ACAVIS PUBLISHERS

Current Trends in Biological Science

Review Article

Volume 2, Issue 1

Alcohol-Associated Liver Disease: From Pathogenesis to Treatment Through the View of Personalized & Precision Healthcare Services

Alexey O Bueverov[1], Robert H Lustig[4], Mikhail V Kalashnikov[1], Holland Cheng R[3], Steven Dooley[5], Sergey V Suchkov[2,*]

[1]M.F. Vladimirsky Moscow Regional Clinical Research Institute (MONIKI), Russia
[2]N.D. Zelinskii Institute for Organic Chemistry of the Russian Academy of Sciences, Russia
[3]Dept of Molecular and Cellular Biology, College of Biological Sciences, University of California Davis (UC Davis), USA
[4]Division of Pediatric Endocrinology, Institute for Health Policy Studies, University of California, USA
[5]Molekulare Hepatologie – Alkoholfolgeerkrankungen II. Medizinische Klinik, Medizinische Fakultät Mannheim, der Universität Heidelberg, Germany

***Correspondence:**
Sergey V Suchkov
N.D. Zelinskii Institute for Organic Chemistry of the Russian Academy of Sciences, Moscow, Russia.
Email: ssuchkov57@gmail.com

Article Info:
Received Date: May 06, 2026
Published Date: June 09, 2026

Citation:
Alexey O Bueverov, Robert H Lustig, Mikhail V Kalashnikov, Holland Cheng R, Steven Dooley, Sergey V Suchkov. Alcohol-Associated Liver Disease: From Pathogenesis to Treatment Through the View of Personalized & Precision Healthcare Services. Curr Trends Biol Sci. 2026;2(1):1-17.

ABSTRACT

Patients with chronic liver disease require a fresh approach that focuses on the genetic and environmental factors that contribute to disease initiation and progression. In this context, alcohol-associated liver disease (ALD) is a group of disease including different variants of liver damage caused by ethanol and its metabolites. Moreover, ALD is a chronic condition that requires a multidisciplinary approach involving medical, nutritional, and psychosocial interventions, which are key to avoiding disease recurrence and managing complications. The development of the disease is multifactorial, involving interactions between genetic susceptibility and lifestyle factors, such as alcohol consumption. The latter means that early intervention and adherence to treatment plans are crucial for improving outcomes in patients with ALD.

According to clinical, laboratory and histological criteria there are three main forms of ALD: steatosis, steatohepatitis (ASH) and liver cirrhosis (ALC).

KEYWORDS: Liver disease, ALD, Liver cirrhosis, ASH

ABBREVIATIONS

ADH: Alcohol Dehydrogenase; AU: Alcohol Unit; ALD: Alcohol-Associated Liver Disease; ALC: Alcohol-Associated Liver Cirrhosis; ASH: Alcohol-Associated Steatohepatitis; CLR: C-type Lectin Receptors; CYP: Cytochrome; DAMPs: Damage-Related Molecular Patterns; ER: Endoplasmic Reticulum; Gzm; Granzyme-mediated Pathway; GPX: Glutathione Peroxidase; IL: Interleukin; IRF: Interferon Regulatory Factor; LSEC: Liver Sinusoidal Endothelial Cell; LSC: Liver Stellate Cell; NLRs: Nucleotide Oligomerization Domains-Like Receptors; MIF: Migration Inhibition Factor; miRNA: MicroRNA; NAD: Nicotinamide Dinucleotide; NF-kB: Nuclear Factor Kappa B; PAMPs: Pathogen-Associated Molecular Patterns; PCD: programmed cell death; RIP: Receptor-Interacting Protein Kinase 3; TGF-β: Transforming Growth Factor B; TNF: Tumor Necrosing Factor; VEGF: Vascular Endothelial Growth Factor; ER: Endoplasmic

Reticulum; PCD: Programmed Cell Death; KC: Kupffer Cell; Nf: Neutrophil; NKT: Natural Killer Cell; LPS: Lipopolysaccharide; PAMPs: Pathogen-Associated Molecular Patterns; BA: Bile Acids; LCFA: Long Chain Fatty Acids; AMP: Antimicrobial Peptides.

EPIDEMIOLOGY

Globally, in 2021, the number of people with ALD was approximately 3.02 million cases, which is 38.7% more than in 2000.[1-5] In 2021, ~354,250 people died from ALD, 92,230 of them from ethanol-associated hepatocellular carcinoma.[6] A relatively higher number of cases are reported in Eastern Europe and Central Asia.[5,7]. Severe forms of the disease are more likely to develop in older age groups, which is primarily due to a longer alcohol load, although this factor is not the only one.[8] Despite the predominance of men, in recent decades there has been an accelerated increase in the incidence among women.[9] Modeling forecasts show that the prevalence of ALD and mortality from it will increase by the middle of the 21st century.[4,5,10]

ETHIOLOGY AND RISK FACTORS

The risk of ALD increases when consuming >30 g of pure ethanol per day for men and >20 g of ethanol per day for women.[11] The development of ASH is usually associated with regular intake of alcoholic beverages at least twice the minimum hepatotoxic for more than 10 years.[8,12] Consumption of >80 g of pure ethanol per day for 10 years or more increases the likelihood of ALD.[8,13] Since not all abusing patients take alcoholic beverages daily, it is customary to calculate weekly doses. The upper limits of safe alcohol doses are 21 and 14 alcohol units (AU) per week for men and women, respectively; 1 AU averages 14 grams of ethanol, with variations in different countries from 8 to 20 g.[11,13,14] There is no direct correlation between the progression of liver pathology and the amount of alcohol consumed: less than 20% of people who consume it in dangerous doses suffer from clinically significant forms of liver damage.[13,15] The risk of ASH increases in binge drinking, which refers to the consumption of more than 5 AU within 2 hours for men and 4 AU for women.[3,13,16]

In women, low activity of gastric alcohol dehydrogenase (ADH), a greater amount of adipose tissue, dependence of ethanol absorption on the cycle phase, as well as increased sensitivity of Kupffer cells to bacterial endotoxin under the influence of estrogens are mentioned as risk factors for ASH.[17,18] Easily digestible fructose, contained primarily in sugar-containing beverages, in combination with alcohol promotes the differentiation of Kupffer cells according to the pro-inflammatory M1 phenotype, characterized by the hyperproduction of TNFα and monocytic chemoattractant protein-1.[19,20] On the contrary, physical activity helps slow the progression of hepatosteatosis and sarcopenia.[21] Dry wine contains resveratrol, which has a certain hepatoprotective effect.[22] Natural coffee suppresses hepatic fibrogenesis by unclear, probably antioxidant mechanisms; plant polysaccharides also have antioxidant properties.[23,24] Vinegar and garlic inhibit cytochrome (CYP) P4502E1, reducing the formation of acetaldehyde; some alkaloids of garlic also have anti-inflammatory properties.[25,26] The data on the last two protective factors are mostly experimental.

PATHOGENESIS

Ethanol Metabolism

Ethanol is metabolized by both oxidative, including ADH, microsomal CYP P450 enzymes and peroxisomal catalase, and non-oxidative pathways.[27,28] ADH, belonging to the class of zinc-containing dehydrogenases, are located in the cytosol, catalyze the oxidation of ethanol to aldehydes or ketones with transformation of nicotinamide dinucleotide (NAD+) to NADH, and can also catalyze the reverse reaction.[29]

Genes involved in alcoholism and the risk for chronic liver disease include taste receptors, neurotransmitter receptors, alcohol-metabolizing enzymes, and steatotic genes that are highly polymorphic worldwide. Human ADHs are encoded by at least seven genes on chromosome 4 and divided into five classes.[28] ADHs are most active in the liver.[27,29] Class I ADHs (ADH1A, ADH1B and ADH1C) are responsible for hepatic oxidation of most of the ethanol, generating acetaldehyde.[29]

Acetaldehyde has a high reactivity and forms adducts with cellular proteins, nucleic acids and lipids, disrupting cell function and thereby determining the main pathogenic properties of alcohol.[30] Acetaldehyde also competes with other endogenous aldehydes such as dopamine, norepinephrine and serotonin. Toxic acetaldehyde is rapidly converted to less toxic acetate by aldehyde dehydrogenases.[27,30]

Chronic alcohol consumption increases the expression and activity of a number of cytochromes, primarily CYP2E1, a conserved isoform that is expressed in various tissues.[27,31] CYP2E1 plays a significant role in the oxidation of ethanol to acetaldehyde, especially in the presence of high concentrations of ethanol. Catalase decomposes H_2O_2 into H_2O and O_2 in the presence of an electron donor, in particular, ethanol, which is oxidized by catalase to acetaldehyde.[32] Although CYP2E1 and catalase play a much smaller role in alcohol oxidation compared to ADH, they significantly affect the rate of oxidation of ethanol to acetaldehyde in the brain, where ADH activity is low.[27,32]

Metabolic dysfunction- and alcohol-associated liver disease (MetALD) is a poorly understood condition that bridges metabolic and alcohol-related pathological characteristics. Several non-oxidative metabolic pathways cause the enzymatic conjugation of ethanol with endogenous substrates to form non-oxidized end products such as ethylglucuronide, ethyl sulfate, phosphatidylethanol, and fatty acid ethyl ether.[33] These ethanol metabolites may be useful as retrospective biomarkers in assessing alcohol consumption due to their relatively slower rate of elimination.[3,13,33]

The formation of highly reactive acetaldehyde and excess reactive oxygen species during the oxidative metabolism of ethanol leads to liver cell damage. The liver's reaction to the accumulation of damaged proteins, nucleic acids, and lipids disrupts cellular functions and stimulates the activation of signaling pathways such as unfolded protein response or stress of endoplasmic reticulum (ER), which in turn triggers multiple cell death pathways.[34,35]

MECHANISMS OF PROGRAMMED CELL DEATH

The complex balance between the survival and death pathways of parenchymal and non-parenchymal cells is crucial for the regulation of liver damage and inflammation during the progression of ALD.[34] Programmed cell death (PCD) is a process that serves to maintain tissue homeostasis in multicellular organisms.[36] There are four main variants of PCD: apoptosis, necroptosis, pyroptosis, and ferroptosis.[36-38] Recently, a new pathway of proinflammatory PCD, called panoptosis, has been described, which is activated by bacterial and viral triggers and controlled by a multidimensional protein complex, the panoptosome.[39,40] The panoptosome can simultaneously involve pyroptosis, apoptosis, and necroptosis.[39,40] In addition, autophagy and membrane transport, which have common components and influence each other, play an important role in repairing damage and cell survival.[41] Dysregulation or hyperactivation of autophagy and membrane transport are associated with cell damage and death, contributing to the progression of ALD.[42] Ethanol induces cellular oxidative stress and/or ER stress during its metabolism, which leads to an increase in damage-related molecular patterns (DAMPs).[34,43] The liver is also exposed to pathogen-associated molecular patterns (PAMPs) as a result of ethanol exposure to intestinal integrity.[43] Together, these damages lead to the activation of various cell death pathways.[34,44=]

Apoptosis

The external apoptosis pathway is activated by members of the tumor necrosing factor (TNF) death receptor ligand family, which includes TNFα, Fas ligand, and TNF-related apoptosis-inducing ligand (TRAIL).[45,46] The internal pathway is usually triggered by members of the B-cell lymphoma 2 (Bcl-2) family, which control the permeability of the outer mitochondrial membrane, the release of cytochrome c and, subsequently, the activation of caspases.[46] Ethanol exposure induces external apoptotic pathways mediated by the Fas ligand and death receptor-5 (DR5) via microRNA-21 (miRNA-21).[47,48] Later, an apoptotic pathway mediated by a receptor like retinoic acid-induced gene I and interferon regulatory factor 3 (IRF3) was described.[49] In the last branch, IRF3 is activated by linear ubiquitination and triggers its interaction with the Bax protein, causing mitochondrial activation and apoptotic cell death.[50,51]

Activation of IRF3 initiates alcohol−induced hepatocyte apoptosis, which triggers a secondary inflammatory reaction that leads to the initiation and progression of steatohepatitis.[49,52] IRF3 signaling, spreads through the intercellular gap junctions in the liver between hepatocytes through connexin 32 (Cx32), thereby increasing inflammation and accelerating apoptosis of hepatocytes.[52] In addition, apoptosis of hepatic monocytes/macrophages also contributes to disruption of hepatic liver homeostasis and modulates responses to ethanol-induced damage.[53]

Interleukin 10 (IL-10), released from Kupffer cells with a pro-regenerative M2 phenotype, promotes the death of Kupffer cells with a pro-inflammatory M1 phenotype through apoptosis, protecting against alcohol-induced inflammation and damage.[54] Based on these data, it can be assumed that intervention in the pathway of apoptotic death is a potential strategy for preventing alcohol-induced damage.[55,56] However, the genetic (Bid −/−, caspase-8 −/−) or pharmacological (VX166, pan-caspase inhibitor) suppression of apoptosis did not provide complete protection, which was demonstrated in mouse models of early-stage ALD.[57] These data indicate that cell-specific and/or additional forms of PCD are crucial in the progression of ASH.[56]

Necroptosis

The classical variant of necroptosis is initiated by phosphorylation of receptor-interacting protein kinase 3 (RIP3) using RIP1.[58,59] RIP3 then phosphorylates the critically important MLKL effector, which leads to its translocation to the plasma membrane, where it oligomerizes and forms pores that trigger necroptotic cell death.[58,60] In addition to death receptors, Toll-like receptors and interferon receptors are involved in the induction of MLKL-mediated necroptosis.[61] Numerous studies have established the differentiated role of the RIP1-RIP3-MLKL axis in the progression of steatohepatitis in mouse models of ALD.[62] Chronic alcohol consumption induces RIP3 expression in mouse liver and primary hepatocytes, while RIP1 mRNA and protein levels decrease significantly.[62,63]

Inhibition of RIP1 by necrostatin-1 attenuates ethanol−induced inflammation, but not damage to hepatocytes, while RIP3-/− mice, as noted earlier, are completely protected from chronic ASH.[64] These data suggest that RIP3 contributes to the progression of ALD through a mechanism independent of RIP1. Indeed, members of the casein kinase family directly phosphorylate RIPK3 to activate necroptosis, probably by interacting with RIP3 through its RHIM domain.[65] MLKL −/− mice show only partial attenuation of the hepatotoxic effect of ethanol, indicating that RIP3 and MLKL also probably act through independent, non-canonical mechanisms in ASH.[66]

From the point of view of translational medicine, circulating concentrations of RIP1 and RIP3 make it possible to distinguish patients with AHS from both healthy individuals and patients with metabolically associated steatohepatitis.[67] Moreover, RIP3, but not RIP1, represents a potentially promising biomarker for predicting the outcome of ASH.[66,67] These data are consistent with reports that the ratio of the circulating concentration of cytokeratin-18 to its cleavage product mediated by caspase-3, released during necrotic/necroptotic and apoptotic cell death, respectively, are also diagnostic and prognostic indicators in these patients.[67]

Pyroptosis

The canonical pathway of pyroptotic cell death requires the preparation and integration of multiple signals triggered by DAMPs and PAMPs through Toll-like receptors.[69] The integration of signals is carried out by assembling cytosolic pattern recognition receptors, including receptors of the family of nucleotide oligomerization domains (NOD)-like receptors (NLRs) containing pyrin domain 1 (NLRP1), NLRP3, NLRC4, AIM2 (absent in melanoma 2) and the pyrin, as well as activation of caspase-1.[69] Non-canonical pyroptosisis caused by caspase-4 and caspase-5 (in humans) or caspase-11 (in mice).[70] Upon activation, these caspases cleave gasdermine D, which then binds to lipids on the plasma membrane and forms oligomeric pores, which leads to pyroptosis.[71]

Activated caspase-1 controls the maturation of IL-1b and IL-18. Activated caspases-4, -5, and -11 also cleave pannexin-1, causing ATP release and pyroptotic cell death associated with P2X7R.[72] Pyroptosis can also be initiated by other members of the gasdermine family; for example, active caspases-3 and caspases-8 cleave gasdermines E and D, respectively.[71] In addition, under hypoxic conditions, programmed death ligand 1 (PDL1) moves to the nucleus and regulates gasdermine C transcription along with phosphorylated signal transductor and transcription activator 3 (p-STAT3), which leads to the transformation of apoptosis into pyroptosis after activation of caspase-8 by TNFα.[70,71] In the granzyme-mediated pathway (Gzm), GzmA and GzmB in cytotoxic lymphocytes enter target cells through perforin and cause pyroptosis. GzmA hydrolyzes gasdermine B, and GzmB, in turn, directly activates gasdermine E.[72]

There is growing evidence that pyroptosis mediated by the gasdermine family is a key factor in the development of ASH in both experimental animals and humans.[73] Thus, ethanol induces pyroptosis mediated by caspase-1 through overexpression of TXNIP in hepatocytes directed at microRNA-148a.[47,48] The NLRP3 inflammasome pathway is activated in hepatocytes in response to lipopolysaccharide-induced ER stress.[67] Metabolically produced DAMPs, including ATP and soluble uric acid, released from damaged hepatocytes in response to the action of ethanol, trigger secretion of inflammasome-dependent IL-1β by immune cells.[69]

NLRP3-deficient mice are resistant to ethanol-induced inflammation and damage.[67] Inhibition of ATP or uric acid prevents the activation of the inflammasome and the production of IL-1β, thereby protecting mice from the development of steatohepatitis.[73] Pharmacological inhibition of IL-1β/IL-1R1 signaling by recombinant human IL-1R antagonist resulted in a decrease in ASH activity.[74] The process of transformation of chronic alcohol-associated steatosis into steatohepatitis is accompanied by activation of the caspase-11/gasdermine D signal, but not the caspase-1/IL-1β signal.[70,73] Caspase-11 deficiency prevented ethanol-mediated gasdermine D activation, hepatocyte death, and bacterial translocation.[71]

Ferroptosis

Chronic ethanol exposure leads to iron-dependent ferroptotic cell death, which is characterized by excessive accumulation of intracellular lipid ROS and subsequent lipid peroxidation as a result of depletion of iron-dependent glutathione and inactivation of glutathione peroxidase 4 (GPX4).[75] Thus, ferrostatin-1, which serves as a lipid ROS scavenger, significantly mitigates ethanol-induced damage to hepatocytes both in vitro and in vivo.[76] Ferroptosis is also involved in the progression of ALD through the liver-intestine and liver-adipose tissue axes.[77] Adipose tissue-specific overexpression of lipin-1 exacerbates steatosis and hepatobiliary inflammation and leads to initial fibrotic changes through GPX4-independent induction of lipid peroxidation caused by liver iron overload.[75] Intestinal SIRT1 is also necessary for the implementation of ethanol-induced dysfunction of iron metabolism in the liver and ferroptosis.[76,78] There are serious reasons to believe that suppression of ferroptosis signals in the liver represents a certain therapeutic potential in ASH.[76]

AUTOPHAGY AND MEMBRANE TRANSPORT

The role of autophagy of hepatocytes in the pathogenesis of ALD is complex. Acute alcohol consumption activates autophagy, while chronic alcohol exposure reduces lysosome-mediated lipid droplets turnover in hepatocytes by inactivating Rab7 and/or reducing dynamin 2 activity.[79] In both acute and acute on chronic cases of ethanol exposure, lysosome biogenesis mediated by transcription factor EB (TFEB) is disrupted by activation of mTORC1, what leads to decrease of autophagy activity. In addition, dysregulation of autophagy and lysosome function is associated with the production of exosomes in ALD.[80] The total number of circulating extracellular vesicles increases both in mice after chronic ethanol intake and in patients with ASH.[81,82] It has been demonstrated that the contents of extracellular vesicles, microRNAs-192 and -30a, as well as heat shock protein 90 and CD40 ligand, are potential biomarkers and mediators of ethanol-induced damage.[82,83]

There is a close interaction between autophagy and membrane transport, as well as various forms of PCD. Autophagy is considered as an early adaptive response to damage that occurs before the stage of apoptosis; however, overactivation of autophagy leads to apoptotic cell death through common regulators such as beclin1 and Bcl-2.[84] Proteins during autophagy can control the switching of PCD between apoptosis and necroptosis [84]. Moreover, autophagy can inhibit or, conversely, promote pyroptosis and the release of inflammatory cytokines, depending on the cellular environment.[85]

In general, the regulatory mechanisms for maintaining a balance between the pathways of cell survival and death in the liver are very multifaceted. It is assumed that apoptosis may prevail in the early stages of ALD, but with the progression of steatohepatitis, necrotic/necroptotic cell death supports inflammation.[86,87] At the next stage of progression, with the addition of endotoxinemia/ bacteremia, hepatocyte death by pyroptosis begins to dominate, contributing to the attraction of polymorphonuclear neutrophils and further increased inflammation.[34,43] The predominance of one type or another of PCD probably depends on the specific microenvironment.[36]

IMMUNE REACTIONS

Innate and adaptive immunity

In ALD, the role of the immune system is both to clear bacteria and their products formed in the intestine through PAMPs, and to respond to tissue damage through DAMPs.[88] The immune system reacts to signals with a combination of pro-inflammatory and anti-inflammatory reactions, which ensures the elimination of pathogens and dead cells, ideally leading to the resolution of inflammation.[89]

Excessive alcohol consumption causes massive intake of bacterial lipopolysaccharide from the gut through the portal vein to the liver, which leads to activation of toll-like receptors (primarily TLR4) on resident Kupffer cells and monocytes.[8,43] In ALD patients' macrophages become hypersensitive to lipopolysaccharide, responding by increasing the production of pro-inflammatory cytokines [54]. PAMPs and DAMPs transmit signals through TLR and activate immune system.[89] We can say that pattern-recognizing receptors are involved in the progression of ASH, including both intracellular TLR3/7/8/9 ,cGAS, AIM2, NLR, and extracellular TLR2/4 and C-type lectin receptors (CLR).[90]

CLRS are of particular interest because they recognize a much broader repertoire of PAMPs compared to the TLR family, including a wide variety of fungi, viruses, commensal bacteria, eukaryotic pathogens, and DAMPs from various cells and tissues.[91] The expression of various CLRS in ASH appears to be increased both in the liver and in peripheral blood mononuclears.[92] Dectin-1 is CLR, directed at pathogenic strains of Candida albicans, is elevated in patients with ASH and increases liver inflammation in response to β-glucans of intestinal Candida albicans.[93]

The expression of other CLRS, including Mincle, dectin-2, and dectin-3, increases in response to lipopolysaccharide stimulation.[94] The CLR-mediated response to TLR4 signaling is a secondary pathway of immune surveillance that increases the sensitivity of monocytes to a wide range of PAMPs and DAMPs, which, in turn, promotes inflammatory infiltration of tissues with the presence of damaged cells and foreign agents.[89,94] Mice with knockout of both the Mincle gene and the dectin-1 gene are protected from ethanol-induced liver damage.[34]

Activation of pattern-recognizing signaling in ASH enhances the expression of cytokines and chemokines, contributing to further tissue damage.[88,90] Neutrophils, which are attracted to the focus of inflammation by specific mediators, play a controversial role in the progression of the disease. On the one hand, they contribute to elimination of dead and dying cells, and on the other, they have a damaging effect on tissues.[95] Natural killer (NK) cells and T cells also respond to these inflammatory signals, however, despite an increase in their number in the liver, they show reduced activity in ASH.[96]

Modeling of ASH in experimental animals, primarily mice, has serious limitations. Apart from species differences, these models do not take into account such important factors as gender, genetic diversity, dietary habits, comorbidity, etc.[97] Therefore, in recent years, omix technologies have been used in most of the research. In particular, RNA sequencing of individual cells (scRNA-seq) and RNA sequencing in large volumes (bulk RNA-seq) have already proved informative for understanding the role of immune cells in ASH.[98] Thus, the scRNA-seq study demonstrated that peripheral monocytes of patients with ASH are characterized by less functional diversity than monocytes of healthy people.[99] In response to exposure to lipopolysaccharide, various subpopulations of monocytes in the control groups reacted with a variety of pro-inflammatory and anti-inflammatory response options, whereas in patients with ASH, all monocytes were pro-inflammatory. Since both hepatic and peripheral inflammation is observed in ALD, and especially in ASH, a number of new treatment methods being developed are aimed at suppressing inflammation by affecting the cells of the innate immune system.[100]

Cytokines

Both animals chronically exposed to ethanol and patients with ASH have elevated serum levels of various cytokines, including TNF-α, interleukins (such as IL-1, IL-4, IL-6, IL-10, IL-12, IL-17, and IL-22), interferon-γ, highly sensitive C-reactive protein, transforming growth factor β (TGF-β) and adiponectin.[8,101] Most of them play a dual role in the pathogenesis of ASH.

TNF-α is a critically important proinflammatory cytokine in ASH.[101] Chronic exposure to ethanol leads to an excessive flow of lipopolysaccharide from the intestine to the liver, which leads to activation of Kupffer cells through TLR4.[43] Their increased production of pro-inflammatory cytokines, primarily TNF-α and IL-1, contributes to the disruption of the normal functioning of hepatocytes and their PCD, as well as the activation of liver stellate cells that generate profibrogenic extracellular matrix proteins.[54] Mice with TNF-α knockout, deficiency of various components of the IL-1 pathway, as well as mice treated with IL-1 receptor antagonist, were protected from ethanol induced liver damage.[74] Other cytokines, in particular TGF-β, are also associated with activation of liver stellate cells and collagen production, promoting fibrogenesis in patients with ASH.[102]

IL-6 is another pleiotropic cytokine that plays a dual role in liver homeostasis. Elevated levels of IL-6 can reduce liver damage and inflammation by activating STAT3 and participate in the repair of mitochondrial DNA in animals exposed to chronic alcohol exposure and in patients with alcohol-related disorders, both with and without liver damage.[103,104] On the other hand, IL-6 promotes the differentiation of human Th17 cells and the production of IL-17, thereby contributing to the progression of ASH due to increased neutrophil recruitment.[105]

Interestingly, that IL-10, an anti-inflammatory cytokine known for its hepatoprotective effects, is secreted simultaneously with pro-inflammatory cytokines. When mice with IL-10 gene knockout are chronically exposed to ethanol, they demonstrate intensification of inflammatory reactions in the liver associated with IL-6/STAT3 activation, but with less pronounced steatosis and lower transaminase activity compared to normal animals.[106]

IL-22, another member of the IL-10 cytokine family, also demonstrates protecting properties from ethanol-induced damage. In a mouse model of ASH, the use of recombinant IL-22 activated liver STAT3, suppressing oxidative stress and hepatocytes damage.[107] In a phase II clinical trial with recombinant IL-22, clinical improvement and a decrease in liver damage markers were observed in patients with ASH.[108]

Chemokines

The serum concentrations of a variety of chemokines, including Gro-α/CXCL1, PF-4/CXCL4, CXCL5, CXCL6, IL-8/CXCL8, CXCL10, CCL2, and CCL20, positively correlate with patient's mortality in severe ASH.[109,110] Thus, hepatic CXCL8/IL-8, which expression dramatically increases in ASH, is specifically associated with the attraction of neutrophils to the liver.[111] IL-8 expression is induced by TNF-α and TLR-dependent activation of nuclear factor kappa B (NF-kB).[112] It has been demonstrated in mouse models of ASH that blockade of IL-8 (CXCR1/2) receptors by the specific antagonist pepducin prevents liver damage.[113] Among CC chemokines, CCL20– the ligand for CCR6– is one of the most expressed chemokines in the liver of patients with ASH.[114] CCL20 expression is induced by many inflammatory mediators, such as lipopolysaccharide, TNF-α and IL-1b, and, acting as a chemoattractant for lymphocytes and neutrophils, regulates hepatic inflammation and fibrogenesis.[114,115]

High concentrations of macrophage migration inhibition factor (MIF), another pleiotropic cytokine/chemokine, in the prehepatic bloodstream correlate with mortality in ASH.[116] MIF produced by hepatocytes contributes to hypersecretion of many chemokines in the liver of mice with ethanol-induced acute-on-chronic liver failure, including CXCl1, CXCl5, CXCl6, cxcl8, CGl2 and CGl20.[117]

COMPLEMENT

Experimental data indicate the role of complement in the initiation and development of ASH.[118] C3 or C5 deficient miceare protected from chronic ethanol-initiated liver damage, while mice deficient in CD55, a complement regulator, experience an aggravation of the process.[119] Specific inhibition of C3 activation involving the complement receptor 2 (CR2)-Crry suppresses the activity of inflammation and the severity of liver steatosis in mice exposed to ethanol.[120] It has been established that one of the mechanisms of complement activation in response to ethanol exposure is the binding of C1q to apoptotic hepatocytes, upregulating of proinflammatory cytokines expression.[121]

The toxic effect of chronic ethanol exposure is significantly reduced in C1qa deficient mice, as well as after C1 – C1-INH inhibitor – exposure.[121,122] Combined results of these studies suggest that the classical pathway of complement activation contributes to alcoholic liver damage. In contrast, activation of complement alternative pathway protects the liver from chronic ethanol exposure.[119]

A number of studies also point to the role of complement in patients with ALD. In particular, it was found that increased concentration of C3a in plasma is associated with development of fatty liver and damage to hepatocytes in alcohol abusers.[123]

In another study, the immunoreactivity of C1q, C3, C5, and C5aR was increased in liver biopsies of patients with ASH compared with healthy ones; hepatic expression of C1q and C5 mRNAs, but not C3, was also significantly higher in steatohepatitis.[124] Quantitative determination of complement components in plasma of patients with moderate and severe ASH demonstrated the importance of factors C4b, C4d, CFD, CFI, C5 and sC5b9 for differentiating healthy people from those suffering from ASH.[125] Both CFI and sC5b9 were negatively associated with 90-day mortality in ASH patients.[125]

LIVER REGENERATION: THE ROLE OF INTERCELLULAR INTERACTION

The liver is considered the only fully regenerating organ in the human body, but with its chronic diseases, such as ALD, the ability of hepatocytes to regenerate is impaired.[8,100] In a healthy liver, hepatocytes perform various functions depending on their position between the portal triad and the central vein.[126] The Hippo/YAP signaling pathway is necessary for the expression of periportal hepatocyte genes.[127] In severe ASH, increased YAP expression, decreased ESRP2 expression, and differential splicing of the HNF4a nuclear receptor lead to an aberrant increase in expression of periportal hepatocyte genes, their fetal reprogramming, and activation of ductular reaction, in which periportal hepatocytes and liver progenitor cells can transform into either mature hepatocytes or cholangiocytes.[128]

Periportal, central venous, and sinusoidal endothelial cells (SEC) also play an important role in regeneration through direct interaction with macrophages and hepatocytes.[129] While the number of periportal hepatocytes increases during regeneration, and the number of pericentral hepatocytes decreases, the number of periportal ECPs, on the contrary, decreases.[129] In severe ASH, there is an increase in the concentration of central venous ECPs.[130] ECPs can promote inductive angiogenesis through the release of angiocrine factors, including hepatocyte growth factor, Wnt2 and Wnt9.[131] Wnt2 is expressed in both central venous and sinusoidal ECPs and macrophages, while Wnt9b is specifically expressed in central venous ECPs and secondarily in macrophages.[131,132]

Pericentral hepatocytes are regulated by the Wnt signaling pathway, which is disrupted by ASH.[132] In patients with ASH, the expression of Wnt and their FZD family receptors varies depending on the disease severity.[133] In a healthy liver, Wnt2 and FZD4 predominate, whereas in moderate ASH, there is an increase in the expression of Wnt5a and FZD5.[133]. Wnt5a probably plays a role in liver regeneration.[134] In severe ASH, expression of Wnt5a decreases, while the expression of other Wnt and FZD family members is unchanged.[133] Some of the FZD genes are associated with hepatocellular carcinoma.[135] Wnt signaling plays a role both in regeneration of liver tissue with the restoration of its normal structure, and in pathological regeneration leading to dysplasia and, subsequently, to malignant transformation.[132,135] The first scenario is usually realized in mild and moderate ASH, the second – in severe ASH on the background of septal fibrosis or cirrhosis.[8,100]

LIVER SINUSOIDAL ENDOTHELIAL CELLS (LSECS) DYSFUNCTION

The liver filters toxins through sinusoidal tubules lined with Kupffer cells.[136] Filtration is mediated by LSECs which, upon contact with blood from the intestine and systemic circulation, remove and process incoming proteins and lipids due to the presence of highly permeable fenestra.[137] The absence of a basement membrane promotes the permeability of the sinusoidal endothelium, allowing LSECs and Kupffer cells to absorb and remove invading pathogens by endocytosis. Dynamic changes in the number and size of liver fenestrae are strictly regulated.[137,138] Vascular endothelial growth factor (VEGF) plays an important role in the regulation of this process.[139]. Ethanol and food components can also modulate fenestra function by altering the access of macromolecules to parenchymal cells and enabling circulating viruses to infect hepatocytes.[140] LSECs maintain a balance between tolerance and effector immune response, which is facilitated by their innate and adaptive immune functions.[141] LSECs defenestration and activation are already observed in the early stages of ASH, contributing to the activation of liver stellate cells (LSCs) and fibrogenesis.[142] Capillarization also enhances Hedgehog signaling and suppresses VEGF-dependent endothelial NO synthase activity.[143] It is noteworthy that LSECs also contribute to the return of activated LSCs to the resting phenotype through the production of NO.[144] Under the influence of damage factors, LSCs undergo many changes that promote attraction of proinflammatory immune cells, including increased expression of adhesion molecules such as intercellular adhesion molecule 1, vascular adhesion protein 1 and

stabilin 1, causing the adhesion of T and B cells.[145] There is also a high expression of chemokines, including CXCL16, CXCL9, and CX3C-chemokine ligand 1, initiating adhesion of transmigrating T cells and monocytes, as well as hyaluronan, which ensures adhesion of neutrophils.[145,146]

LIVER STELLATE CELLS ACTIVATION

The long process of fibrogenesis leads to accumulation of extracellular matrix proteins and replacement of liver parenchyma with non-functional scar tissue.[147] LSCs are cells primarily responsible for production of extracellular matrix in this process.[148] The LSCs located in the Disse space are surrounded by hepatocytes and sinusoidal LSECs.[148] LSCs secrete laminin, proteoglycans, and type IV collagen which form basal membrane structures and remain dormant until activation.[149] Activated and proliferating LSCs express α-smooth actin and enhance synthesis of types I and III collagens, as well as extracellular matrix proteins such as fibronectin.[148,150]

LSCs activation is stimulated by a number of factors accumulating in the liver microenvironment during chronic exposure to ethanol.[151] Thus, LSCs are activated by apoptotic hepatocytes, as well as numerous paracrine signals from neighboring cells, including Kupffer cells, LSECs, platelets, and infiltrating immune cells.[151,152] Kupffer cells produce cytokines such as TGF-β, TNF-α, and IL-1, which stimulate proliferation of LSCs.[153] The latter also react to ROS released by neutrophils and lipid peroxidation products released from damaged hepatocytes during the progression of ASH, and complement C5a stimulates chemotaxis and migration of LSCs.[154,155]

MICRORNAS

MicroRNAs play a significant role in regulating of steatosis, inflammation, cell damage, and intestinal permeability in the pathogenesis of ASH.[47] Ethanol and its metabolites cause microRNA dysregulation in various organs, as well as in the bloodstream.[156] Sequencing revealed total changes in microRNA regulation associated with polarization phenotypes in rat Kupffer cells under chronic ethanol exposure and in peripheral blood mononuclear cells of patients with ASH.[157] The microRNAs associated with polarization are locacted in coordinated regulated clusters. For example, in patients with ASH, microRNA-125a-5p, microRNA-125a-3p, and mcroiRNA-99b-5p, as well as acrosome-associated protein 6 of the sperm protein encoding gene (SPACA6), are significantly elevated.[157]

MicroRNA-122 regulates fat accumulation in hepatocytes, while microRNA-155 in Kupffer cells maintains a pro-inflammatory status, exacerbating liver tissue damage.[158,159] MicroRNA-212 is also involved in the process of impaired intestinal barrier permeability caused by ethanol.[160] In addition, ASH is accompanied by accelerated death of hepatocytes mediated by death receptor ligands; the latter are partially regulated by E1–E3 ubiquitination enzymes, which control protein degradation and localization.[161] MicroRNA-150-5p affects degradation of the Fas-associated death domain (FADD) by inhibiting expression of cytokine-induced SH2-containing protein (CISH). The level of microRNA-150-5p increases in the liver of both mice and patients with ASH after ethanol exposure, directly indicating its role in the pathogenesis.[162]

The microRNA profiles of human LSCs change during activation in cell culture, and modulating effect of microRNAs on the expression of genes associated with liver fibrosis is evident.[163] Several microRNAs have antifibrotic properties, such as microRNA-19b, 34a-5p, 146a, 133, 23b-27, 134 and 129-5p.[164,165] Thus, overexpression of microRNA-133 in LSCs inhibits collagen synthesis during TGF-β-induced fibrogenesis, and microRNA-129-5p reduces expression of type I collagen in activated LSCs.[166]

Profibrogenic microRNAs include mcroiRNA-942 and 125b.[167] The combination of microRNA-29b1 with the Hedgehog inhibitor reduces the level of collagen and α-actin.[168] Expression of microRNA-542-3p increases in fibrosis;it controls LSCs activation and promotes fibrogenesis by reducing expression of BMP-7.[169] Overexpression of microRNA-199 and 200 families correlates with activation of TGF-β/SMAD signaling pathway during hepatic fibrogenesis both in mouse models of fibrosis and in patients with ASH.[170]

Gut-Liver Axis

Liver and intestine interact through the portal vein and biliary tract via soluble circulating mediators.[171] The liver is the first organ exposed to microbial components and metabolites from the intestine.[88] Alcohol consumption influences many aspects of intestinal physiology, but in the pathogenesis of ASH, the most important is that ethanol increases intestinal permeability and alters its microbial landscape and metabolism.[172]

Dysbiosis

Chronic alcohol consumption leads to a dramatic decrease in the diversity of fungi and bacteria in the intestine.[173] Dysbiosis is not only a consequence of ethanol exposure;it also acts as a regulator of individual susceptibility to ethanol.[174] Moreover, data is accumulating on the role of dysbiosis in the likelihood of developing and severity of ASH.[173,174] Against the background of chronic ethanol intoxication, the number of commensal fungi decreases, while at the same time an excessive growth of Candida species is observed.[93] Similarly, the number of bacteria such as *Ruminococcaceae, Faecalibacterium* and *Prevotella* producing short chain fatty acids decreases, with a concomitant increase in the pool of gram-negative microorganisms, such *as Proteobacteria, Enterobacteriaceae, Escherichia*. Due to dysbiosis, some bacteria begin to produce pathogenic factors.[175] For example, cytolysin produced by *Enterococcus faecalis* negatively affects the survival of hepatocytes.[176] While increasing the total number of *E. faecalis*is not observed, the intensity of cytolysin production closely correlates with the severity of the disease in patients with ASH.[176]

Increased Intestinal Permeability

The permeability of the intestinal wall increases with regular use of ethanol and serves as a prerequisite for the development of ASH in mouse models.[43,177] Ethanol reduces the mRNA levels of several intercellular junction proteins, such as occludin, ZO-1, and claudins 3 and 4.[178] Loss of permeability promotes the translocation of microbes and microbial components into the systemic circulation.[43,178] It is important to note that the epithelial barrier has additional protective mechanisms, including a thick mucosal layer consisting mainly of mucin-2 produced by goblet cells and secretes various

antimicrobial peptides.[179] Chronic ethanol exposure has a complex effect on these mechanisms. Thus, the level of mucin-2 in patients with ALD is increased, and mice deficient in this type of mucin are better protected from the toxic effects of ethanol during its chronic exposure.[179,180] On the contrary, the expression of protective C-type lectins Reg3b and Reg3y decreases.[181]

Translocation of PAMPs, Microbes, and Microbial Metabolites

As discussed above, intestinal integrity disorders and dysbiosis contribute to an increased burden of PAMPs on the liver.[43] In addition, viable bacteria can also cross the damaged intestinal epithelial barrier, contributing to liver damage and an increased risk of infectious complications.[182] In patients with ASH, microbial metabolites are found not only in the portal, but also in the systemic bloodstream, which supports the development of a systemic immune and inflammatory response.[183] Due to ethanol-induced dysbiosis, the concentration of short-chain fatty acids in the intestine decreases, which negatively affects the survival of colonocytes and enterocytes and the maintenance of integrity of the intestinal barrier.[184] In patients with decompensated liver cirrhosis, a low concentration of butyrate in the blood correlates with elevated levels of pro-inflammatory markers and serum endotoxin.[184] Trimethylamine, a metabolite of the intestinal microbiota, is also elevated in patients with ASH; its role in the progression of chronic ethanol-induced liver damage in mice has been proven.[185]

Bile Acids

Chronic ethanol consumption alters the qualitative and quantitative composition of bile acids in both the liver and gut. Intestinal bacteria deconjugate primary bile acids using bile salt hydrolase.[186,187] Deconjugation prevents their reabsorption, thereby maintaining homeostasis.[187] With ALD, simultaneously with an increase in hepatic synthesis, the concentration of unconjugated bile acids in plasma and feces increases.[188] In patients with ASH, a violation of bile acid homeostasis leads to a change in the associated signaling.[189] In particular, FXR signaling, which is an important part of the negative feedback mechanism regulating the synthesis of bile acids in the liver, as well as glucose and lipid metabolism, is significantly reduced in these patients.[190]

Adipose Tissue–Liver Axis

Although functional changes in adipose tissue are traditionally associated with metabolically associated fatty liver disease, there are convincing evidence that chronic alcohol consumption leads to impaired metabolic, endocrine, and immune functions.[191] Moreover, these changes are highly likely to contribute to the progression of ALD.[192]

Adipose Tissue Metabolism

Chronic ethanol exposure enhances lipolytic activity in adipose tissue, thereby increasing the amount of circulating esterified fatty acids and their exposure in the liver, where they are estherified and contribute to the development of steatosis.[193] Saturated fatty acids has a hepatotoxic effect and causes hepatocyte apoptosis by activating the c-Jun N-terminal kinase pathway.[194] They also has a pro-inflammatory effect through the NF-kB pathway and activation of Kupffer cells, thereby exacerbating the course of ASH.[195]

Endocrine System

Alcohol abuse increases the levels of leptin, visfatin and chemerin in the blood, causing enhancement of fibrogenesis, production of proinflammatory cytokines by myeloid cells and infiltration by immune cells, respectively. Injection of exogenous adiponectin to mice protects them from ethanol-initiated liver damage, although the relevance of these data for ASH in humans is unknown.[196-198]

Immune System

Chronic ethanol exposure can support inflammation in adipose tissue.[199] Interestingly, thatadipocytes express CYP2E1 in response to prolonged exposure to ethanol, which appears to contribute to oxidative stress and adipocyte death.[200] Dying adipocytes attract the complement component C1q, which is in physiological conditions facilitates their elimination, but after ethanol exposition this reaction leads to complement activation, which in turn leads to both increased expression of inflammatory cytokines and impaired regulation of lipid metabolism.[201,202] In the context of translational medicine, the aspect of the interaction between alcohol and obesity is of particular importance, since the progression of ALD in people with metabolic syndrome develops more rapidly.[203]

The key links in the pathogenesis of ASH are summarized in Figure 1.

TREATMENT OF ALCOHOLIC STEATOHEPATITIS: PRESENT AND FUTURE

The main condition for successful treatment is abstinence from alcohol intake or, at least, reducing its use to less dangerous doses.[3,100] If there are signs of violations of the trophological status, its correction is required. The implementation of these recommendations in the early stages leads to regression of steatosis and inflammation of the liver with the restoration of its normal structure within a few months.[100]

Alcohol dependence is overcome by the use of opioid receptor antagonists (naltrexone, nalmefene) and gamma-aminobutyric acid receptor agonists (baclofen).[204,205] The duration of the course of therapy is determined by the clinical situation. The majority of patients on the background of addiction therapy are recommended additional administration of antidepressants, benzodiazepines, and other psychopharmacological agents.[206] There is accumulating evidence that GLP-1 receptor agonists, as well as dual agonists, reduce alcohol cravings in about 70% of patients, which opens up new prospects in the treatment of mixed-origin steatohepatitis.[206,207]

It is necessary to provide a sufficient nutritional support to prevent endogenous protein catabolism and hypoglycemia.[3,209] The caloric content of the daily diet should be calculated based on 40 kcal/ kg of body weight and 1.5 g of protein per kg of body weight.[209] In patients with hepatic encephalopathy, the dose of proteins is selected individually depending on its tolerability, preference is given to dairy and vegetable proteins.[3] Limiting the daily intake of dietary protein is undesirable. In the case of anorexia, repeated vomiting,

malabsorption, or severe impaired consciousness, probe or parenteral nutrition is prescribed.[3,209] It is necessary to remember the benefits of natural food intake, which should be switched to after the patient's condition improves. With a confirmed diagnosis of Wernicke's encephalopathy, thiamine is prescribed at a dose of 200-500 mg trice a day intravenously with a transition to an oral regimen.[209]

Prednisone at dose of 0.5 mg / kg / day per osis prescribed to patients with severe ASH (MELD ≥21 or Maddrey index≥32). The course duration is 4-6 weeks.[3] The response to prednisone is determined by the Lille index and by the dynamics of serum bilirubin: a decrease in the level by 25% from baseline or more on the 6th-9th day of treatment is associated with a 5-fold increase in survival compared with patients without appropriate dynamics.[210] The use of prednisone can significantly increase short-term, but not long-term survival.[211] According to the indications, antibacterial agents, albumin solution, and medicines for the treatment of hepatic encephalopathy are prescribed.[3] For patients who do not respond to prednisone, early liver transplantation is considered as the main option.[3,210]

With moderate and mild ASH, in addition to abstinence, attention should be paid to correction of nutritional status and treatment of combined liver pathology.[3,100]

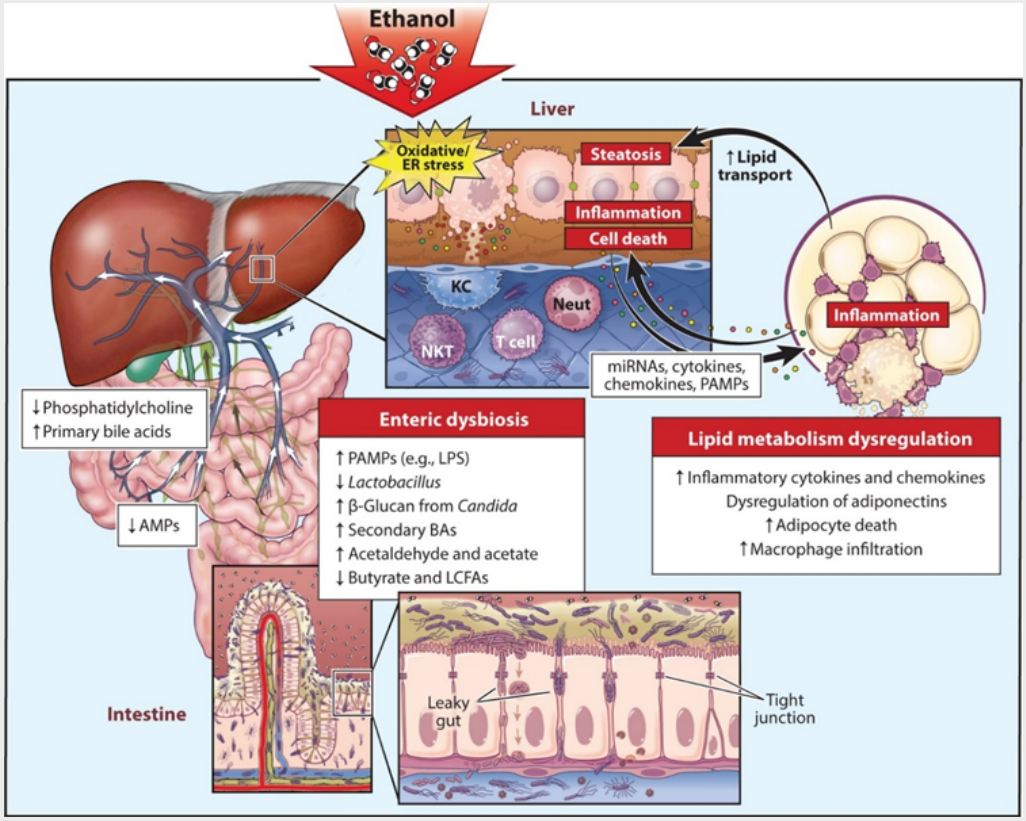

Figure 1. Inter-organ interactions in the pathogenesis of alcoholic steatohepatitis.[34]

POTENTIAL THERAPEUTIC TARGETS IN ALCOHOLIC STEATOHEPATITIS

Hepatocyte Impairment

Oxidative stress, closely associated with depletion of the glutathione pool, is one of the key mechanisms leading to impairment hepatocytes in ASH.[27,34] At the same time, such classic antioxidants as N-acetylcysteine and methadoxine have not demonstrated efficacy in severe ASH.[212,213] Since one of the reasons for failure may be the lack of a specific mitochondrial antioxidant effect, the development of such agents seems promising.[34]

Since different forms of PCD are observed in ASH, inhibition of its pathways is insufficient, as can be seen in the example of an unsuccessful clinical trial of selonsertib, an inhibitor of kinase-1, which regulates apoptosis signals.[214]

Stimulation of liver regeneration is considered as an additional therapeutic strategy. The first meta-analysis of granulocyte colony stimulating factor (G-CSF) studies demonstrated a more than 70% reduction in 90-day mortality in patients with severe AH, however, due to the heterogeneity of the included groups in Asia and Europe, the results were recommended to be interpreted with caution.[215] In the second meta-analysis, the 28-day survival in the groups receiving G-CSF and standard therapy was comparable, but the 90-day survival in the main group was significantly higher than that in the control group.[216]

Preliminary results of the use of recombinant IL-22 indicate an improvement in the prognostic MELD and Lille scales, a decrease in the levels of inflammatory markers and, conversely, an increase in the values of liver regeneration markers.[108,206,217]

Inflammation

Prednisone, which is used as a first-line anti-inflammatory agent in patients with severe ASH, is not effective in all patients and increases the risk of bacterial and fungal infections.[211] Since many immune cells (Kupffer cells, neutrophils, NK cells, etc.) and inflammatory mediators (TNF-α, TLR4, IL-1b, etc.) are involved in both liver damage and regeneration, the strategy of anti-inflammatory therapy is not limited to simply suppressing inflammatory reactions.[218] Two RCTs with monoclonal antibodies to TNF-α (infliximab and etanercept) demonstrated negative results, with a greater mortality in anti-TNF-α groups.[219,220]

Anti-IL-1 antibodies (anakinra and kanakinumab) in three RCTs also showed no advantage over prednisone with a higher incidence of adverse events.[221] A similar fate befell obeticholic acid, a steroid agonist of FXR.[222] Larsukosterol, a DNA methyltransferase inhibitor, inhibits DNA hypermethylation and modulates genes involved in inflammation, lipid metabolism, and PCD.[223] The phase 2a study demonstrated safety, good tolerability, and improved biochemical parameters in patients with severe ASH.[223] However, the results of the phase 2b study did not reveal the effect of larsukosterol on 90-day mortality without liver transplantation.[224]

Dysbiosis

Probiotics in meta-analysis of 15 RCTs demonstrated a significant decrease in ALT and AST activity in ASH patients,but GGT activity, bilirubin and albumin levels did not significantly change comparing with the control group.[225] The effectiveness of antibiotics, both local (rifaximin) and systemic (amoxicillin, vancomycin, gentamicin, meropenem) has also not been proven.[226,227] Patients after fecal microbiota transplantation had significantly higher survival rates after 1 and 3 months compared with those who received standard therapy; however, this advantage turned out to be on the verge of significance after 6 months and became insignificant after 1 year of follow-up.[228]

CONCLUSION

In recent years, the understanding of the pathogenesis of ASH has significantly expanded and deepened: new mechanisms of PCD are described, the role of immune reactions, dysbiosis, and hepatocyte regeneration is clarified, and a complex network of interorgan interactions is deciphered. However, a deep understanding of the pathogenesis has not yet led to a revolutionary breakthrough in treatment. Many drugs that were considered promising have not demonstrated sufficient efficacy and safety. This, in particular, is due to the dual function of many inflammatory mediators responsible for both damage to hepatocytes and their regeneration. Of course, the most important condition for ceasing the progression of ALD is to stop or reduce the intake of alcoholic beverages. However, patients with severe ASH are "too sick to drink", and their life prognosis is determined by other factors.

Liver disease and ALD, in particular, is a complex and varied group of conditions that require a thoughtful and individualized approach to treatment. So early identification of high-risk individuals is crucial for timely intervention and improved patient outcomes, whilst using OMICS-related tools, non-invasive biomarkers and AI algorithms as powerful tools for predicting ALD.

Future directions include the development of advanced biomarker discovery, wearable and point-of-care AI-integrated technologies, and PPM-guided approaches tailored to individual risk profiles. AI-driven models hold significant potential in transforming ALD prediction and management, ultimately contributing to early diagnosis and improved clinical outcomes.

Globally, PPM is transforming how we manage ALD by focusing on each patient's unique genetic and health profile. For instance, genetic testing can identify people who are more likely to develop ALD, including congenital liver abnormalities, or liver damage from specific drugs or toxins. Understanding genetic risk factors through a PPM-guided approach makes early treatments and focused preventative actions possible.

Routine screening procedures can also assist in the early identification of liver disease, even in the absence of symptoms. Depending on a person's unique risk factors, such as family history, overweight, diabetes, or alcohol use, customized screening procedures can be developed through PPM-guided protocol. Reducing the risk of liver disease through focused preventive interventions and lifestyle modifications is made possible by understanding an individual's vulnerability to certain exposures. The early interventions can avoid the progression of ALD.

This approach leads to more effective treatments, fewer side effects, and better overall outcomes. In this context, PPM-guided portfolio tailors treatment to the individual, offering a more targeted and effective approach to managing liver diseases. It can be assumed that a PPM-guided approach to the treatment of such patients will make it possible to determine the optimal treatment strategy, including selection for early liver transplantation.

PPM shows significant possibilities for preventing ALD by combining genetic data, lifestyle factors, and focused interventions to improve individual health outcomes. Healthcare practitioners can maximize preventive efforts for liver diseases and improve patient outcomes by integrating environmental risk assessment, early detection and screening, genetic risk assessment, and customized lifestyle interventions.

Chronic alcohol consumption leads to intestinal dysbiosis and bacterial overgrowth. Dysbiosis associated with ASH is characterized by a decrease in the number of lactobacilli and excessive growth of pathogenic candida. Bacterial overgrowth causes an increase of secondary bile acids, which leads to elevated synthesis of primary bile acids in the liver. A decrease of phosphatidylcholine concentration is associated with the accumulation of triglycerides in the liver. The biosynthesis of long-chain and short-chain bile acids, including butyrate, is suppressed. Ethanol and especially its metabolite acetaldehyde disrupt the tight intercellular contacts and reduce the level of antimicrobial peptides in the intestine. As a result, increased translocation of PAMPs and bacterial lipopolysaccharide initiates inflammatory reactions leading to progressive liver damage. Ethanol also contributes to the death of adipocytes, metabolic and immune dysfunction of adipose tissue. The interaction between

adipose tissue and the liver is mediated by different mediators, including neurotransmitters, cytokines, chemokines, adipocytokines, microRNAs, extracellular vesicles, and metabolites.

ACKNOWLEDGEMENTS

None.

FUNDING

The author received no financial support for the research, authorship, and/or publication of this article.

CONFLICT OF INTEREST

The author declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

1. O'Shea RS, Dasarathy S, McCullough AJ. Alcoholic liver disease. *Hepatology.* 2010;51(1):307-328.
2. Seitz HK, Bataller R, Cortez-Pinto H, et al. Alcoholic liver disease. *Nat Rev Dis Primers.* 2018;4:16.
3. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of alcohol-related liver disease. *J Hepatol.* 2018;69(1):154-181.
4. Danpanichkul P, Díaz LA, Suparan K, et al. Global epidemiology of alcohol-related liver disease, liver cancer, and alcohol use disorder, 2000-2021. *Clin Mol Hepatol.* 2025;31(2):525-547.
5. Hernández-Évole H, Jiménez-Esquivel N, Pose E, Bataller R. Alcohol-associated liver disease: Epidemiology and management. *Ann Hepatol.* 2024;29(1):101162.
6. Devarbhavi H, Asrani SK, Arab JP, Nartey YA, Pose E, Kamath PS. Global burden of liver disease: 2023 update. *J Hepatol.* 2023;79(2):516-537.
7. Rehm J, Shield KD. Global Burden of Alcohol Use Disorders and Alcohol Liver Disease. *Biomedicines.* 2019;7(4):99.
8. Gao B, Bataller R. Alcoholic liver disease: pathogenesis and new therapeutic targets. *Gastroenterology.* 2011;141(5):1572-1585.
9. White AM, Castle IP, Hingson RW, Powell PA. Using Death Certificates to Explore Changes in Alcohol-Related Mortality in the United States, 1999 to 2017. *Alcohol Clin Exp Res.* 2020;44(1):178-187.
10. Asrani SK, Devarbhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. *J Hepatol.* 2019;70(1):151-171.
11. Rehm J, Gmel GE Sr, Gmel G, et al. The relationship between different dimensions of alcohol use and the burden of disease-an update. *Addiction.* 2017;112(6):968-1001.
12. Mathurin P, Bataller R. Trends in the management and burden of alcoholic liver disease. *J Hepatol.* 2015;62(1 Suppl):S38-S46.
13. Singal AK, Bataller R, Ahn J, Kamath PS, Shah VH. ACG Clinical Guideline: alcoholic liver disease. *Am J Gastroenterol.* 2018;113(2):175-194.
14. World Health Organization. *Global status report on alcohol and health.* Geneva: WHO; 2018.
15. Teschke R. Alcoholic Liver Disease: Current Mechanistic Aspects with Focus on Their Clinical Relevance. *Biomedicines.* 2019;7(3):68.
16. Dunn N, Al-Khouri N, Abdellatif I, Singal AK. Metabolic dysfunction and alcohol-associated liver disease: a narrative review. *Clin Transl Gastroenterol.* 2025;16(5):e00828.
17. Frezza M, di Padova C, Pozzato G, et al. High blood alcohol levels in women. *N Engl J Med.* 1990;322(2):95-99.
18. Becker U, Deis A, Sørensen TI, et al. Prediction of risk of liver disease by alcohol intake, sex, and age: a prospective population study. *Hepatology.* 1996;23(5):1025-1029.
19. Softic S, Cohen DE, Kahn CR. Role of Dietary Fructose and Hepatic De Novo Lipogenesis in Fatty Liver Disease. *Dig Dis Sci.* 2016;61(5):1282-1293.
20. Tilg H, Moschen AR. Evolution of inflammation in nonalcoholic fatty liver disease: the multiple parallel hits hypothesis. *Hepatology.* 2010;52(5):1836-1846.
21. Keating SE, Hackett DA, George J, Johnson NA. Exercise and non-alcoholic fatty liver disease: a systematic review and meta-analysis. *J Hepatol.* 2012;57(1):157-166.
22. Baur JA, Sinclair DA. Therapeutic potential of resveratrol: the in vivo evidence. *Nat Rev Drug Discov.* 2006;5(6):493-506.
23. Poole R, Kennedy OJ, Roderick P, et al. Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes. *BMJ.* 2017;359:j5024.
24. Wang J, Wang H, Yang X, Wang K, Zhang Y. Recent advances in the role of polysaccharides in liver diseases: a review. *Front Pharmacol.* 2025;16:1535717.
25. Lieber CS. Cytochrome P-4502E1: its physiological and pathological role. *Physiol Rev.* 1997;77(2):517-544.
26. Bayan L, Koulivand PH, Gorji A. Garlic: a review of potential therapeutic effects. *Avicenna J Phytomed.* 2014;4(1):1-14.
27. Cederbaum AI. Alcohol metabolism. *Clin Liver Dis.* 2012;16(4):667-685.
28. Edenberg HJ. The genetics of alcohol metabolism: role of alcohol dehydrogenase and aldehyde dehydrogenase variants. *Alcohol Res Health.* 2007;30(1):5-13.
29. Hurley TD, Edenberg HJ. Genes encoding enzymes involved in ethanol metabolism. *Alcohol Res.* 2012;34(3):339-344.
30. Setshedi M, Wands JR, Monte SM. Acetaldehyde adducts in alcoholic liver disease. *Oxid Med Cell Longev.* 2010;3(3):178-185.
31. Lu Y, Cederbaum AI. CYP2E1 and oxidative liver injury by alcohol. *Free Radic Biol Med.* 2008;44(5):723-738.
32. Zimatkin SM, Deitrich RA. Ethanol metabolism in the brain. *Addict Biol.* 1997;2(4):387-400.
33. Wurst FM, Thon N, Yegles M, et al. Ethanol metabolites: their role in the assessment of alcohol intake. *Alcohol Clin Exp Res.*

2015;39(11):2060-2072.

34. Wu X, Fan X, Miyata T, et al. Recent advances in understanding of pathogenesis of alcohol-associated liver disease. *Annu Rev Pathol.* 2023;18:411-438.
35. Galluzzi L, Vitale I, Aaronson SA, et al. Molecular mechanisms of cell death: recommendations of the Nomenclature Committee on Cell Death 2018. *Cell Death Differ.* 2018;25(3):486-541.
36. Elmore S. Apoptosis: a review of programmed cell death. *Toxicol Pathol.* 2007;35(4):495-516.
37. Dixon SJ, Lemberg KM, Lamprecht MR, et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death. *Cell.* 2012;149(5):1060-1072.
38. Karki R, Kanneganti TD. Diverging inflammasome signals in tumorigenesis and potential targeting. *Nat Rev Cancer.* 2019;19(4):197-214.
39. Place DE, Kanneganti TD. The innate immune system and cell death in autoinflammatory and autoimmune disease. *Curr Opin Immunol.* 2020;67:95-105.
40. Mizushima N, Levine B. Autophagy in Human Diseases. *N Engl J Med.* 2020;383(16):1564-1576.
41. Klionsky DJ, Petroni G, Amaravadi RK, et al. Autophagy in major human diseases. *EMBO J.* 2021;40(19):e108863.
42. Malhi H, Kaufman RJ. Endoplasmic reticulum stress in liver disease. *J Hepatol.* 2011;54(4):795-809.
43. Szabo G, Bala S. Alcoholic liver disease and the gut-liver axis. *World J Gastroenterol.* 2010;16(11):1321-1329.
44. Ashkenazi A. Targeting the extrinsic apoptosis pathway in cancer. *Cytokine Growth Factor Rev.* 2008;19(3-4):325-331.
45. Van Herreweghe F, Festjens N, Declercq W, Vandenabeele P. Tumor necrosis factor-mediated cell death: to break or to burst, that's the question. *Cell Mol Life Sci.* 2010;67(10):1567-1579.
46. Youle RJ, Strasser A. The BCL-2 protein family. *Nat Rev Mol Cell Biol.* 2008;9(1):47-59.
47. Szabo G, Satishchandran A. MicroRNAs in alcoholic liver disease. *Semin Liver Dis.* 2015;35(1):36-42.
48. Torres JL, Novo-Veleiro I, Manzanedo L, et al. Role of microRNAs in alcohol-induced liver disorders and non-alcoholic fatty liver disease. *World J Gastroenterol.* 2018;24(36):4104-4118.
49. Dong H, Guo W, Zhou Z. Interferon Regulatory Factors in Alcohol-Associated Liver Disease: Cell-Type Programs, Danger Signaling, and Therapeutic Opportunities. *Curr Issues Mol Biol.* 2026;48(1):92.
50. Roberts JZ, Crawford N, Longley DB. The role of Ubiquitination in Apoptosis and Necroptosis. *Cell Death Differ.* 2022;29(2):272-284.
51. Schattenberg JM, Galle PR, Schuchmann M. Apoptosis in liver disease. *Liver Int.* 2006;26(8):904-911.
52. Maes M, Crespo Yanguas S, Willebrords J, et al. Connexin and pannexin signaling in gastrointestinal and liver disease. *Transl Res.* 2015;166(4):332-343.
53. Tacke F. Targeting hepatic macrophages to treat liver diseases. *J Hepatol.* 2017;66(6):1300-1312.
54. Mandrekar P, Szabo G. Signalling pathways in alcohol-induced liver inflammation. *J Hepatol.* 2009;50(6):1258-1266.
55. Ishii H, Adachi M, Fernández-Checa JC, et al. Role of apoptosis in alcoholic liver injury. *Alcohol Clin Exp Res.* 2003;27(7):1207-1212.
56. Wang K. Molecular mechanisms of hepatic apoptosis. *Cell Death Dis.* 2014;5(1):e996.
57. Hao F, Cubero FJ, Ramadori P, et al. Inhibition of Caspase-8 does not protect from alcohol-induced liver apoptosis but alleviates alcoholic hepatic steatosis in mice. *Cell Death Dis.* 2017;8:e3152.
58. Pasparakis M, Vandenabeele P. Necroptosis and its role in inflammation. *Nature.* 2015;517(7534):311-320.
59. Sun L, Wang H, Wang Z, et al. Mixed lineage kinase domain-like protein mediates necrosis signaling downstream of RIP3 kinase. *Cell.* 2012;148(1-2):213-227.
60. Newton K. RIPK1 and RIPK3: critical regulators of inflammation and cell death. *Trends Cell Biol.* 2015;25(6):347-353.
61. Li X, Dong G, Xiong H, Diao H. A narrative review of the role of necroptosis in liver disease: a double-edged sword. *Ann Transl Med.* 2021;9(5):422.
62. Afonso MB, Rodrigues PM, Mateus-Pinheiro M, et al. RIPK3 acts as a lipid metabolism regulator contributing to inflammation and carcinogenesis in non-alcoholic fatty liver disease. *Gut.* 2021;70(12):2359-2372.
63. Saeed WK, Jun DW, Jang K, Koh DH. Necroptosis signaling in liver diseases: An update. *Pharmacol Res.* 2019;148:104439.
64. Roychowdhury S, McMullen MR, Pisano SG, Liu X, Nagy LE. Absence of receptor interacting protein kinase 3 prevents ethanol-induced liver injury. *Hepatology.* 2013;57(5):1773-1783.
65. He S, Huang S, Shen Z. Biomarkers for the detection of necroptosis. *Cell Mol Life Sci.* 2016;73(11-12):2177-2181.
66. Arya RK, Huang E, McMullen MR, et al. RIP3 and MLKL regulate ER stress in alcohol-associated liver disease and pharmacological ER stress models: Insights beyond necroptosis. *JHEP Rep.* 2025;8(2):101628.
67. Miyata T, Wu X, Fan X, et al. Differential role of MLKL in alcohol-associated and non-alcohol-associated fatty liver diseases in mice and humans. *JCI Insight.* 2021;6(4):e140180.
68. Eguchi A, Wree A, Feldstein AE. Biomarkers of liver cell death. *J Hepatol.* 2014;60(5):1063-1074.
69. Guo H, Callaway JB, Ting JP. Inflammasomes: mechanism of action, role in disease, and therapeutics. *Nat Med.* 2015;21(7):677-687.

70. Shi J, Gao W, Shao F. Pyroptosis: Gasdermin-Mediated Programmed Necrotic Cell Death. *Trends Biochem Sci.* 2017;42(4):245-254.
71. Kayagaki N, Stowe IB, Lee BL, et al. Caspase-11 cleaves gasdermin D for non-canonical inflammasome signalling. *Nature.* 2015;526(7575):666-671.
72. Tsuchiya K. Inflammasome-associated cell death: Pyroptosis, apoptosis, and physiological implications. *Microbiol Immunol.* 2020;64(4):252-269.
73. Szabo G, Csak T. Inflammasomes in liver diseases. *J Hepatol.* 2012;57(3):642-654.
74. Petrasek J, Bala S, Csak T, et al. IL-1 receptor antagonist ameliorates inflammasome-dependent alcoholic steatohepatitis in mice. *J Clin Invest.* 2012;122(10):3476-3489.
75. Friedmann Angeli JP, Schneider M, Proneth B, et al. Inactivation of the ferroptosis regulator Gpx4 triggers acute renal failure in mice. *Nat Cell Biol.* 2014;16(12):1180-1191.
76. Tsurusaki S, Tsuchiya Y, Koumura T, et al. Hepatic ferroptosis plays an important role as the trigger for initiating inflammation in nonalcoholic steatohepatitis. *Cell Death Dis.* 2019;10(6):449.
77. Gao M, Monian P, Quadri N, Ramasamy R, Jiang X. Glutaminolysis and transferrin regulate ferroptosis. *Mol Cell.* 2015;59(2):298-308.
78. Stockwell BR, Friedmann Angeli JP, Bayir H, et al. Ferroptosis: A regulated cell death nexus linking metabolism, redox biology, and disease. *Cell.* 2017;171(2):273-285.
79. Li Y, Ding WX. Impaired Rab7 and Dynamin2 block fat turnover by autophagy in alcoholic fatty livers. *Hepatol Commun.* 2017;1(6):473-476.
80. Chao X, Wang S, Zhao K, et al. Impaired TFEB-mediated lysosome biogenesis and autophagy promote chronic ethanol-induced liver injury and steatosis in mice. *Gastroenterology.* 2018;155(3):865-879.e12.
81. Momen-Heravi F, Saha B, Kodys K, et al. Increased number of circulating exosomes and their microRNA cargos are potential novel biomarkers in alcoholic hepatitis. *J Transl Med.* 2015;13:261.
82. Wang C, Liu J, Yan Y, Tan Y. Role of exosomes in chronic liver disease development and their potential clinical applications. *J Immunol Res.* 2022;2022:1695802.
83. Szabo G, Momen-Heravi F. Extracellular vesicles in liver disease and potential as biomarkers and therapeutic targets. *Nat Rev Gastroenterol Hepatol.* 2017;14(8):455-466.
84. Marquez RT, Xu L. Bcl-2:Beclin 1 complex: multiple mechanisms regulating autophagy/apoptosis toggle switch. *Am J Cancer Res.* 2012;2(2):214-221.
85. Guo R, Wang H, Cui N. Autophagy regulation on pyroptosis: mechanism and medical implication in sepsis. *Mediators Inflamm.* 2021;2021:9925059.
86. Wang L, Khambu B, Zhang H, Yin XM. Autophagy in alcoholic liver disease, self-eating triggered by drinking. *Clin Res Hepatol Gastroenterol.* 2015;39(Suppl 1):S2-S6.
87. Ding WX, Li M, Chen X, et al. Autophagy reduces acute ethanol-induced hepatotoxicity and steatosis in mice. *Gastroenterology.* 2010;139(5):1740-1752.
88. Szabo G. Gut-liver axis in alcoholic liver disease. *Gastroenterology.* 2015;148(1):30-36.
89. Takeuchi O, Akira S. Pattern recognition receptors and inflammation. *Cell.* 2010;140(6):805-820.
90. Shen H, Liangpunsakul S, Iwakiri Y, et al. Immunological mechanisms and emerging therapeutic targets in alcohol-associated liver disease. *Cell Mol Immunol.* 2025;22:1190-1204.
91. Brown GD, Gordon S. Immune recognition of fungal beta-glucans. *Cell Microbiol.* 2005;7(4):471-479. 92
92. Thurman RG. Alcoholic liver injury involves activation of Kupffer cells by endotoxin. *Am J Physiol.* 1998;275(4):G605-G611.
93. Yang AM, Inamine T, Hochrath K, et al. Intestinal fungi contribute to development of alcoholic liver disease. *J Clin Invest.* 2017;127(7):2829-2841.
94. Yamasaki S, Ishikawa E, Sakuma M, et al. Mincle is an ITAM-coupled activating receptor that senses damaged cells. *Nat Immunol.* 2008;9(10):1179-1188.
95. Jaeschke H. Neutrophil-mediated tissue injury in alcoholic hepatitis. *Alcohol.* 2002;27(1):23-27.
96. Gao B, Radaeva S, Park O. Liver natural killer and natural killer T cells: immunobiology and emerging roles in liver diseases. *J Leukoc Biol.* 2009;86(3):513-528.
97. Bertola A, Mathews S, Ki SH, Wang H, Gao B. Mouse model of chronic and binge ethanol feeding (the NIAAA model). *Nat Protoc.* 2013;8(3):627-637.
98. Ramachandran P, Dobie R, Wilson-Kanamori JR, et al. Resolving the fibrotic niche of human liver cirrhosis at single-cell level. *Nature.* 2019;575(7783):512-518.
99. Liu X, Liu ZX, Morgan TR, Norden-Krichmar TM. Single-cell transcriptomics of peripheral blood mononuclear cells indicates impaired immune and inflammatory responses in alcohol-associated hepatitis. *Hum Immunol.* 2024;85(1):110735.
100. Louvet A, Mathurin P. Alcoholic liver disease: mechanisms of injury and targeted treatment. *Nat Rev Gastroenterol Hepatol.* 2015;12(4):231-242.
101. Tilg H, Diehl AM. Cytokines in alcoholic and nonalcoholic steatohepatitis. *N Engl J Med.* 2000;343(20):1467-1476.
102. Dooley S, ten Dijke P. TGF-β in progression of liver disease. *Cell Tissue Res.* 2012;347(1):245-256.
103. Gao B. Hepatoprotective and anti-inflammatory cytokines in alcoholic liver disease. *J Gastroenterol Hepatol.* 2012;27 Suppl 2:89-93.
104. Horiguchi N, Wang L, Mukhopadhyay P, et al. Cell type-

dependent pro- and anti-inflammatory role of signal transducer and activator of transcription 3 in alcoholic liver injury. *Gastroenterology*. 2008;134(4):1148-1158.

105. Korn T, Bettelli E, Oukka M, Kuchroo VK. IL-17 and Th17 cells. *Annu Rev Immunol*. 2009;27:485-517.
106. Miller AM, Wang H, Bertola A, et al. Inflammation-associated interleukin-6/signal transducer and activator of transcription 3 activation ameliorates alcoholic and nonalcoholic fatty liver diseases in interleukin-10-deficient mice. *Hepatology*. 2011;54(3):846-856.
107. Ki SH, Park O, Zheng M, et al. Interleukin-22 treatment ameliorates alcoholic liver injury in a murine model. *Hepatology*. 2010;52(4):1300-1310.
108. Arab JP, Sehrawat TS, Simonetto DA, et al. An open-label, dose-escalation study of IL-22 in patients with alcoholic hepatitis. *Hepatology*. 2020;71(1):306-317.
109. Affò S, Dominguez M, Lozano JJ, et al. Transcriptome analysis identifies TNF superfamily receptors as potential therapeutic targets in alcoholic hepatitis. *Gut*. 2013;62(3):452-460.
110. Dominguez M, Miquel R, Colmenero J, et al. Hepatic expression of CXC chemokines predicts portal hypertension and survival in patients with alcoholic hepatitis. *Gastroenterology*. 2009;136(5):1639-1650.
111. Taïeb J, Mathurin P, Elbim C, et al. Blood neutrophil functions and cytokine release in severe alcoholic hepatitis: effect of corticosteroids. *J Hepatol*. 2000;32(4):579-586.
112. Kawai T, Akira S. TLR signaling. *Semin Immunol*. 2007;19(1):24-32.
113. Wieser V, Adolph TE, Enrich B, et al. Reversal of murine alcoholic steatohepatitis by pepducin-based functional blockade of interleukin-8 receptors. *Gut*. 2017;66(5):930-938.
114. Affò S, Morales-Ibanez O, Rodrigo-Torres D, et al. CCL20 mediates lipopolysaccharide induced liver injury and is a potential driver of inflammation and fibrosis in alcoholic hepatitis. *Gut*. 2014;63(11):1782-1792.
115. Schutyser E, Struyf S, Van Damme J. The CC chemokine CCL20 and its receptor CCR6. *Cytokine Growth Factor Rev*. 2003;14(5):409-426.
116. Marin V, Poulsen K, Odena G, et al. Hepatocyte-derived macrophage migration inhibitory factor mediates alcohol-induced liver injury in mice and patients. *J Hepatol*. 2017;67(5):1018-1025.
117. Barnes MA, McMullen MR, Roychowdhury S, et al. Macrophage migration inhibitory factor contributes to ethanol-induced liver injury by mediating cell injury, steatohepatitis, and steatosis. *Hepatology*. 2013;57(5):1980-1991.
118. Molina PE, Happel KI, Zhang P, Kolls JK, Nelson S. Focus on: Alcohol and the immune system. *Alcohol Res Health*. 2010;33(1-2):97-108.
119. Pritchard MT, McMullen MR, Stavitsky AB, et al. Differential contributions of C3, C5, and decay-accelerating factor to ethanol-induced fatty liver in mice. *Gastroenterology*. 2007;132(3):1117-1126.
120. Zhong F, Hu Z, Jiang K, et al. Complement C3 activation regulates the production of tRNA-derived fragments Gly-tRFs and promotes alcohol-induced liver injury and steatosis. *Cell Res*. 2019;29(7):548-561.
121. Cohen JI, Roychowdhury S, McMullen MR, et al. Complement and alcoholic liver disease: role of C1q in the pathogenesis of ethanol-induced liver injury in mice. *Gastroenterology*. 2010;139(2):664-674.e1.
122. Zhou Y, Yuan G, Zhong F, He S. Roles of the complement system in alcohol-induced liver disease. *Clin Mol Hepatol*. 2020;26(4):677-685.
123. Wlazlo N, van Greevenbroek MM, Ferreira I, et al. Activated complement factor 3 is associated with liver fat and liver enzymes: the CODAM study. *Eur J Clin Invest*. 2013;43(7):679-688.
124. Shen H, French BA, Liu H, et al. Increased activity of the complement system in the liver of patients with alcoholic hepatitis. *Exp Mol Pathol*. 2014;97(3):338-344.
125. Taiwo M, Huang E, Pathak V, et al. Proteomics identifies complement protein signatures in patients with alcohol-associated hepatitis. *JCI Insight*. 2024;9(9):e174127.
126. Jungermann K, Katz N. Functional hepatocellular heterogeneity. *Hepatology*. 1982;2(3):385-395.
127. Yimlamai D, Fowl BH, Camargo FD. Emerging evidence on the role of the Hippo/YAP pathway in liver physiology and cancer. *J Hepatol*. 2015;63(6):1491-1501.
128. Hyun J, Sun Z, Ahmadi AR, et al. Epithelial splicing regulatory protein 2-mediated alternative splicing reprograms hepatocytes in severe alcoholic hepatitis. *J Clin Invest*. 2020;130(4):2129-2145.
129. Ding BS, Nolan DJ, Butler JM, et al. Inductive angiocrine signals from sinusoidal endothelium are required for liver regeneration. *Nature*. 2010;468(7321):310-315.
130. Xia Y, Yang J, Sanyal AJ, et al. Persistent hyperactivation of endothelial cells in patients with alcoholic hepatitis. *Alcohol Clin Exp Res*. 2020;44(5):1075-1087.
131. Rocha AS, Vidal V, Mertz M, et al. The angiocrine factor Rspondin3 is a key determinant of liver zonation. *Cell Rep*. 2015;13(9):1757-1764.
132. Preziosi ME, Monga SP. Update on the mechanisms of liver regeneration. *Semin Liver Dis*. 2017;37(2):141-151.
133. Shree Harini K, Ezhilarasan D, Mani U. Molecular insights on intracellular Wnt/β-catenin signaling in alcoholic liver disease. *Cell Biochem Funct*. 2024;42(1):e3916.
134. Nishikawa K, Osawa Y, Kimura K. Wnt/β-Catenin signaling as a potential target for the treatment of liver cirrhosis using antifibrotic drugs. *Int J Mol Sci*. 2018;19(10):3103.

135. Nusse R, Clevers H. Wnt/β-Catenin signaling, disease, and emerging therapeutic modalities. *Cell*. 2017;169(6):985-999.
136. Knolle PA, Wohlleber D. Immunological functions of liver sinusoidal endothelial cells. *Cell Mol Immunol*. 2016;13(3):347-353.
137. Poisson J, Lemoinne S, Boulanger C, et al. Liver sinusoidal endothelial cells: physiology and role in liver diseases. *J Hepatol*. 2017;66(1):212-227.
138. Shetty S, Lalor PF, Adams DH. Liver sinusoidal endothelial cells - gatekeepers of hepatic immunity. *Nat Rev Gastroenterol Hepatol*. 2018;15(9):555-567.
139. DeLeve LD. Liver sinusoidal endothelial cells in hepatic fibrosis. *Hepatology*. 2015;61(5):1740-1746.
140. Ortega-Ribera M, Hunt NJ, Gracia-Sancho J, et al. The hepatic sinusoid in aging and disease: update and advances from the 20th Liver Sinusoid Meeting. *Hepatol Commun*. 2020;4(7):1087-1098.
141. Knolle PA, Thimme R. Hepatic immune regulation and its involvement in viral hepatitis infection. *Gastroenterology*. 2014;146(5):1193-1207.
142. Zhou J, Wang J, Zhang L, et al. Defenestration of liver sinusoidal endothelial cells: the trigger of liver fibrosis. *Pharmaceuticals (Basel)*. 2025;18(6):893.
143. Xie G, Choi SS, Syn WK, et al. Hedgehog signalling regulates liver sinusoidal endothelial cell capillarisation. *Gut*. 2013;62(2):299-309.
144. DeLeve LD, Wang X, Guo Y. Sinusoidal endothelial cells prevent rat stellate cell activation and promote reversion to quiescence. *Hepatology*. 2008;48(3):920-930.
145. Lalor PF, Shields P, Grant A, et al. Recruitment of lymphocytes to the human liver. *Immunol Cell Biol*. 2002;80(1):52-64.
146. Heymann F, Tacke F. Immunology in the liver—from homeostasis to disease. *Nat Rev Gastroenterol Hepatol*. 2016;13(2):88-110.
147. Bataller R, Brenner DA. Liver fibrosis. *J Clin Invest*. 2005;115(2):209-218.
148. Friedman SL. Hepatic stellate cells: protean, multifunctional, and enigmatic cells of the liver. *Physiol Rev*. 2008;88(1):125-172.
149. Wake K. Perisinusoidal stellate cells (fat-storing cells) of the liver: a historical review. *Int Rev Cytol*. 1980;66:303-353.
150. Kisseleva T, Brenner DA. Mechanisms of fibrogenesis. *Exp Biol Med (Maywood)*. 2008;233(2):109-122.
151. Tsuchida T, Friedman SL. Mechanisms of hepatic stellate cell activation. *Nat Rev Gastroenterol Hepatol*. 2017;14(7):397-411.
152. Tacke F, Weiskirchen R. Update on hepatic stellate cells: pathogenic role in liver fibrosis and novel isolation techniques. *Expert Rev Gastroenterol Hepatol*. 2012;6(1):67-80.
153. Seki E, Brenner DA. Toll-like receptors and adaptor molecules in liver disease: update. *Hepatology*. 2008;48(1):322-335.
154. Parola M, Robino G. Oxidative stress-related molecules and liver fibrosis. *J Hepatol*. 2001;35(2):297-306.
155. Hillebrandt S, Wasmuth HE, Weiskirchen R, et al. Complement factor 5 is a quantitative trait gene that modifies liver fibrogenesis in mice and humans. *Nat Genet*. 2005;37(8):835-843.
156. Bala S, Petrasek J, Mundkur S, et al. Circulating microRNAs in exosomes indicate hepatocyte injury and inflammation in alcoholic, drug-induced, and inflammatory liver diseases. *Hepatology*. 2012;56(5):1946-1957.
157. Sabater L, Locatelli L, Oakley F, et al. RNA sequencing reveals changes in the microRNAome of transdifferentiating hepatic stellate cells that are conserved between human and rat. *Sci Rep*. 2020;10(1):21708.
158. Esau C, Davis S, Murray SF, et al. miR-122 regulation of lipid metabolism revealed by in vivo antisense targeting. *Cell Metab*. 2006;3(2):87-98.
159. Bala S, Marcos M, Kodys K, et al. Up-regulation of microRNA-155 in macrophages contributes to increased tumor necrosis factor alpha production via increased mRNA half-life in alcoholic liver disease. *J Biol Chem*. 2011;286(2):1436-1444.
160. Tang Y, Banan A, Forsyth CB, et al. Effect of alcohol on miR-212 expression in intestinal epithelial cells and its potential role in alcoholic liver disease. *Alcohol Clin Exp Res*. 2008;32(2):355-364.
161. Wang S, Pacher P, De Lisle RC, et al. A mechanistic review of cell death in alcohol-induced liver injury. *Alcohol Clin Exp Res*. 2016;40(6):1215-1223.
162. Chen W, Yan X, Yang A, et al. miRNA-150-5p promotes hepatic stellate cell proliferation and sensitizes hepatocyte apoptosis during liver fibrosis. *Epigenomics*. 2020;12(1):53-67.
163. Roderburg C, Urban GW, Bettermann K, et al. Micro-RNA profiling reveals a role for miR-29 in human and murine liver fibrosis. *Hepatology*. 2011;53(1):209-218.
164. Lakner AM, Steuerwald NM, Walling TL, et al. Inhibitory effects of microRNA 19b in hepatic stellate cell-mediated fibrogenesis. *Hepatology*. 2012;56(1):300-310.
165. Li J, Ghazwani M, Zhang Y, et al. miR-122 regulates collagen production via targeting hepatic stellate cells and suppressing P4HA1 expression. *J Hepatol*. 2013;58(3):522-528.
166. Zhao Z, Lin CY, Cheng K. siRNA- and miRNA-based therapeutics for liver fibrosis. *Transl Res*. 2019;214:17-29.
167. You K, Li SY, Gong J, et al. MicroRNA-125b promotes hepatic stellate cell activation and liver fibrosis by activating RhoA signaling. *Mol Ther Nucleic Acids*. 2018;12:57-66.
168. Huang YH, Yang YL, Wang FS. The role of miR-29a in the regulation, function, and signaling of liver fibrosis. *Int J Mol Sci*. 2018;19(7):1889.
169. Ji F, Wang K, Zhang Y, et al. MiR-542-3p controls hepatic stellate cell activation and fibrosis via targeting BMP-7. *J Cell Biochem*. 2019;120(3):4573-4581.

170. Murakami Y, Toyoda H, Tanaka M, et al. The progression of liver fibrosis is related with overexpression of the miR-199 and 200 families. *PLoS One*. 2011;6(1):e16081.

171. Tripathi A, Debelius J, Brenner DA, et al. The gut-liver axis and the intersection with the microbiome. *Nat Rev Gastroenterol Hepatol*. 2018;15(7):397-411.

172. Bajaj JS. Alcohol, liver disease and the gut microbiota. *Nat Rev Gastroenterol Hepatol*. 2019;16(4):235-246.

173. Mutlu E, Keshavarzian A, Engen P, et al. Intestinal dysbiosis: a possible mechanism of alcohol-induced endotoxemia and alcoholic steatohepatitis in rats. *Alcohol Clin Exp Res*. 2009;33(10):1836-1846.

174. Leclercq S, Matamoros S, Cani PD, et al. Intestinal permeability, gut-bacterial dysbiosis, and behavioral markers of alcohol-dependence severity. *Proc Natl Acad Sci U S A*. 2014;111(42):E4485-E4493.

175. Chen P, Schnabl B. Host-microbiome interactions in alcoholic liver disease. *Gut Liver*. 2014;8(3):237-241.

176. Duan Y, Llorente C, Lang S, et al. Bacteriophage targeting of gut bacterium attenuates alcoholic liver disease. *Nature*. 2019;575(7783):505-511.

177. Rao R. Endotoxemia and gut barrier dysfunction in alcoholic liver disease. *Hepatology*. 2009;50(2):638-644.

178. Tang Y, Forsyth CB, Farhadi A, et al. Nitric oxide-mediated intestinal injury is required for alcohol-induced gut leakiness and liver damage. *Alcohol Clin Exp Res*. 2009;33(7):1220-1230.

179. Johansson ME, Larsson JM, Hansson GC. The two mucus layers of colon are organized by the MUC2 mucin, whereas the outer layer is a legislator of host-microbial interactions. *Proc Natl Acad Sci U S A*. 2011;108(Suppl 1):4659-4665.

180. Hartmann P, Chen WC, Schnabl B. The intestinal microbiome and the leaky gut as therapeutic targets in alcoholic liver disease. *Front Physiol*. 2012;3:402.

181. Wang L, Fouts DE, Stärkel P, et al. Intestinal REG3 lectins protect against alcoholic steatohepatitis by reducing mucosa-associated microbiota and preventing bacterial translocation. *Cell Host Microbe*. 2016;19(2):227-239.

182. Wiest R, Lawson M, Geuking M. Pathological bacterial translocation in liver cirrhosis. *J Hepatol*. 2014;60(1):197-209.

183. Bajaj JS, Heuman DM, Hylemon PB, et al. Altered profile of human gut microbiome is associated with cirrhosis and its complications. *J Hepatol*. 2014;60(5):940-947.

184. Bloemen JG, Venema K, van de Poll MC, et al. Short chain fatty acids exchange across the gut and liver in humans measured at surgery. *Clin Nutr*. 2009;28(6):657-661.

185. Helsley RN, Miyata T, Kadam A, et al. Gut microbial trimethylamine is elevated in alcohol-associated hepatitis and contributes to ethanol-induced liver injury in mice. *Elife*. 2022;11:e76554.

186. Chiang JY. Bile acid metabolism and signaling in liver disease and therapy. *Liver Res*. 2017;1(1):3-9.

187. Ridlon JM, Kang DJ, Hylemon PB. Bile salt biotransformations by human intestinal bacteria. *J Lipid Res*. 2006;47(2):241-259.

188. Kakiyama G, Hylemon PB, Zhou H, et al. Colonic inflammation and secondary bile acids in alcoholic cirrhosis. *Am J Physiol Gastrointest Liver Physiol*. 2014;306(11):G929-G937.

189. Keller MI, de Zawadzki A, Thiele M, et al. Alcohol-related liver disease disrupts bile acid homeostasis and gut microbial bile acid metabolism. *JHEP Rep*. 2026;101848.

190. Manley S, Ding W. Role of farnesoid X receptor and bile acids in alcoholic liver disease. *Acta Pharm Sin B*. 2015;5(2):158-167.

191. You M, Arteel GE. Effect of ethanol on lipid metabolism. *J Hepatol*. 2019;70(2):237-248.

192. Zhong W, Zhao Y, Tang Y, et al. Chronic alcohol exposure stimulates adipose tissue lipolysis in mice: role of reverse triglyceride transport in the pathogenesis of alcoholic steatosis. *Am J Pathol*. 2012;180(3):998-1007.

193. Lafontan M, Langin D. Lipolysis and lipid mobilization in human adipose tissue. *Prog Lipid Res*. 2009;48(5):275-297.

194. Malhi H, Bronk SF, Werneburg NW, et al. Free fatty acids induce JNK-dependent hepatocyte lipoapoptosis. *J Biol Chem*. 2006;281(17):12093-12101.

195. Shi H, Kokoeva MV, Inouye K, et al. TLR4 links innate immunity and fatty acid-induced insulin resistance. *J Clin Invest*. 2006;116(11):3015-3025.

196. Kema VH, Mojerla NR, Khan I, et al. Effect of alcohol on adipose tissue: a review on ethanol mediated adipose tissue injury. *Adipocyte*. 2015;4(4):225-231.

197. Ren RZ, Zhang X, Xu J, et al. Chronic ethanol consumption increases the levels of chemerin in the serum and adipose tissue of humans and rats. *Acta Pharmacol Sin*. 2012;33(5):652-659.

198. Xu A, Wang Y, Keshaw H, et al. The fat-derived hormone adiponectin alleviates alcoholic and nonalcoholic fatty liver diseases in mice. *J Clin Invest*. 2003;112(1):91-100.

199. Gopal T, Ai W, Casey CA, et al. A review of the role of ethanol-induced adipose tissue dysfunction in alcohol-associated liver disease. *Alcohol Clin Exp Res*. 2021;45(10):1927-1939.

200. Tang H, Sebastian BM, Axhemi A, et al. Ethanol-induced oxidative stress via the CYP2E1 pathway disrupts adiponectin secretion from adipocytes. *Alcohol Clin Exp Res*. 2012;36(2):214-222.

201. Saleh J, Al-Maqbali M, Abdel-Hadi D. Role of Complement and Complement-Related Adipokines in Regulation of Energy Metabolism and Fat Storage. *Compr Physiol*. 2019;9(4):1411-1429.

202. Phieler J, Garcia-Martin R, Lambris JD, et al. The role of the complement system in metabolic organs and metabolic diseases. *Semin Immunol*. 2013;25(1):47-53.

203. Naveau S, Giraud V, Borotto E, et al. Excess weight risk factor for alcoholic liver disease. *Hepatology*. 1997;25(1):108-111.

204. Jonas DE, Amick HR, Feltner C, et al. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. *JAMA*. 2014;311(18):1889-1900.

205. Morley KC, Baillie A, Leung S, et al. Baclofen for the Treatment of Alcohol Dependence and Possible Role of Comorbid Anxiety. *Alcohol Alcohol*. 2014;49(6):654-660.

206. Blaney H, Asgharpour A. The alcohol-associated hepatitis treatment landscape. *Curr Opin Gastroenterol*. 2026;42(3):107-113.

207. Srinivasan NM, Farokhnia M, Farinelli LA, et al. GLP-1 therapeutics and their emerging role in alcohol and substance use disorders: An endocrinology primer. *J Endocr Soc*. 2025;9(11):bvaf141.

208. Quddos F, Hubshman Z, Tegge A, et al. Semaglutide and tirzepatide reduce alcohol consumption in individuals with obesity. *Sci Rep*. 2023;13:20998.

209. Plauth M, Bernal W, Dasarathy S, et al. ESPEN guideline on clinical nutrition in liver disease. *Clin Nutr*. 2019;38(2):485-521.

210. Louvet A, Naveau S, Abdelnour M, et al. The Lille model: a new tool for therapeutic strategy in patients with severe alcoholic hepatitis treated with steroids. *Hepatology*. 2007;45(6):1348-1354.

211. Mathurin P, O'Grady J, Carithers RL, et al. Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis: meta-analysis of individual patient data. *Gut*. 2011;60(2):255-260.

212. Nguyen-Khac E, Thevenot T, Piquet MA, et al. Glucocorticoids plus N-acetylcysteine in severe alcoholic hepatitis. *N Engl J Med*. 2011;365(19):1781-1789.

213. Leggio L, Kenna GA, Ferrulli A, et al. Preliminary findings on the use of metadoxine for the treatment of alcohol dependence and alcoholic liver disease. *Hum Psychopharmacol*. 2011;26(8):554-559.

214. Harrison SA, Wong VW, Okanoue T, et al. Selonsertib for patients with bridging fibrosis or compensated cirrhosis due to NASH: Results from randomized phase III STELLAR trials. *J Hepatol*. 2020;73(1):26-39.

215. Marot A, Singal AK, Moreno C, et al. Granulocyte colony-stimulating factor for alcoholic hepatitis: A systematic review and meta-analysis of randomized controlled trials. *JHEP Rep*. 2020;2(5):100139.

216. Baig M, Walayat S, Dhillon S, et al. Efficacy of granulocyte colony stimulating factor in severe alcoholic hepatitis: A systematic review and meta-analysis. *Cureus*. 2020;12(9):e10474.

217. Rutledge S, Brown RS Jr. Acute alcoholic hepatitis: new and experimental medications. *Clin Liver Dis*. 2026;30(1):71-92.

218. Gao B, Tsukamoto H. Inflammation in alcoholic and nonalcoholic fatty liver disease: Friend or foe? *Gastroenterology*. 2016;150(8):1704-1709.

219. Naveau S, Chollet-Martin S, Dharancy S, et al. A double-blind randomized controlled trial of infliximab associated with prednisolone in acute alcoholic hepatitis. *Hepatology*. 2004;39(5):1390-1397.

220. Boetticher NC, Peine CJ, Kwo P, et al. A randomized, double-blinded, placebo-controlled multicenter trial of etanercept in the treatment of alcoholic hepatitis. *Gastroenterology*. 2008;135(6):1953-1960.

221. Vergis N, Patel V, Bogdanowicz K, et al. IL-1 signal inhibition in alcohol-related hepatitis: A randomized, double-blind, placebo-controlled trial of canakinumab. *Clin Gastroenterol Hepatol*. 2025;23(5):797-807.e5.

222. Pimienta M, Tien C, Terraterra NA. Prospective clinical trials and novel therapies in the medical management of severe alcohol-associated hepatitis. *Clin Liver Dis (Hoboken)*. 2022;20(6):202-208.

223. Hassanein T, McClain CJ, Vatsalya V, et al. Safety, pharmacokinetics, and efficacy signals of larsucosterol (DUR-928) in alcohol-associated hepatitis. *Am J Gastroenterol*. 2024;119(1):107-115.

224. Shiffman M, Da B, Goel A, et al. Larsucosterol for the treatment of alcohol-associated hepatitis. *NEJM Evid*. 2025;4(2):EVIDoa2400243.

225. Xiong SY, Wu GS, Li C, et al. Clinical efficacy of probiotics in the treatment of alcoholic liver disease: a systematic review and meta-analysis. *Front Cell Infect Microbiol*. 2024;14:1358063.

226. Louvet A, Labreuche J, Dao T, et al. Effect of prophylactic antibiotics on mortality in severe alcohol-related hepatitis: A randomized clinical trial. *JAMA*. 2023;329(18):1558-1566.

227. Kimer N, Meldgaard M, Hamberg O, et al. The impact of rifaximin on inflammation and metabolism in alcoholic hepatitis: A randomized clinical trial. *PLoS One*. 2022;17(3):e0264278.

228. Taha AM, Abouelmagd K, Nada SA, et al. Impact of fecal microbiota transplantation in severe alcoholic hepatitis: A systematic review and meta-analysis. *JGH Open*. 2024;8(8):e70007.