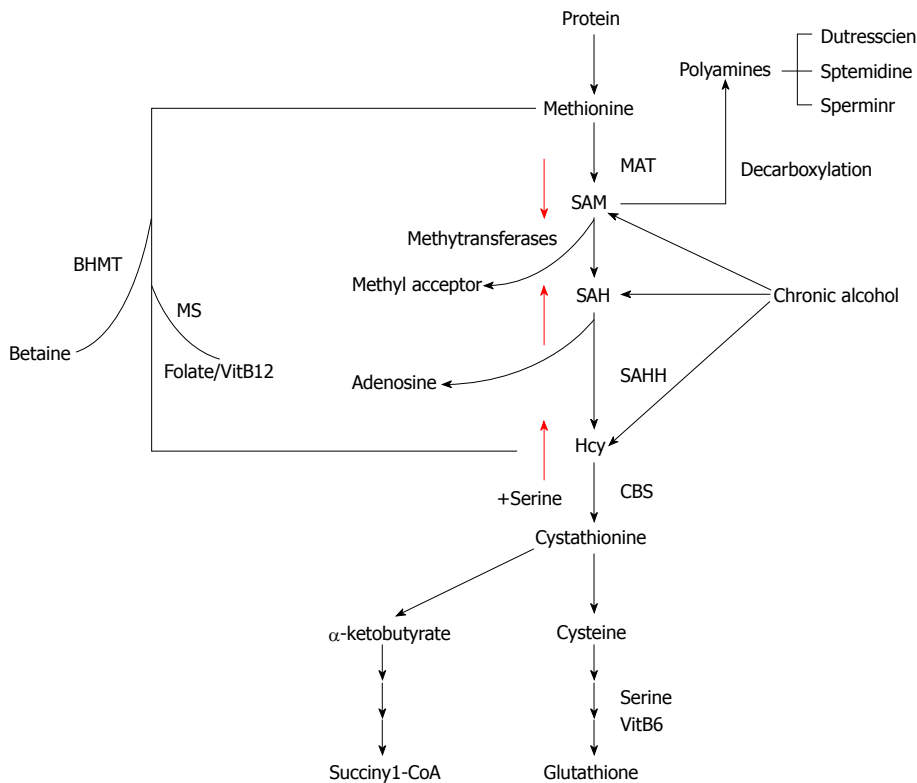


Figure 1 Intracellular methionine metabolism. Chronic alcohol consumption causes SAM deficiency, but enhancement of homocysteine and SAH. MAT: Methionine adenosyl-transferase; SAM: S-adenosylmethionine; SAH: S-adenosylhomocysteine; Hcy: Homocysteine; CBS: Cystathionine beta synthase; SAHH: S-adenosylhomocysteine hydrolase; MS: Methionine synthase; BHMT: Betaine-homocysteine methyltransferase.

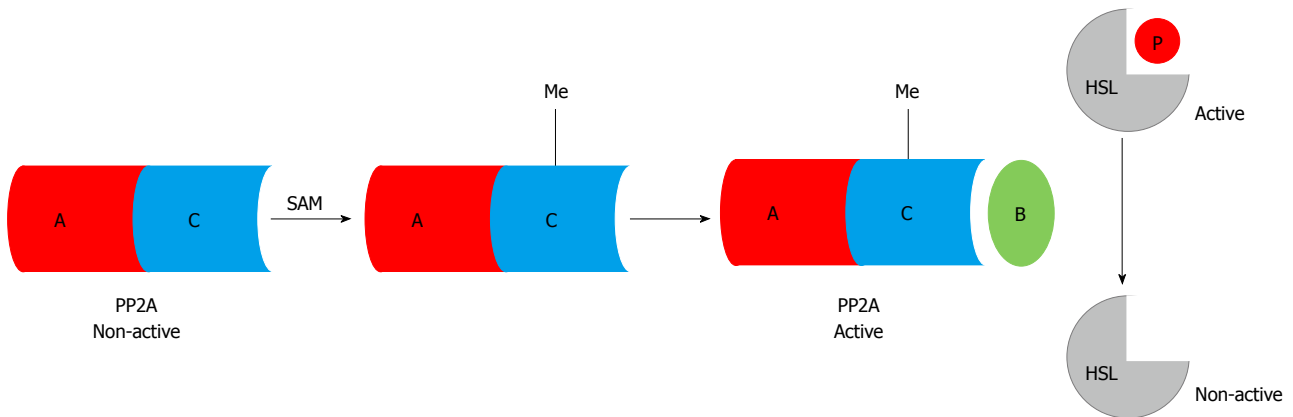


Figure 2 S-adenosylmethionine-dependent methylation reactions are required for protein phosphatase 2A activation, which dephosphorylates (inhibits) hormone sensitive lipase. Chronic alcohol consumption induces intracellular hypomethylation status in adipocytes, which suppresses PP2A activity, leading to uncontrolled HSL activation. SAM: S-adenosylmethionine; Me: Methyl group; PP2A: Protein phosphatase 2A; HSL: Hormone sensitive lipase.

converted to S-adenosylhomocysteine (SAH), followed by homocysteine (Hcy) and cysteine, a precursor for glutathione biosynthesis, *via* transsulfuration pathway. SAH is a potent competitive inhibitor of most methyltransferases studied and decreased SAM:SAH ratio has been widely employed as an indicator of suppressed transmethylation reactions^[105,106]. While chronic alcohol exposure leads to hepatic SAM deficiency, both SAH and Hcy are increased in the liver in response to alcohol^[101,104,107]. HHcy is associated with ER stress induction, leading to hepatocyte dysfunction^[108], while

increased intracellular SAH level enhances the sensitivity of hepatocytes to TNF- α -induced hepatotoxicity^[104], both contributing to the pathogenesis of ALD.

Aberrant adipose methionine metabolism and hyper-lipolytic response in adipose tissue: Studies using both genetic and dietary animal models demonstrated that HHcy is associated with adipose tissue dysfunction^[71,108-112], suggesting that methionine metabolism regulates adipose tissue function. We are the first to report that, similar to its effect on the liver, chronic alcohol feeding induces methionine metabolism

abnormality in adipose tissue, which is characterized by SAM deficiency, and accumulation of Hcy and SAH^[71,113], leading to significant decrease of the SAM/SAH ratio, a strong indicator of inhibitory transmethylation reactions (hypomethylation). HSL is considered a rate-limiting lipase for adipose tissue lipolysis^[114]. Upon lipolytic hormone stimulation, such as with catecholamine, cAMP/PKA-mediated-phosphorylations in certain serine residues activate HSL^[115]. In contrast, protein phosphatase 2A-catalyzed dephosphorylation at Ser660 leads to HSL inactivation^[116,117]. PP2A is a heterotrimeric protein phosphatase. The catalytic and scaffold subunits of PP2A are ubiquitously expressed and have remarkable sequence conservation within eukaryotes. Interestingly, accumulating evidence reveals that PP2A activation is under control of intracellular methylation status^[118,119]. Carboxyl methylation of the PP2A catalytic subunit, catalyzed by PP2A-specific methyltransferase/leucine carboxyl methyltransferase-1, plays a critical role in regulating holoenzyme assembly^[120]. These previous studies provide rationale for us to posit that altered intracellular methylation status in adipocytes may affect adipose tissue lipolytic response. In a very recent study, we provided evidence supporting that intracellular hypomethylation status in adipocytes in the setting of chronic alcohol feeding contributes to adipose tissue hyper-lipolytic response in ALD *via* suppressing PP2A activity, leading to HSL overactivation^[114] (Figure 2). Our data support that rectification of methionine metabolism through dietary supplementation of betaine protects against alcohol-induced liver damage, at least partially *via* improving adipose tissue function. Taken together, the recent research in our group suggest that aberrant methionine metabolism in adipocytes contributes to alcohol-elicited adipose tissue dysfunction and liver damage.

CONCLUSION

Despite its high prevalence, ALD has received limited attention during past decades and no major breakthrough in terms of its clinical management. Emerging evidence shows that adipose tissue plays an important role in both initiation and progression of liver damage induced by chronic alcohol consumption. However, the exact underlying cellular/molecular mechanisms involved in adipose tissue dysfunction in ALD remain to be fully elucidated. Future efforts in identifying the common factors that promote dysfunctions in both adipose tissue and the liver in response to chronic alcohol consumption will pave the way for the discovery of new therapeutic approach.

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