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Alcoholic liver disease: A current molecular and clinical perspective☆

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Abstract

Heavy alcohol use is the cause of alcoholic liver disease (ALD). The ALD spectrum ranges from alcoholic steatosis to steatohepatitis, fibrosis, and cirrhosis. In Western countries, approximately 50% of cirrhosis-related deaths are due to alcohol use. While alcoholic cirrhosis is no longer considered a completely irreversible condition, no effective anti-fibrotic therapies are currently available. Another significant clinical aspect of ALD is alcoholic hepatitis (AH). AH is an acute inflammatory condition that is often comorbid with cirrhosis, and severe AH has a high mortality rate. Therapeutic options for ALD are limited. The established treatment for AH is corticosteroids, which improve short-term survival but do not affect long-term survival. Liver transplantation is a curative treatment option for alcoholic cirrhosis and AH, but patients must abstain from alcohol use for 6 months to qualify. Additional effective therapies are needed. The molecular mechanisms underlying ALD are complex and have not been fully elucidated. Various molecules, signaling pathways, and crosstalk between multiple hepatic and extrahepatic cells contribute to ALD progression. This review highlights established and emerging concepts in ALD clinicopathology, their underlying molecular mechanisms, and current and future ALD treatment options.

Keywords

Alcoholic liver disease (ALD); Alcoholic hepatitis (AH); Alcoholic cirrhosis; Corticosteroids; Liver transplantation

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Authors' contributions

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Conflict of interest

The authors declare that they have no conflict of interest.

1 Introduction

Excessive or chronic alcohol intake causes serious health problems that affect the brain, heart, liver, pancreas, gastrointestinal tract, and immune system. In the United States (US) and Europe, alcohol use disorder (AUD) is the fifth leading cause of death. Worldwide, alcohol use kills 3.3 million people annually, which accounts for 5.9% of all deaths.[1–3] Although low alcohol consumption might have a beneficial effect on ischemic heart disease, alcohol consumption dose-dependently increases the risk of alcoholic liver disease (ALD).[4] In the last two decades, alcohol consumption has decreased slightly in some European countries but increased in China and the US.[5,6] Concomitantly, the prevalence of ALD has increased and is expected to increase further.[7]

ALD is a spectrum of conditions that ranges from alcoholic steatosis to steatohepatitis, fibrosis, and cirrhosis. Up to 50% of cirrhosis-associated deaths are due to alcohol abuse in the US.[8] To date, there are no US Food and Drug Administration (FDA)-approved anti-fibrotic agents for cirrhosis. Cirrhosis treatments rely on supportive care measures, such as ascites control and the treatment of esophageal varices. Liver transplantation is a potential curative treatment, but it is only indicated for end-stage decompensated cirrhosis, and patients must abstain from alcohol use for 6 months prior to transplantation.

Excessive and prolonged alcohol use can also cause a distinct clinical syndrome called alcoholic hepatitis (AH), which produces severe clinical symptoms including signs of liver decompensation (*e.g.*, jaundice, infection, bleeding from esophageal varices, ascites, hepatic encephalopathy). Currently, the primary therapy for AH comprises corticosteroids, but the 6-month-mortality of severe AH is still high (approximately 40%).[9] While liver transplantation is a treatment option, severe AH patients often die before meeting the transplantation criteria. Therefore, only a limited number of severe AH patients can undergo liver transplantation.[10,11] A better under-standing of molecular mechanisms underlying ALD is urgently needed to develop effective therapies. This review highlights the established and emerging concepts in ALD clinicopathology and the associated molecular mechanisms as well as current and future treatment options for ALD.

2. Risk factors for ALD

Chronic alcohol consumption, the consumption of large quantities of alcohol, and specific drinking patterns are associated with progression from steatosis to steatohepatitis, liver fibrosis, and cirrhosis (Fig. 1).[12] Most patients with ALD do not develop cirrhosis even with long-term alcohol use (Fig. 1). Various factors influencing disease progression include gender, ethnicity, genetic variants, viral hepatitis, and obesity.[13]

2.1 Gender and ALD

Women tend to use alcohol less than men; therefore, women have a lower risk for AUD than men.[14] Large national longitudinal surveys found AUD prevalence to be three-fold greater for men than women in the 2001e2002 survey and two-fold greater in the 2012e2013 survey. [15] Despite lower levels of alcohol consumption, women are more susceptible to the hepatotoxic effects of alcohol. Women progress rapidly to fibrosis and cirrhosis compared

with men, and fibrosis persists even after cessation.[16] Women have less gastric alcohol dehydrogenase (ADH) activity than men. The reduced gastric alcohol breakdown in women allows larger amounts of alcohol to enter the bloodstream and increases alcohol bioavailability.[17] This alcohol bioavailability has downstream effects on hormone activity.

The liver is the site of steroid hormone metabolism and a target organ of hormonal actions. Estrogen receptors are expressed in both parenchymal and non-parenchymal cells of the liver. Alcohol consumption increases estrogen receptor expression in human and animal livers.[18] Hormone activity also affects ALD. For example, estrogen treatment increases but ovariectomy reduces alcohol-induced hepatic steatosis. Moreover, estrogen treatment increased and ovariectomy decreased tumor necrosis factor (TNF) α production in Kupffer cells and plasma endotoxin levels in alcoholfed rats.[19] These estrogen-induced changes in portal endotoxin, TNFα, and CD14 levels were diminished by treatment with oral antibiotics,[20] suggesting that estrogen affects Kupffer cell sensitivity and intestinal permeability in ALD. Indeed, treatment of human intestinal cells with estrogen in doses equivalent to those found in women enhanced alcohol-induced apoptosis.[21] These studies show that estrogen enhances the sensitivity of Kupffer cells to alcohol and endotoxin, and increases alcohol-induced gut permeability.

On the other hand, basal levels of hepatoprotective betaine-homocysteine methyltransferase are increased in male mice compared with female mice after ethanol administration.[22,23] The ratio of pro-inflammatory ω−6 and anti-inflammatory ω−3 fatty acids (FAs), which affects ALD development, is also different between genders. This ratio was shifted towards a pro-inflammatory state in female drinkers but not male drinkers. Levels of the anti-inflammatory FAs docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) were higher in male drinkers but not female drinkers.[24] These studies show that differences in hormone activity and levels of hepatoprotective factors between females and males may account for the increase of the susceptibility of females to alcohol-induced liver injury.

2.2. Drinking pattern as a risk for ALD

Recently, there has been the shift in high-risk drinking patterns, such as heavy drinking and binge drinking.[25] Binge drinking, defined by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) as drinking episodes of five or more drinks in men, or four or more drinks in women, is on the rise. A 2010 survey by the Centers for Diseases Control reported that approximately 38 million US adults (1 in 6) engage in binge drinking. Binge drinking is particularly concerning in young adults. Approximately 50% of college students reported engaging in binge drinking.[26] Binge drinking in young adulthood is a risk factor for alcohol abuse and dependence later in life, with consequent risks for developing ALD.[27] Because women are more susceptible to ALD and the consumption gender gap is narrowing, younger women who are more likely to binge drink than drink chronically are particularly vulnerable to the deleterious effects of alcohol. Interestingly, experimental animal models suggest that female hormones may contribute to high levels of binge drinking in female mice.[28] These results are consistent with previous studies showing that depleting circulating female hormones in rodents reduces alcohol intake.[29]

Epidemiological data suggest that binge drinking is partially responsible for increasing rates of cirrhosis and cirrhosis-related death, although this conclusion is controversial.[30] Experimental data has shown intra- and extrahepatic changes that acute alcohol intoxication and repeated binge drinking exacerbate liver injury, such as Kupffer cell activation, increased intestinal permeability, elevated cytokine production, increased oxidative stress, mitochondrial dysfunction, and hepatic apoptosis.[31–34] The studies investigating the pathophysiological effects of binge drinking on the liver have their limitations. Further studies investigating the quality of alcohol consumed per binge and binge frequency are needed to evaluate how extensively this drinking pattern exacerbates liver injury. Table 1 shows the various alcohol contents of different alcoholic beverages, which helps to calculate the consumption of quantities of alcohol by drinking different beverages.

2.3. Genetic variants

Many common diseases have heritable traits that confer protective or susceptibility effects. ALD is a complex disease because both environmental and host factors modify disease progression. For example, Hispanics are more prone to ALD, and twin studies showed that alcoholic cirrhosis prevalence was increased in monozygotic versus dizygotic twins.[35] Few heavy drinkers progress to severe ALD, supporting the hypothesis that genetic background influences the course of the disease. Aldehyde dehydrogenase 2 (ALDH2) is an enzyme that degrades the toxic acetaldehyde resulting from ethanol metabolism. The inactive ALDH2*2 variant (E487K) is associated with an alcohol flush reaction, and approximately 40% of East Asians have this variant.[36] The ALDH2*2 variant promoted chemically-induced hepatocellular carcinoma (HCC) development when knocked in to a mouse model.[36] While several reports have studied the relationship between ALDH2*2 and HCC, the evidence of this variant as an independent risk factor for HCC is weak to date.[37,38]

The patatin-like phospholipase domain-containing protein 3 (PNPLA3) I148M variant, a known risk factor for non-alcoholic steatohepatitis (NASH), is strongly associated with the development of ALD to cirrhosis.[39] A genome-wide association study evaluating two independent cohorts of European descent showed that variants of membrane-bound O-acyltransferase domain-containing 7 (MBOAT7) and transmembrane 6 superfamily member 2 (TM6SF2) are also risk factors for alcohol-related cirrhosis.[38] Unlike the PNPLA3, MBOAT7 and TM6SF2 variants, which increase the risk for alcoholic cirrhosis, a recent study has revealed that a variant of hydroxysteroid 17-beta dehydrogenase 13 (HSD17B13) is associated with reduced alcoholic cirrhosis.[40] All four genes are associated with lipid metabolism, suggesting that molecules produced during lipid metabolism may play a more important role in ALD progression than those produced during alcohol metabolism.

2.4. Obesity

The World Health Organization defines overweight and obesity as having a body mass index (BMI) greater than 25 kg/m^2 and 30 kg/m^2, respectively. Given the rising prevalence of obesity and metabolic syndrome in the US, weight control is among the top public health concerns. The earliest derangement in the ALD spectrum is steatosis, an excessive accumulation of triglycerides in hepatocytes. In fact, up to 90% of alcoholics have histological evidence of fatty liver.[41] The interaction between adipose tissue and alcohol

consumption is complex. Epidemiological data shows strong independent associations between alcohol intake and BMI, with individuals who consume more alcohol having higher BMIs.[42] Results from the Third National Health and Nutrition Examination Survey (NHANES III) showed that ALD patients had an obesity prevalence of 44.5% and increased liver-related mortality.[43] Obesity and high alcohol intake synergistically elevated liver enzymes. This interaction had multiplicative effects, raising serum alanine aminotransferase (ALT) and aspartate transaminase (AST) levels 8.9- and 21-fold, respectively. Obese individuals were more susceptible to alcohol-induced liver injury at lower doses than healthy-weight counterparts.[44] To date, it is unclear if NAFLD is associated with ALD progression because of additive injury or if it intensifies alcohol-mediated hepatotoxicity. Studies investigating the combined effects of alcohol and body fat on extrahepatic mechanisms involved in ALD progression are discussed later in this review.

2.5. Hepatitis C virus (HCV)

An estimated 170 million people are infected with HCV world-wide, and chronic HCV infection is a major cause of chronic liver disease.[45] Alcohol intake negatively modifies the course and outcome of HCV infection. A study of liver biopsies from 1574 HCV patients showed that patients consuming over 50 g of alcohol per day had a 34% increase in the rate of fibrosis progression per year compared with non-drinkers.[46] Another study showed dose-dependent increases in liver injury at even lower consumption levels among patients with HCV. This study showed that as little as 20 g per day in women and 30 g per day in men increased histological activity and fibrosis, illustrating the impact of moderate alcohol intake on liver injury and steatosis.[47] Furthermore, in patients with HCV, alcohol intake increases viremia.[47]

The mechanism underlying the synergistic effect of alcohol and HCV on liver injury remains elusive. However, studies implicated altered immune responses, increased oxidative stress, viral replication, and fatty changes of the liver in this synergistic effect.[48–53] HCV patients who drink alcohol develop HCC 2–3 times more frequently than those who do not drink.[54] Studies have suggested that toll-like receptor 4 (TLR4) is one of the factors implicated in the synergistic effect of alcohol and HCV on hepatic oncogenesis.[55] Despite improvements in available HCV treatments, alcohol consumption still increases mortality in patients with HCV.[56] Among HCV patients who completed anti-HCV interferon therapy, the sustained virologic response (SVR) of those who consumed alcohol was comparable to those who did not drink; however, alcohol use was associated with treatment discontinuation and a subsequent reduction in SVR.[57] The effect of direct acting antivirals on liver disease mediated by HCV and alcohol needs further investigations.

3. Clinicopathology and spectrum of ALD

3.1. Alcoholic fatty liver

As mentioned above, alcoholic liver steatosis is the earliest stage of ALD and is developed in 90% of heavy drinkers. While alcoholic steatosis does not present significant clinical symptoms, patients have a slight elevation in the blood levels of AST, ALT, and gamma-glutamyl transferase as well as an AST/ALT ratio, >2. ALD is often comorbid with

metabolic syndrome, which includes hyperlipidemia, diabetes, hypertension, and obesity. The presence of metabolic syndrome and a prior history of heavy alcohol consumption independently affect ALD progression. Histology of tissues with alcoholic steatosis has numerous large- and small-sized lipid droplets in the hepatocyte cytosol. These changes begin in zone 3 (centrilobular zone) and subsequently extend into zone 2 and zone 1 (periportal zone).[58] These changes can be reversed by 4e6 weeks of abstinence.[59]

3.2. Alcoholic steatohepatitis, fibrosis, and cirrhosis

Approximately 20%e40% of heavy drinkers progress from alcoholic steatosis to steatohepatitis and fibrosis. Alcoholic steatohepatitis and fibrosis are characterized histologically by neutrophil infiltration, hepatocyte ballooning, necrosis, the appearance of Mallory-Denk bodies, cholestatic changes, megamitochondria, and perivenular and pericellular fibrosis (Fig. 1).[60] These pathological changes start in zone 3 due to the higher cytochrome P450 2E1 (CYP2E1) expression compared with other zones and progress towards the portal vein area (zone 1) or neighboring central vein. Patients with alcoholic steatohepatitis can be asymptomatic (sub-clinical alcoholic steatohepatitis) or present with severe clinical symptoms, defined as AH. Among patients with fibrosis, including those who are asymptomatic, 8%–20% will develop cirrhosis.[41] Alcohol abuse is the leading cause of cirrhosis-mediated death in the US (44%–48% of all cirrhosis-mediated deaths), higher even than that caused by HCV.[41] Because direct acting antivirals are highly effective treatments for hepatitis B and C virus, ALD and NAFLD are likely to become the leading indications for liver transplantation in the near future. Alcoholic cirrhosis is a significant risk factor for the development of HCC, which is associated with the consumption of large quantities of alcohol. The 10-year cumulative incidence of HCC ranges from 6.8% to 28.7%.[61–64]

3.3. AH

Consuming large quantities of ethanol (>100 g/day) can cause AH, an acute clinical syndrome of ALD. Patients with severe AH present with severe clinical symptoms, including fever, jaundice, ascites, hepatic encephalopathy, gastrointestinal tract bleeding from esophageal varices and gastro-duodenal ulcers. While AH can develop at any stage of ALD, 40% of alcoholic cirrhosis may develop AH and 80% of severe AH occurs in patients with alcoholic cirrhosis (acute-on-chronic condition) (Fig. 1). The prognosis of these patients is very poor compared with that of AH patients with steatosis alone.[65] The American Association for the Study of Liver Diseases (AASLD) guidelines demonstrated correlations between AH severity and serum bilirubin levels, prothrombin time (PT)/ international normalized ratio (INR), Maddrey's discriminant function (MDF) score, serum creatinine levels, and model for end-stage liver disease (MELD) score. Severe AH is defined by an MDF score >32 or MELD score >18. The 1-month mortality rate of this condition is as high as 30%–50%.[66,67] Of the patients who survive to 6 months, 70% will progress to cirrhosis (Fig. 1).

Several histological features are associated with AH outcomes. Neutrophil accumulation was associated with better outcomes in severe AH patients despite neutrophils playing a prominent role in promoting alcohol-induced liver inflammation.[65] Reduced regenerative response and the presence of proliferating hepatocytes were associated with poorer and

better prognosis, respectively.[68,69] In addition, the presence of proliferative hepatic progenitor cells and ductular reactions were associated with poorer prognosis.[70] A recent study identified 123 genes associated with survival in severe AH patients.[71] Among the 123 dysregulated genes, 51 were associated with patients with severe AH and poor prognosis, and 72 were associated with patients with alcoholic cirrhosis or non-severe AH. This study showed that *lipocalin-2 (LCN2), interleukin 1 receptor like 1 (IL1RL1), C-X-C motif chemokine ligand (CXCL) 1, CXCL2, and keratin 19 (KRT19)* were associated with poorer prognosis, whereas *interleukin (IL)-33* and fi*broblast growth factor (FGF) 21* were associated with better prognosis.[71]

4. Established and emerging molecular mechanisms of ALD

4.1. Oxidative stress in ALD

Hepatocytes are the primary cell type that metabolizes ethanol. Ethanol is primarily metabolized to acetaldehyde by ADH (Fig. 2). Acetaldehyde is then metabolized to non-toxic acetate by cytosolic ALDH1 and mitochondrial ALDH2. When ethanol concentrations are high, CYP2E1, another alcohol-metabolizing enzyme, metabolizes ethanol to acetaldehyde and generates reactive oxygen species (ROS).[72] While both ethanol and acetaldehyde are direct hepatotoxins, excessive ROS production and the subsequent production of inflammatory cytokines can promote alcohol-induced liver injury and inflammation (Fig. 2). Chronic alcohol consumption leads to the upregulation of hepatic CYP2E1 levels, which enhances ROS production.[72] In addition, ethanol and acetaldehyde directly injure hepatocyte mitochondria, upregulating mitochondrial ROS production and further promoting liver injury and inflammation.

Another source of ROS is neutrophil that plays a key role in AH. The presence of neutrophils impacts AH disease severity.[65] Ethanol upregulates intercellular adhesion molecule-1 (ICAM-1) expression on the surface of neutrophils and E-selectin expression on sinu-soidal endothelial cells, enhancing the trafficking of circulating neutrophils to the liver. Additionally, the secretion of chemokines (CXCL1, C-C motif chemokine ligand (CCL2), and CXCL8) produced by Kupffer cells and hepatic stellate cells promote neutrophils migration and infiltration to damaged liver tissues.[73,74] ROS from neutrophils, as well as IL-1β and TNFα from Kupffer cells, promote hepatocyte apoptosis and local inflammation.[75] Thus, ROS produced by excessive alcohol metabolism, damaged mitochondria and neutrophils mediates ethanol-induced liver injury and inflammation.

4.2. The gut-liver axis and hepatic inflammation in ALD

Excessive alcohol consumption can cause bacterial overgrowth and change the composition of the intestinal microbiome (*e.g.* decreased *Lactobacillus* and *Bacteroides*).[76–78] Alcohol abuse also increases intestinal permeability by disrupting intestinal barrier function and tight junction integrity through decreased expression of occludins and zonula occludens. This disruption facilitates the translocation of bacterial products from the intestine to the liver through the portal vein (Fig. 3).[79,80] Bacterial products include lipopolysaccharide (LPS, a.k.a. endotoxin), a Gram-negative bacterial cell-wall component. LPS translocation activates TLR4 in Kupffer cells and hepatic stellate cells, inducing the production of pro-

inflammatory cytokines and mediators (*e.g.*, IL-1, IL-6, TNFα, and ROS) and subsequently promoting liver inflammation and fibrosis.[81] Intestinal fungi also play a role in ALD. Ethanol consumption increased the population of fungi in the intestine and β-D-glucan, a fungal cell wall component, in plasma.[82] Importantly, mice treated with antifungals and those with a knockout of Dectin-1, a pattern recognition receptor for β-D-glucan, had less alcohol-induced steatosis and injury compared with control mice, indicating that intestinal fungi play a detrimental role in ALD development.[82]

Similar to microbe-derived molecules, host-derived alarmins, called damaged-associated molecular patterns (DAMPs), can activate liver-disease-promoting inflammatory signals. In ethanol- and acetaldehyde-damaged hepatocytes, the nuclear protein high mobility group box 1 (HMGB1) is translocated to the cytosol and released into systemic circulation.[83,84] Hepatocyte-specific *HMGB1* knockout mice had reduced alcohol-induced liver injury compared with controls, indicating the detrimental effect of HMGB1 in ALD.[83] Thus, gut-derived pathogen-associated molecular patterns (PAMPs) and damaged-liver-derived DAMPs contribute to ALD progression.

4.3. Altered lipid metabolism in ALD

Alcohol-induced steatosis is characterized by the formation of lipid droplets containing triglyceride and esterified cholesterol in the cytosol of hepatocytes, because of ethanol-induced alteration of hepatic lipid metabolism. Ethanol reduces the activity of adenosine monophosphate-activated kinase (AMPK), peroxisome proliferator-activated receptor (PPAR) a, and sirtuin 1 (SIRT1), which reduces FA β-oxidation (Fig. 2).[85–87] Reduced β-oxidation promotes steatosis. Reductions in AMPK activity increases mammalian target of rapamycin complex 1 (mTORC1) activity, which triggers the transcription and activation of sterol regulatory element-binding protein-1c (SREBP-1c) and PPARg.[88] Reduction of AMPK also directly enhances SREBP-1c by increasing its stability.[86,87] Further, when AMPK is activated, it phosphorylates and inactivates acetyl-Co A carboxylase 1 (ACC1). Thus, ethanol upregulates ACC1 activity through the reduction of AMPK activity.[87] The ethanol-induced reduction in hepatic SIRT1 activity also enhances the transcriptional activity of SREBP-1c.[86,87] The reduced SIRT1 activity by ethanol is associated with reduced DEP domain-containing mTOR-interacting protein (DEPTOR), a negative regulator of mTORC1, which enhances SREBP-1c transcription and cytoplasmic translocation of lipin-1, and inhibits transcriptional activity of PPARα.[89] Together, ethanol exposure reduces AMPK, SIRT1 and PPARα activity and upregulates the expression and activity of SREBP-1c, ACC1, and PPARγ, which promotes lipogenesis.[85,86,89–91] The pivotal role of lipin-1 has been implicated in ALD. Ethanol upregulated hepatic lipin-1 expression but blocked lipin-1 nuclear translocation, which suppresses FA β-oxidation, promoting alcohol-induced fatty liver.[92] Decreased very-low-density lipoproteins (VLDL) secretion is also associated with alcohol-induced steatosis. Microsomal triglyceride transfer protein (MTP) assembles VLDL for the lipid secretion. Hepatic MTP levels were decreased in ethanol-fed animals and the PPARα agonist can increase VLDL secretion by upregulating MTP.[93] Decreased VLDL secretion is also mediated by increased lipin-1 in ALD.[94] In addition, ethanol upregulates lipolysis in peripheral and visceral fat tissues, increasing the overload of circulating FAs in

the liver, which promotes alcoholic steatosis (Fig. 2).[11,95,96] Circulating FAs can also activate TLR4 signaling, promoting liver inflammation (Fig. 3).[97]

Alcohol abuse also impairs lipid-droplet catabolism and lipolysis in hepatocytes. Lipolysis is regulated by cytosolic neutral lipases, such as adipose triglyceride lipase (ATGL), and lipophagy, a specialized form of autophagy associated with lysosomal degradation of lipid droplets (Fig. 2). In hepatocytes, alcohol impairs the b-adrenergic-mediated breakdown of lipid droplets by inhibiting protein-kinase A-mediated phosphorylation of hormone-sensitive lipase and ATGL recruitment to lipid droplets.[98] Autophagy is upregulated by increased AMPK and/or reduced mTORC1 activity. Ethanol exposure decreases AMPK and increases mTORC1 activity, thereby reducing autophagy activity.[93,99] Reduced autophagy could enhance lipid accumulation through impaired lipophagy. Enhanced autophagy by autophagy inducers, rapamycin and carbamazepine, suppressed ethanol-induced hepatic steatosis and injury.[100] Recent studies of alcohol-induced steatosis showed that Rab7 and dynamin 2 (Dyn2) play roles in lipophagy.[101,102] Rab7 is a Rab family guanosine triphosphate-binding protein that mediates the fusion of autophagosomes and lysosomes with lipid droplets. Rab7 activity is reduced in hepatocytes following ethanol exposure.[101] In hepatocytes, Dyn2, a guanosine triphosphatase, is associated with autophagic lysosomal reformation, the terminal step of autophagy. Ethanol impairs Dyn2 activity.[102] These studies implicated that reduced Rab7 and Dyn2 activities by ethanol exposure impair lipophagy, promoting the accumulation of lipid droplets.

With respect to FA b-oxidation, ethanol and acetaldehyde suppress this activity by directly damaging mitochondria. Damaged mitochondria are eliminated via mitophagy. Mitophagy is an autophagy-mediated mitochondrial regulation mechanism that plays a role in maintaining mitochondrial functions, including β-oxidation. Parkin is an E3 ubiquitin ligase that regulates mitophagy through ubiquitination of damaged mitochondrial proteins. Mice deficient in Parkin had increased alcohol-induced liver injury, steatosis, and inflammation compared with controls because mitochondria-mediated β-oxidation was suppressed and ROS production increased.[103] A very recent study demonstrated that chronic ethanol exposure induced the mTORC1 translocation to lysosome, in which mTORC1 inhibited transcription factor EB (TFEB) activity through the phosphorylation of TFEB. TFEB plays a crucial role in lysosomal biogenesis and the induction of autophagy-related gene expression. Additionally, TFEB controls mitochondrial biogenesis and FA β-oxidation through peroxisome proliferator-activated receptor gamma coactivator (PGC)-1α regulation.[99] Thus, the inhibited TFEB activity by ethanol enhances alcohol-mediated steatosis and injury through the inhibition of lysosomal and mitochondrial biogenesis and autophagy. p62/sequestosome 1 (SQSTM1) is an adaptor protein of autophagosome and binds to ubiquitinated damaged proteins.[104] These damaged proteins are degraded through proteasome and/or autolysosome. In ALD, both autophagy and proteasome functions are impaired. p62 is accumulated in hepatocytes.[99] Interestingly, p62 is a component of Mallory-Denk body. The accumulation of p62, ubiquitinated proteins, and cytokeratin 8/18 by impaired autophagy and proteasome is associated with the formation of Mallory-Denk body in ALD.[105] Because p62 can activate mTORC1, accumulated p62 may contribute to hepatic steatosis in ALD.[106] Taken together, ethanol and acetaldehyde promote hepatic lipid accumulation by inhibiting lipid degradation through the suppression of autophagy activity,

mitochondrial and liposomal dysfunctions, impaired FA β-oxidation and lipid secretion, and by increasing lipogenesis in the liver.

4.4. The crosstalk between adipose tissue and the liver

Alcohol consumption promotes adipose-tissue lipolysis via ATGL and inhibits the uptake of circulating free FAs for storage in adipose tissue. The result is an increase in circulating non-esterified FA levels, which increases FA flux to the liver and promotes alcohol-induced fatty liver.[107] Experimental evidence suggests that adipose tissue has roles in regulating immunity and inflammation, and recent data support a role for adipose-tissue dysfunction in ALD pathogenesis. Studies have demonstrated that alcohol mediates oxidative stress, inflammation, and cell death in adipose tissue. ALD severity and adipose-tissue inflammation have been correlated in humans.[44] In rats, chronic ethanol administration increased adipocyte CYP2E1 expression. This increased CYP2E1 induced oxidative stress and adipocyte death, provoking inflammatory responses.[108] Another study showed alcohol-mediated adipocyte death was facilitated by CYP2E1, Bcl-2 homology 3 (BH3)-interacting domain death agonist, and complement component C1Q, causing adipose-tissue inflammation.[109] Alcohol consumption also alters adipokine production. Alcohol abuse increased serum levels of leptin, a pro-inflammatory and pro-fibrogenic adipokine that promotes inflammation in adipose tissue and the liver.[110,111] Adiponectin is an anti-inflammatory adipokine that inhibits TNFα production in Kupffer cells via AMPK.[112] Acute and moderate ethanol consumption increased serum adiponectin levels, whereas chronic alcohol abuse decreased them.[113,114] Together, these data show that FAs, inflammatory cytokines, and adipokines derived from adipose tissue affect ALD development.

4.5. Extracellular vesicles (EVs)

Exosomes are small EVs (50e150 nm) that are shed from most cell types, including hepatocytes, macrophages, and hepatic stellate cells. They contain various macromolecules, including proteins, messenger ribonucleic acids (mRNAs), microRNAs (miRNAs), and other non-coding RNAs.[115] Ethanol exposure increases EV production in hepatocytes. The cargo contained in ethanol-mediated EVs are thought to regulate ALD pathogenesis. Ethanol-mediated EV release was mediated through caspase-3 activation in damaged hepatocytes.[116] Ethanol-induced EVs contained CD40 ligand, which stimulated macrophages and subsequently promoted ALD.[116] EVs derived from damaged hepatocyte also contained mitochondrial deoxyribonucleic acid (DNA) that promoted ALD through activation of TLR9.[117–119] The miRNAs present in EV cargos also contributed to ALD development. One study demonstrated that hepatocyte-derived EVs horizontally transfer miR-122 to monocytes, promoting ALD.[120] ALD-mediated circulating EVs also contain heat shock protein 90 (Hsp90), which enhances monocyte chemotactic protein (MCP-1) production in macrophages and reduces the number of M2 macrophages in ALD.[121] Further, ethanol-exposed human monocytes secrete EVs containing miR-27a that polarize naïve monocytes to M2 macrophages. These M2 polarized macrophages have increased IL-10 and transforming growth factor (TGF)-β production and phagocytic activity.[122] In ALD, EV-mediated cargos released from damaged hepatocytes and monocytes regulate liver inflammation by modulating macrophage activation and polarization.

4.6. Impaired liver regeneration in ALD

Although hepatocytes have the profound capacity to regenerate after liver injury or loss of liver tissues, the regenerative capacity of hepatocytes is significantly impaired in ALD. This was observed in rodent models with chronic ethanol exposure and patients with AH.[68,123] In rodent models, chronic ethanol-feeding impairs regenerative response by lacking an induction of cell cycle genes and altered hepatic miRNA profile after partial hepatectomy.[124] MiR-21 was significantly upregulated in the ALD liver and suppressed regenerative responses after hepatectomy in ethanol-treated rats.[125] In AH patients, p21 and p27, cell cycle inhibitors, were upregulated. p27 upregulation might be induced by miR-34a that is upregulated in AH patients.[126] These factors could contribute to the inhibition of liver regeneration in AH patients. Impaired hepatocyte regeneration is associated with the poor prognosis of AH patients.[68] IL-1 inhibits liver regeneration and is upregulated in ALD.[127] Inhibition of IL-1 signaling by IL-1 receptor antagonist recovered regenerative capacity in ALD.[128] IL-22 has a capacity to promote liver regeneration.[129] IL-22 treatment and IL-1 inhibition might be good therapeutic strategies, not only to inhibit inflammation, but also to promote regeneration in ALD.

4.7. Animal models for preclinical studies of ALD

To elucidate the numerous mechanisms of ALD, we need animal models that mimic the broad spectrum of ALD in humans. Currently, there are several rodent ALD models, with each having different feeding durations and methods as well as the presence or absence of binge ethanol gavage. Different models present with different degrees of hepatocyte injury, fatty changes, inflammatory cell infiltration, and fibrosis. The acute single-binge injection model can be used to study of acute ethanol response or mild steatosis. Experimental conditions for this model are easily performed, but the mice do not develop fibrosis.[130] The most widely used ALD model involves chronically feeding an ethanol-containing Lieber-DeCarli diet to mice for 4e8 weeks. This model produces a mild elevation in serum ALT levels, hepatic fat accumulation, and mild liver inflammation but no fibrosis.[131] A chronic ethanol-containing Lieber-DeCarli diet model modified to include ethanol binges for 3 days results in severe liver damage and some degree of fibrosis; however, this model is associated with high mortality.[127] NIAAA researchers developed a 10 day-chronic ethanol feeding with binge ethanol injection model (a.k.a. NIAAA model or Gao-Binge model) that presents with increased serum ALT levels, steatosis, and neutrophil accumulation, resembling early AH pathophysiology in humans. However, this model again does not develop fibrosis.[74] The experimental conditions of this model are easy to perform, and it is widely used in the basic research field. The Tsukamoto-French intra-gastric ethanol-feeding model is one of the best models of alcoholic steatohepatitis, recapitulating most of the human pathophysiology. The combination of the Tsukamoto-French intra-gastric ethanol-feeding model with weekly ethanol binges and *ad libitum* feeding of a high-fat diet presents with robust neutrophil infiltration and liver fibrosis, which mimic severe AH and alcoholic fibrosis, respectively, as well as steatosis, inflammation, and elevated serum ALT levels. However, the use of this model is limited due to the advanced surgical skills required and the associated animal maintenance.[132]

5. Existing and potential therapies for ALD

5.1. Currently available management for ALD

5.1.1. Abstinence and supportive care—Abstinence is the most common preventative measure for ALD patients. Abstinence can improve liver steatosis, injury, and unfavorable outcomes in patients with early-stage ALD. However, some patients with the progressive ALD can still progress to cirrhosis despite sobriety.[133] There are several FDA-approved medications (*e.g.*, disulfiram, naltrexone) for AUD, but these medications often have hepatoxic properties; therefore, their use is limited for ALD patients.[134] Baclofen and metadoxine can effectively preventing alcohol relapse with fewer hepatotoxic effects; however, these agents are not approved for this indication by the FDA.[134] Because obesity, sarcopenia, and malnutrition are associated with ALD, weight management and nutritional support (*e.g.*, ~2000 kcal with 1.2–1.5 g/kg/d protein and supplementation with amino acids (branched, leucine), zinc, vitamin D, thiamine, folate, cyanocobalamin, and selenium) can improve the course of ALD.[11,135]

5.1.2. Corticosteroids—Corticosteroids have been used to treat patients with AH for several decades. Corticosteroids downregulate TNFα production and upregulate IL-10 production in AH, reducing short-term mortality and incidence of encephalopathy.[136] However, these measures do not improve long-term survival.[66,137] Because corticosteroids can improve short-term survival, it is critical to identify severe AH that responds to corticosteroids early. The Lille model was developed to evaluate the response to corticosteroids in severe AH patients following 7 days of treatment.[138] The Lille model is useful for predicting short-term survival in patients with severe AH. Based on this model, 40% of severe AH patients do not respond to corticosteroids, and their 6-month mortality is approximately 75%.[138] The high mortality may be associated with the increased risk of infection (spontaneous bacterial peritonitis, urinary tract infection, pneumonia) due to corticosteroid use; corticosteroid-treated AH patients with an infection have significantly lower survival compared with those without an infection.[139]

5.1.3. N-acetylcysteine (NAC)—NAC, a glutathione precursor antioxidant, is widely used in clinical settings to treat acetaminophen-induced acute liver failure.[140] Because ROS plays a central role in ALD progression, NAC has been investigated as a treatment for ALD. However, treatment of severe AH with NAC alone did not improve the short-term survival compared with corticosteroids alone. By contrast, combination therapy using NAC and corticosteroids significantly improved 28-day-survival, but there was no observed long-term survival benefit.[141,142]

5.1.4. Pentoxifylline—Pentoxifylline, an antioxidant with an anti-TNFα effect, has been examined in patients with severe AH. Similar to NAC, treatment of severe AH with pentoxifylline alone showed no significant long-term survival benefit compared with corticosteroids. Even when combined with corticosteroids, pentoxifylline did not produce significant survival improvement. Accordingly, pentoxifylline is no longer considered a viable treatment for severe AH.[9]

5.1.5. Anti-TNFα antibodies—TNFα is one of the most critical inflammatory cytokines for ALD development. Anti-TNFα therapy such as infliximab, a chimeric monoclonal anti-TNFα antibody, is commonly used to treat arthritis and inflammatory bowel disease and could have therapeutic properties in ALD. Clinical studies showed that treatment of severe AH patients with anti-TNFα antibody improved disease severity and survival.[143] Furthermore, a randomized controlled pilot study of infliximab plus corticosteroids reported improvements in AH severity at 28 days.[144] However, this combination unexpectedly showed higher incidences of infection and mortality among patients with acute AH.[145]

5.1.6. Liver transplantation—Alcoholic cirrhosis is the second leading indication for liver transplantation, accounting for 25% of all procedures.[146] Liver transplantation is still the best treatment option for patients with severe AH who do not respond to corticosteroids.[147] However, most AH patients cannot apply for liver transplantation because of ethical dilemmas, a high potential for alcohol relapse, and the 6-month-abstinence rule. Recent reports evaluated liver transplantation performed prior to completing the 6 months of abstinence. Early liver transplantation demonstrated a better long-term survival rate (1e3 years) compared with matched AH patients who did not undergo transplantation and a similar survival rate to patients with alcoholic cirrhosis who underwent liver transplantation after 6 months of abstinence.[147–149] Studies did not find differences in alcohol relapse in patients who completed or did not complete the 6 months of abstinence. These studies suggest that clinicians may need to reconsider the selection process for early liver transplantation in severe AH patients.

5.2. Emerging treatment options for ALD

5.2.1. IL-22—IL-22, an IL-10-family cytokine produced by immune cells (*e.g.*, T helper (Th) 17, Th22 cells), has anti-inflammatory and regenerative properties. In animal models of ALD and ALD patients, IL-22 receptor expression is upregulated, but IL-22 expression is unchanged.[150,151] In animal studies, recombinant IL-22 treatment ameliorated alcoholic liver steatosis, injury, and fibrosis by activating signal transducer and activator of transcription 3 (STAT3).[150,151] By contrast, IL-22 has pro-inflammatory effects in patients with hepatitis B virus infections and may promote hepatocarcinogenesis.[152,153] However, because IL-22 promotes liver regeneration in addition to its anti-inflammatory effect,[153] treatment with IL-22 could yield large benefits for severe AH patients. F-652, a recombinant fusion protein containing human IL-22 and human immunoglobulin G2-Fc, is currently being evaluated for use in human AH (ClinicalTrials.gov, NCT02655510).

5.2.2. IL-1 receptor antagonist—IL-1b is initially produced in a pro-form that is processed by the inflammasome complex, consisting of caspase-1, apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), and nucleotide binding and oligomerization domain-like receptor family pyrin domain-containing 3 (NLRP3). The inflammasome converts it to the active form. IL-1β and inflammasome activation are crucial for ALD development.[127] Anakinra is an IL-1 receptor antagonist that inhibits the binding of active IL-1β to the IL-1 receptor. Anakinra has been shown to have therapeutic effects in an animal model.[127] Treatment of severe AH with anakinra is currently being examined in a

clinical trial. This trial is comparing supplementation with a combination of anakinra, pentoxifylline, and zinc in patients being treated with methylprednisolone or placebo (ClinicalTrials.gov, AH/NCT01809132).

5.2.3. Targeting the gut microbiome—Intestinal dysbiosis and bacterial overgrowth are often seen with ALD and contribute to alcohol-induced liver damage.[154] In mice, gut sterilization using orally administered non-absorbable antibiotics prevented alcohol-induced hepatic steatosis and injury and decreased serum endotoxin levels.[80] Probiotics have been reported to ameliorate ALD in both animal and human studies.[155–157] Treatment with prebiotic fructooligosaccharides or pectin prevented ALD development in mice.[78,158] Clinical trials testing the therapeutic effects of gut sterilization using a combination of vancomycin, gentamycin and meropenem (Clinical.gov, NCT03157388) and the effects of probiotics (*Lactobacillus rhamnosus* GG) for AH patients are currently underway (Clinical.gov, NCT01922895). Notably, fecal microbiota transplantation (FMT) from ALD-resistant mice to ALD-sensitive mice improved ALD.[78] FMT from healthy individuals to patients with ALD potentially could be a novel therapeutic approach. In ALD, levels of saturated long-chain FA (LCFA) were reduced in the intestine, and saturated LCFA metabolism is required for the growth of intestinal *Lactobacillus.*[159] Dietary supplementation of saturated LCFA was shown to improve ALD and gut leakiness in mice, indicating that saturated LCFA could maintain intestinal homeostasis and prevent ALD development.[159]

5.2.4. Farnesoid X receptor (FXR) and FGF15/19—The FXR is a nuclear receptor that regulates bile-acid metabolism by inhibiting hepatic CYP7A1. CYP7A1 regulation occurs directly through FXR activity and indirectly through intestine-derived FGF15/19 signaling. FXR signaling can also regulate lipid and glucose metabolism.[160] In animal models and patients with NASH fibrosis, an FXR agonist improved hepatic steatosis, inflammation, and fibrosis.[161,162] FXR signaling can suppress liver inflammation and cancer, improve intestinal barrier integrity, and promote liver regeneration.[163] A clinical trial evaluating the effect of obeticholic acid, a semi-synthetic bile-acid FXR agonist, in patients with severe AH is underway (Clinical.gov, NCT0239219). In a trial evaluating the use of obeticholic acid for NASH fibrosis, the intervention produced side effects. Given this result, researchers hypothesized that an intestine-restricted approach might reduce unfavorable effects. The intestine-restricted FXR agonist fexaramine mitigated alcohol-induced liver injury without affecting the systemic bile-acid pool in mice.[164] With respect to FGF19, over-expression of the FGF19 variant M52 attenuated alcohol-induced liver injury in mice.[164] These findings suggest that targeting intestinal FXR or FGF15/19 could be safer approaches for treating ALD than targeting systemic FXR.

5.2.5. S-adenosyl methionine (SAMe)—Long-term ethanol consumption decreases hepatic levels of SAMe, a major methyl donor, and its synthesizing enzyme methionine adenosyltransferase (MAT) α1. This reduction affects DNA and histone methylation in hepatocytes.[165] SAMe supplementation has antioxidative effects that maintain mitochondrial function and downregulate TNFα, which produces protective effects in ALD.[166] This result suggests that long-term treatment with SAMe could improve long-term survival or extend

the timing for liver transplantation in patients with alcoholic liver cirrhosis.[167] However, a previous randomized control study did not find SAMe treatment to be effective in patients with ALD.[168] SAMe potentially could be safe agent that can be delivered orally, but more evidence demon-strating the benefit in ALD requires further investigations.[157]

6. Conclusions and future perspectives

Here, we have discussed the established molecular mechanisms and those currently emerging, such as EVs and the crosstalk between liver and adipose tissues, and reviewed potential targets, such as IL-22, IL-1, and FXR signaling, for effective therapies. To develop effective future therapies for ALD, a precise understanding of its molecular mechanisms is required, and translational research using human specimens will be crucial. Testing new therapies also requires the use of consistent animal models. Unfortunately, currently available animal models of ALD do not fully recapitulate all the features of ALD, including AH and alcoholic cirrhosis. Therefore, improved animal models are similarly crucial for the development of effective therapies. It has been several decades since the current therapeutic strategies for ALD have been developed. Although corticosteroids and liver transplantation continue to be the mainstay of therapy, new therapeutic approaches should be considered. Currently, an extracorporeal human-cell-based liver support system is being tested under a clinical trial for alcohol-induced liver decompensation and severe AH (Clinical.gov, NCT02612428). In this trial, improved survival was observed only in patients who had a MELD score <28 and were <46.9 years of age.[169] Although additional prospective, randomized, controlled clinical studies in patients with lower MELD score and age are needed to evaluate the reproducibility of this observation, this approach could have a survival benefit for patients with decompensated ALD who cannot undergo liver transplantation and do not respond to corticosteroids. In the future, the combination of effective anti-inflammatory therapies and liver support systems could improve survival for high-mortality AH and alcoholic cirrhosis. If therapies to enhance liver regeneration could be added to this combination, the survival rate would increase further. There is also evidence for reconsidering the selection process for early transplantation in patients with severe AH because recent studies for of early liver transplantation showed excellent outcomes.[147–149] While there is still a long way to go to fully understand the mechanisms under-lying ALD, these promising results suggest that therapeutic advances are on the horizon.

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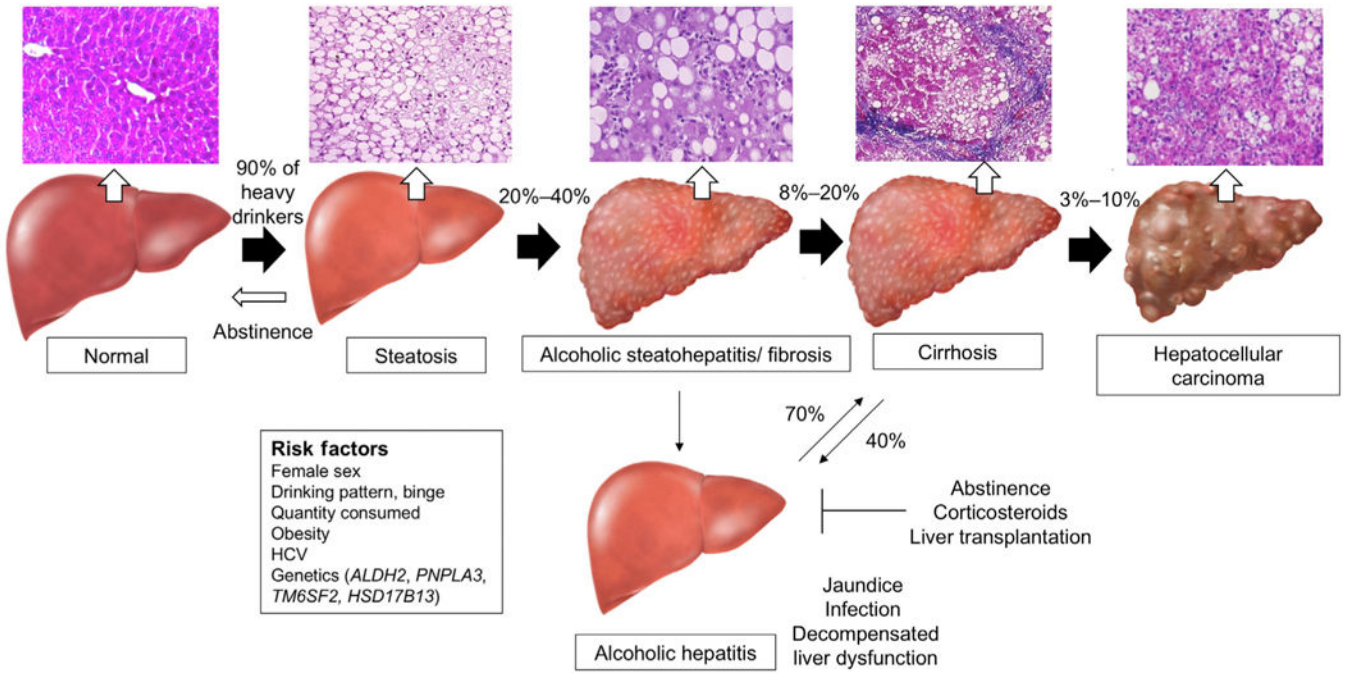

Fig. 1. The progression of ALD.

The spectrum of ALD ranges from steatosis to fibrosis, cirrhosis, and then hepatocellular carcinoma (HCC). Approximately 90% of heavy drinkers develop alcoholic steatosis. This stage is reversible when alcohol use ceases. Risk factors, such as gender, drinking pattern, obesity, viral hepatitis, and genetics, can contribute to ALD progression. About 20%–40% of patients with alcoholic steatosis will progress to alcoholic steatohepatitis, which is histologically characterized by the infiltration of inflammatory cells, especially neutrophils, the appearance of Mallory-Denk bodies, ballooning degeneration, and hepatocyte death in the liver parenchyma. Some of those patients will develop liver fibrosis and subsequently cirrhosis. Fibrosis begins at perivenular region (zone 3) and extends to the neighboring central or portal areas (bridging fibrosis). The surface of cirrhotic liver is irregular. Cirrhosis may further progress to HCC. AH, an acute-on-chronic condition of ALD, presents with clinical symptoms, such as jaundice, infection, and decompensation. AH can occur at any stage of ALD. Treatments for AH include abstinence and corticosteroids, but they are not always effective. However, liver transplantation can be a curative therapy. Abbreviations: ALD, alcoholic liver disease; HCV, hepatitis C virus; AH, alcoholic hepatitis; ALDH2, aldehyde dehydrogenase 2; PNPLA3, patatin-like phospholipase domain-containing protein 3; TM6SF2, transmembrane 6 superfamily member 2; HSD17B13, hydroxysteroid 17-beta dehydrogenase 13.

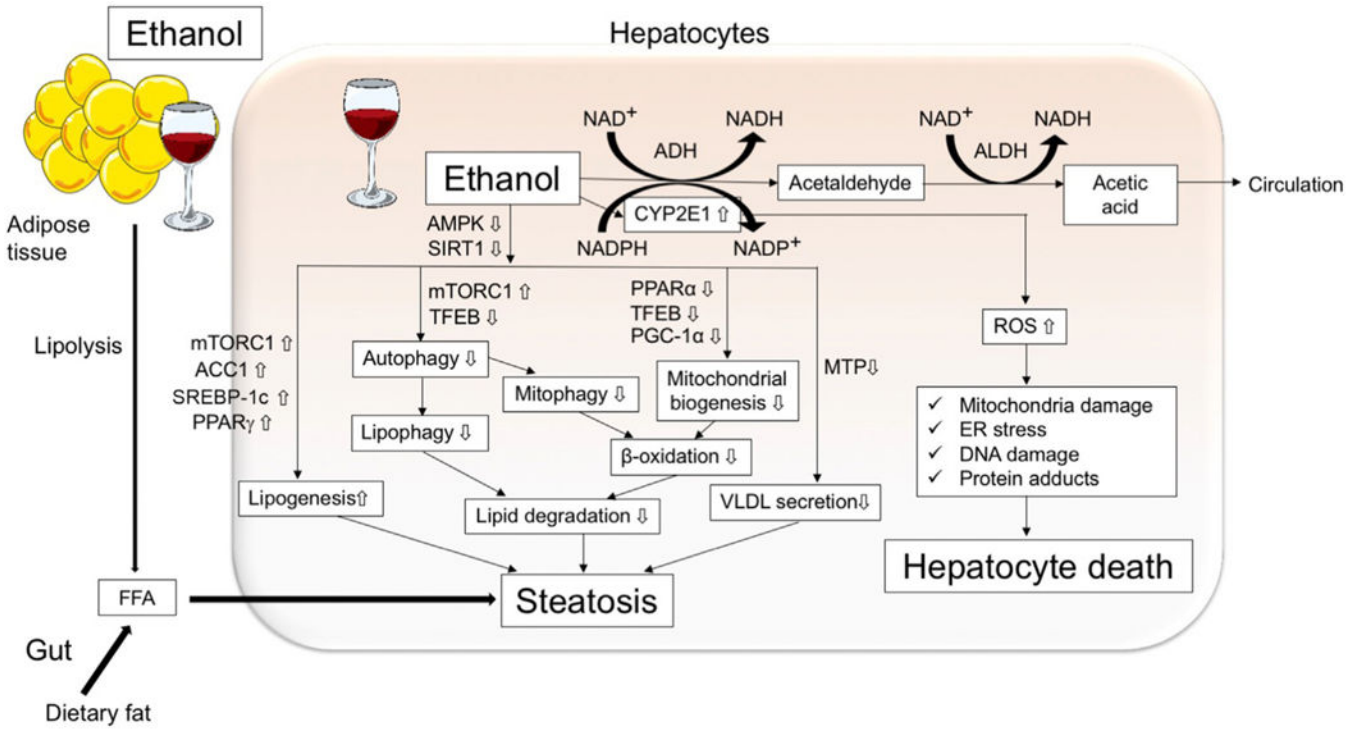

Fig. 2. Ethanol consumption increases hepatic steatosis.

In hepatocytes, ADH oxidizes ethanol to acetaldehyde and converts NAD^+ to NADH. Acetaldehyde entering the mitochondria is converted to acetate and NADH by ALDH through the reduction of NAD^+. Ethanol is also degraded by CYP2E1 through the conversion of NADPH to $NADP^+$. CYP2E1 upregulates ROS production, leading to mitochondria damage, ER stress, DNA damage and the production of protein adducts, resulting in apoptosis. Ethanol reduces AMPK levels, which increases ACC1 activity, decreases PPARa levels, and increases mTORC1 activity. Increased mTORC1 further increases SREBP-1c activity and decreases autophagy. These signaling pathways lead to increased fatty acid synthesis, decreased fatty acid b oxidation, and lipophagy as well as the induction of steatosis. Ethanol also impairs VLDL secretion by inhibiting MTP. Ethanol promotes lipolysis in adipose tissues, resulting in FFA flux to the liver. Excessive intake of dietary fat also promotes alcohol-induced steatosis. Abbreviations: ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; NAD^+, nicotinamide adenine dinucleotide; NADH, reduced nicotinamide adenine dinucleotide; NADPH, reduced nicotinamide adenine dinucleotide phosphate; $NADP^+$, nicotinamide adenine dinucleotide phosphate; CYP2E1, cytochrome P450 2E1; ROS, reactive oxygen species; ER, endoplasmic reticulum; AMPK, adenosine monophosphate-activated protein kinase; ACC1, acetyl-Co A carboxylase 1; PPAR, peroxisome proliferator-activated receptor; mTORC1, mammalian target of rapamycin complex 1; SREBP-1c, sterol regulatory element-binding protein-1c; VLDL, very-low-density lipoproteins; MTP, microsomal triglyceride transfer protein; FFA, free fatty acid; PGC, peroxisome proliferator-activated receptor gamma coactivator; SIRT1, sirtuin 1; TFEB, transcription factor EB; DNA, deoxyribonucleic acid.

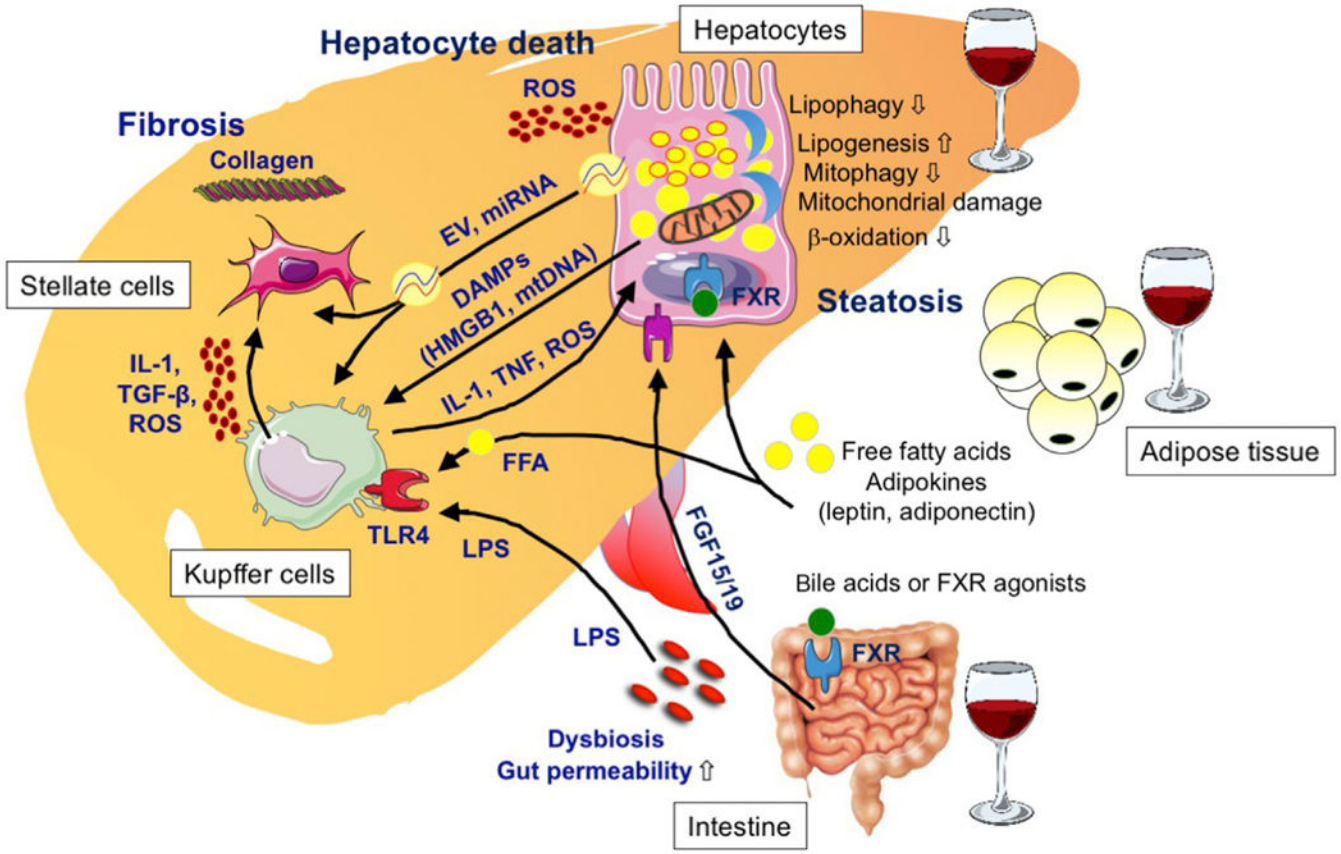

Fig. 3. Gut-adipose tissue-liver network in ALD.

Excessive alcohol consumption can affect the composition of intestinal microbiota and increase intestinal permeability by disrupting intestinal epithelial barrier functions. Intestine-derived PAMPs, such as LPS, translocates to the liver via portal veins. In the liver, translocated LPS binds TLR4 to stimulate neutrophils. Kupffer cells and HSCs produce ROS and pro-inflammatory cytokines, such as TNFα, IL-1, and chemokines, leading to hepatocyte damage and liver inflammation. Chronic LPS stimulation facilitates liver fibrosis by causing Kupffer cells and HSCs to downregulate MMPs and produce extracellular matrix, including collagen. Ethanol and acetaldehyde can damage hepatocytes, leading to release of DAMPs, such as HMGB1, and EVs that contain mitochondrial DNA. Ethanol can promote lipogenesis and inhibit lipid degradation by suppressing β-oxidation and autophagy. Hepatic FXR and intestinal FXR that induces FGF15/19 production regulate bile acid and lipid homeostasis in the liver. Ethanol induces lipolysis and adipokine production in adipose tissues. Fatty acids released from adipocytes promote hepatic steatosis. Adipose-tissue-derived free fatty acids also activate Toll-like receptor 4 (TLR4) signaling. Abbreviations: PAMPs, pathogen-associated molecular patterns; LPS, lipopolysaccharide; HSCs, hepatic stellate cells; MMPs, matrix metalloproteinases; DAMPs, damaged-associated molecular patterns; EVs, extracellular vesicles; FGF, fibroblast growth factor; FXR, farnesoid X receptor; HMGB1, high mobility group box 1; IL, interleukin; miRNA, microRNA; mtDNA, mitochondrial DNA; FFA, free fatty acid; ROS, reactive oxygen species; TGF, transforming

growth factor; TLR, toll-like receptor; TNF, tumor necrosis factor; DNA, deoxyribonucleic acid.

Table 1

Alcohol contents of various alcoholic beverages.

Beverage type	Serving size (fl oz)	ABV (%)	Energy (Cal)
Beer			
Light	12	5	103
Regular			153
Malt	8–9	7	93
Table wine	5	12	121–125
Champagne	4	12	84
Sake	3.5–4.0	16	140
Fortified wine	3–4	17	Varies
Cordial, Liqueur, Aperitif	2–3	24	Varies
Distilled spirits			
Vodka, Rum, Tequila, Gin, Cognac, Brandy	1.5	40	97–98

Abbreviations: fl oz, fluid ounce; ABV, alcohol by volume.