Annals of Hepatology 30 (2025) 101927

Contents lists available at ScienceDirect

Annals of Hepatology

journal homepage: www.elsevier.es/annalsofhepatology

Concise reviews

Alcoholic cirrhosis-associated immune dysfunction: What does it imply for us?

Mingyu Sun[a,1], Ziyi Yang[b,1], Fei Tang[a], Fenghui Li[a], Qing Ye[a], Chao Sun[b,c,*], Jing Liang[a,*]

[a] The Third Central Hospital of Tianjin, 83 Jintang Road, Hedong District, Tianjin 300170, China.
[b] Department of Gastroenterology and Hepatology, Tianjin Medical University General Hospital, Tianjin 300052, China
[c] Department of Gastroenterology, Tianjin Medical University General Hospital Airport Hospital, Tianjin 300308, China

ARTICLE INFO

Article History:
Received 14 January 2025
Accepted 2 April 2025
Available online 14 May 2025

Keywords:
Alcoholic Cirrhosis
CAID
Systemic inflammation
Immune response
Immune deficiency

ABSTRACT

Alcoholic cirrhosis is a leading cause of chronic advanced liver disease. With the gradual eradication of viral hepatitis and the rising levels of alcohol consumption, the incidence of alcoholic cirrhosis is expected to increase steadily. Alcohol is primarily metabolized in the gastrointestinal tract, producing toxic metabolites that enter the portal vein circulation and are subsequently transported to the liver. Excessive alcohol intake activates the microsomal ethanol oxidation system and disrupts the intestinal microbiota-driven microenvironment dictated by intestinal microbiota, and increase intestinal permeability, all of which trigger severe systemic inflammatory responses and impaired immune function. This phenomenon, known as cirrhosis-associated immune dysfunction (CAID), is closely linked to the severity of cirrhosis and can significantly influence disease progression, potentially leading to multi-organ failure. This narrative review sheds light on the relationship between alcoholic cirrhosis and CAID, focusing on tailored interventions to modify immune response and modulate gut microbiota composition in hopes of mitigating the development and deterioration of alcoholic cirrhosis.

1. Introduction

With increasing affluence in densely populated regions and a rising trend in alcohol consumption, global per capita alcohol consumption is projected to reach 7.6 liters by 2030, driven by accelerated economic development [1]. Women exhibit heightened susceptibility to alcohol-induced liver injury at all consumption levels compared to men [2,3]. Even at lower consumption levels, specifically between 12 and 24 grams per day, an elevated risk of developing cirrhosis has been observed compared to those who abstain from alcohol [4]. Globally, alcohol consumption is the third leading cause of liver cirrhosis, following chronic hepatitis infection and non-alcoholic fatty liver disease (NAFLD), and it is the primary cause of chronic liver disease in approximately 45% of patients at risk for acute-on-chronic liver failure (ACLF) [5].

Alcohol is primarily metabolized in the liver, where chronic consumption promotes inflammation and negatively impact immune cell function. Alcoholic liver disease develops through several stages, beginning with hepatic steatosis, and, in some individuals, gradually progressing through alcoholic hepatitis, culminating in alcoholic cirrhosis [6]. Alcoholic cirrhosis is characterized by end-stage fibrotic restructuring of the liver parenchyma, which originates from chronic and persistent alcohol-induced injury that activates hepatic stellate cells and disrupts extracellular matrix homeostasis. Cirrhosis-associated immune dysfunction (CAID) is a multifactorial condition characterized by systemic immune dysfunction, marked by impaired clearance of circulatory cytokines, bacteria, and endotoxins [7,8]. This pathological process is highly dynamic and considerably progressive which includes two key pathways, that is, systemic inflammation and immunodeficiency, whose magnitude depends on the stage of cirrhosis and the presence of detrimental conditions and

Abbreviations: 3-IAC, 3-Indoleacrylic acid; 3-ILA, (3-Indolyl) Lactic Acid; A2M, Alpha-2-macroglobulin; ACLF, Acute-on-chronic liver failure; BCAA, Branched-chain amino acid; CAID, Cirrhosis-associated immune dysfunction; cGAS-STING, Cyclic GMP-AMP synthase-stimulator of interferon gene; DAMPs, Damage-associated molecular patterns; DCs, Dendritic cells; ER, Endoplasmic reticulum; HLA-DR, Human leukocyte antigen; HSC, Hepatic stellate cell; IFNs, Interferons; IRF3, Interferon regulatory factor 3; KCs, Kupffer cells; LPS, Lipopolysaccharide; MALT, Mucosa-associated lymphoid tissue; MCs, Mast cells; NAFLD, Non-alcoholic fatty liver disease; NF-κB, Nuclear factor-kappa B; NKs, Natural killer cells; PAMPs, Pathogen-associated molecular patterns; PGN, Peptidoglycan; PIgR, Polymeric immunoglobulin receptor; PRRs, Pattern recognition receptors; SBP, Spontaneous bacterial peritonitis; SCFAs, Short-chain fatty acids; STAT3, Signal transducer and activator of transcription 3; TBK1, Tumor necrosis factor; TLR, Toll-like receptors; Tregs, Regulatory T cells

* Corresponding authors.
E-mail addresses: chaosun@tmu.edu.cn (C. Sun), haolele77@sina.com (J. Liang).

[1] These authors contributed equally to this work and should be considered co-first authors.

https://doi.org/10.1016/j.aohep.2025.101927

perturbations such as bacterial infections [9]. CAID originates from the compensated cirrhosis, deteriorates across the decompensated stage and reaches its peak in the context of ACLF [9,10]. Alcohol abstinence alone fails to fully reverse intestinal barrier damage or completely arrest cirrhosis progression. Therefore, it is imperative to elucidate the mechanisms underlying immune dysfunction among patients with alcoholic cirrhosis and to develop effective strategies concerning its management. This narrative review focuses on versatile aspects concerning the immune dysfunction in the scenario of alcoholic cirrhosis.

2. Alcoholic cirrhosis and systemic inflammation

Alcohol abuse has been linked to small intestine bacterial overgrowth, shifts in the composition of gut microbial and fungal communities (referred to intestinal microbial dysbiosis) [11], increased microbial translocation, and obvious damage to the gut barrier. These alterations, mediated via the liver-gut axis, drive the pathogenesis of liver damage, cirrhosis, and systemic inflammation, while demonstrating significant associations with the severity of psychiatric manifestations, including anxiety and depression [11]. The colon harbors the most abundant microbial community [12]. Alcohol abuse induces an increase in intestinal permeability to macromolecules [13], while elevated IgA levels exacerbate endotoxin translocation through compromised gut barrier integrity [14,15]. In this regard, the increased systemic translocation of bacterial products, such as lipopolysaccharide (LPS) and peptidoglycan (PGN), has been correlated with elevated levels of inflammatory markers in the plasma. These bacterial products enter the liver via the portal vein, in consequence, activate Kupffer cells and exacerbate or boost the inflammatory cascade. Serum levels of anti-Saccharomyces cerevisiae immunoglobulin G antibodies, a biomarker suggestive of systemic immune response against fungi and fungal products, are elevated in patients with alcoholic cirrhosis [16]. Additionally, alterations in fungal and viral populations are recognized as important contributors to the progression of alcoholic cirrhosis.

Endotoxemia manifests more severely in alcoholic cirrhosis than in cirrhosis of other etiologies [17]. Alcohol binge resulted in a rapid increase in serum endotoxin and 16S rDNA, a marker of bacterial translocation from the gut [3]. The molecular features of alcohol-induced Toll-like receptors (TLR) tolerance and sensitization are well characterized, evident by downstream components of TLR-induced signaling cascades. These include the activation of IRAK-M, IRAK1/4, Bcl-3, and nuclear factor-kappa B (NF-κB), all of which are responsible for proinflammatory cytokine production, resulting in chronic low-grade systemic inflammation [11]. Pathogen-associated molecular patterns (PAMPs) from the gut and damage-associated molecular patterns (DAMPs) from the injurious hepatocytes orchestrate a proinflammatory milieu by activating inflammasome formation [18], significantly increasing NLRP3 and IL-1β protein levels in addition to caspase-1 activity. Studies have shown that, inhibition of spleen tyrosine kinase in mice significantly reduces serum IL-1β levels and caspase-1 activation in the liver [19]. NLRP6 and NLRP12, which are associated with enhanced NF-κB activation, reduce alcohol-induced CCL20 expression and hepatic stellate cell (HSC) activation [20]. sCD137, known for its inflammatory properties, has been reported at higher levels in both obese individuals [21,22] and patients with alcoholic liver disease [23].

Liver inflammation is triggered and sustained by the secretion of cytokines and chemokines from innate immune cells, which express diverse pattern recognition receptors (PRRs), including cyclic GMP-AMP synthase-stimulator of interferon gene (cGAS-STING) signaling pathway [24,25]. Endoplasmic reticulum (ER) stress in response to alcohol stimulation initiates STING activation and interferon regulatory factor 3 (IRF3) phosphorylation, transmitted through gap junctions between hepatocytes, which in turn leads to intense inflammatory response [26,27]. cGAS is a critical cytosolic DNA sensor catalyzing the synthesis of cGAMP from ATP and GTP and activating type I interferons (IFNs) via the ER-resident adaptor protein STING [28,29], which subsequently instigates the transcription factors NF-kB and IRF3 via the TANK-binding kinase 1 (TBK1) [28,29] to harness inflammation activities (Figure 1). In summary, the cGAS-STING pathway is a fundamental mechanism for detecting cellular infections and damage, leading to innate immune activation and an effective defense against various pathogens.

A significant imbalance exists between proinflammatory and anti-inflammatory responses in patients with alcoholic cirrhosis. Excessive proinflammatory responses, such as the release of tumor necrosis factor-α (TNF-α) and IL-6, along with an immunosuppressive status characterized by increased expression of IL-10, contribute to persistent inflammation and immunosuppression responsible for the risk of infections. Studies have shown that serum IL-6 levels correlate positively with the severity of alcoholic cirrhosis, although IL-6 plays a protective role in animal models [30]. In this regard, IL-6 and IL-22 activate signal transducer and activator of transcription 3 (STAT3) dimers to upregulate the translation concerning multiple anti-apoptotic, antioxidant, and mitochondrial DNA repair genes. Moreover, inhibition of lipid metabolism genes like SREBP-1c [31,32] improves steatosis, protects the liver from ethanol-induced damage, and facilitates liver regeneration [33]. However, IL-10 has also been reported to suppress innate immune activation and hepatoprotective cytokines [34], whose deficiency in mice enhances liver regeneration. Collectively, the pathophysiological consequence is defined by the balance and homeostasis between proinflammatory and hepatoprotective cytokines (Figure 2).

3. Alcoholic cirrhosis and immune deficiency

Despite the chronic inflammatory response commonly observed in alcoholic cirrhosis, the immune system of affected patients also exhibits a state of immunosuppression. Alcohol's direct toxicity and the inflammatory milieu collectively impair immune cell function, evident by significant suppression of phagocytes, T cells, and natural killer (NK) cell activities. This immunosuppressive state increases the patient's susceptibility to exogenous pathogens. A standard definition of immunodeficiency is currently lacking, but it can be arbitrarily identified as the presence of cellular abnormalities regarding immune system that impair its effector function and lead to immune paralysis. The immunodeficiency in cirrhosis is secondary to two main factors: structural distortion of the hepatic parenchyma, and functional impairment of circulating immune cells.

Within the hepatic sinusoidal system, endothelial cells form fenestration lacking a continuous basement membrane [35], and the blood flow velocity is notably curtailed, fostering an environment abundant in antigens [36]. These endothelial cells encounter antigen-presenting cells and lymphocytes, therefore a cascade of highly complex immune reactions is triggered, which plays a crucial role in modulating immune balance and determining processes associated with liver cirrhosis [37,38] (Table 1).

3.1. Neutrophils

Neutrophils have served as the primary immune cell type in the early stage of the inflammatory responses [39]. Patients with alcoholic cirrhosis exhibit reduced neutrophil counts and impaired formation of neutrophil extracellular traps [40], a dysfunction characterized by higher susceptibility to bacterial infections [41]. Alcohol consumption and endotoxin aggravate the interaction between neutrophils and liver sinusoidal endothelial cells via the CD11b/ICAM-1 pathway [25]. This reciprocal effect further activates Kupffer cells (KCs), giving rise to the release of IL-1β and the

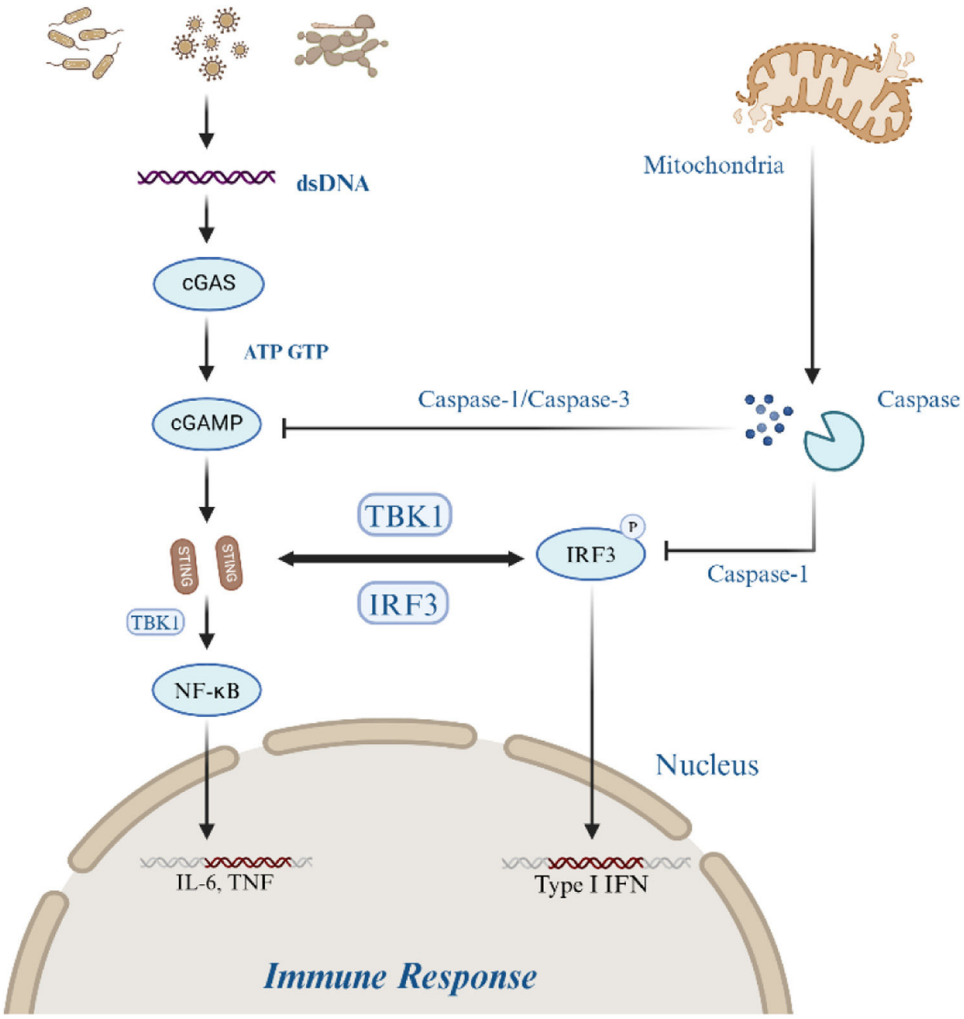

Figure 1. cGAS-STING signaling pathway. cGAS catalyzes the synthesis of cGAMP from ATP and GTP and activates IFNs via the ER-resident adaptor protein STING, which subsequently instigates the transcription factors NF-kB and IRF3 via the TBK1 to harness inflammation activities.TBK1: TANK-binding kinase 1; IRF3: Interferon regulatory factor 3; NF-κB: Nuclear factor kappa-B; TNF: Tumor necrosis factor; IFN: Interferon.

recruitment of invariant NKT cells, which promotes neutrophil accumulation and contributes to the progression of alcoholic cirrhosis.

Cytokines can also harness the adhesion of neutrophils to the vascular endothelium, allowing the neutrophils to move along the vessel walls and migrate towards the infection site with the purpose of engulfing pathogen [42]. The initiation of this process depends on the binding of activated platelets to P-selectin glycoprotein ligand-1, a protein mimicking an antenna on the surface of neutrophils in the bloodstream [43,44]. It has been shown that neutrophil phagocytic capacity and ROS burst may predict the development of infection, organ dysfunction, and 90-day survival in decompensated cirrhosis [45,46].

3.2. Monocytes/macrophages

Monocyte dysfunction is a prominent hallmark of immune paralysis. Monocyte dysfunction has been defined as reduced monocyte HLA-DR expression [47] and declined ex-vivo endotoxin (LPS)-induced TNF-α production [48–52]. PGE2, via its EP4 receptor, downregulates monocyte TNF and IL-6 production in decompensated cirrhosis and represses monocyte HLA-DR expression. There is an opportunity to address alcohol dependence by reducing inflammatory cytokines.

Impaired phagocytic capacity pertaining to resident macrophage has been identified in patients with cirrhosis (primarily attributable to alcoholism) compared to healthy controls, which is positively correlated with liver disease severity, accounting for the development of infection and mortality [43,44]. A study demonstrated that TGF-β, an M2-associated profibrotic factor, is highly expressed in the livers of patients with alcoholic hepatitis, involving various M2 macrophage subtypes (M2a, M2b, and M2c) [53]. In patients undergoing alcohol withdrawal, macrophage infiltration is reduced, while M2 macrophage polarization increases in the subcutaneous adipose tissue. Additionally, studies have unveiled that inhibiting TLR2 expression and promoting TLR3 expression in Kupffer cells can activate STAT3 and induce IL-10 production, fostering the polarization of M1 to M2 macrophages. Macrophage polarization is regulated by the activation of multiple interconnected cellular signaling pathways. In this regard, key pathways involved in inflammation-related polarization comprise the Janus kinase (JAK)/STAT pathway, the NF-κB pathway, and the phosphoinositide 3-kinase (PI3K)/protein kinase B (PKB)/Akt pathway [48]. Consequently, the development of pharmacological treatments targeting specific signaling pathways offers significant potential as therapeutic avenues in the future.

Neutrophil-derived ROS instigate the transition from inflammatory to reparative macrophages. Activation of TLR-3 can induce KCs and HSCs to produce IL-10, whereas TLR4 enhances the transmission of inflammatory signals via calcium-dependent signaling pathways [54,55]. The inflammatory activation of macrophages contributes to the assembly of inflammasomes and the subsequent release of

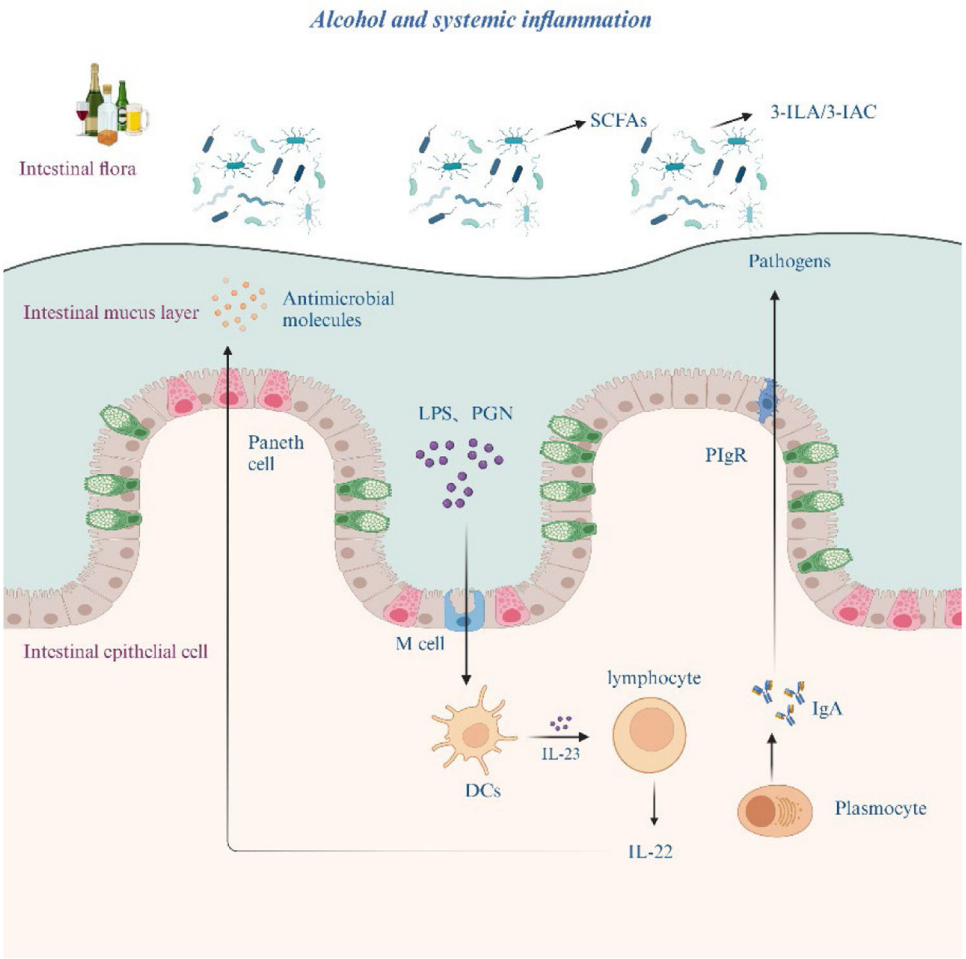

Figure 2. Alcohol and systemic inflammation. Alcohol causes excessive growth of intestinal microbiota, secreting SCFAs and tryptophan metabolites. LPS and PGN are activated by the intestinal mucus layer through M cells and type 3 natural lymphocytes to eventually produce IL-22 acting on antibacterial molecules. At the same time, plasma cells bind pathogenic bacteria through IgA. DCs: Dendritic cells; LPS: Lipopolysaccharides; PGN: Peptidoglycan; SCFAs: Short-chain fatty acids; 3-ILA: (3-Indolyl) Lactic Acid; 3-IAC: 3-Indoleacrylic acid; PIgR: Polymeric immunoglobulin receptor.

proinflammatory cytokines, thereby partially responsible for the pathogenesis of alcoholic cirrhosis [56,57]. Fas is an apoptosis-related receptor to favor early ethanol-induced M1 macrophage polarization and inflammation. Moreover, inhibition of M2 polarization reduces TGF-β production and in consequence, inhibits relevant profibrotic alterations and actions [58].

3.3. DCs

Dendritic cells (DCs) constitute two distinct subsets, conventional DCs and plasmacytoid DCs. Conventional type 1 DCs have been proved to mitigate alcohol-induced liver damage in the murine models by maintaining the local abundance of probiotic *Lactobacillus*

Table 1
Cells involved in the immune response.

Cell type	Alcoholic cirrhosis
Innate immune system	
Neutrophils	Released IL-1β and recruited NKT cells; Adhered to the vascular endothelium;
Monocytes/macrophages	Reduced monocyte HLA-DR expression and declined TNF-α production; Increased ROS; Assembled inflammasomes and released proinflammatory cytokines;
DCs	Impaired antigen presentation;
NKs	Promoted the production of interferon-gamma and IL-4;
MCs	Increased numbers promote fibrosis formation;
Adaptive immune system	
T cells	Increased the proportion of Tregs; Halted the function of CD4+ and CD8+ T cells;
B cells	Reduced B cell populations;
MALT cells	Reduced and hyperactivated MALT cell populations;

CD4+, Cluster of Differentiation 4 positive; CD8+, Cluster of Differentiation 8 positive; DCs, Dendritic cells; HLA-DR, Human leukocyte antigen DR isotype; IL-1β, Interleukin-1 beta; IL-4, Interleukin-4; MALT, Mucosa-associated lymphoid tissue; MCs, Mast cells; NKT, Natural killer T cells; NKs, Natural killer cells; ROS, Reactive oxygen species; Tregs, Regulatory T cells; TNF-α, Tumor necrosis factor alpha.

mucosus [59]. In addition, chronic alcohol consumption is associated with the distribution, immunophenotype, and secretion of inflammatory mediators [60]. Alcohol consumption triggers DCs dysfunction, impairs antigen presentation, and disrupts the initiation of adaptive immune response. However, no studies have investigated the effects of long-term alcohol consumption on DCs in mice or human beings experiencing alcoholic cirrhosis.

3.4. NKs

Patients with alcoholic cirrhosis exhibit reduced NK cell activity alongside decreased NK cell numbers, weakening the body's antiviral defenses. This constructs a conducive environment suitable for the development of viral hepatitis in combination with alcoholic cirrhosis. Alcohol activates Type I NKT cells through direct recognition of specific lipids or TLR ligands, as well as by indirect stimulation via cytokines. This process in turn promotes the production of IFN-gamma (IFN-γ) and IL-4, all-trans retinoic acid through the retinoic acid receptor γ signaling [61]. In contrast, Type 2 T cell receptor lineage NKT cells exhibit immunomodulatory properties in the murine models challenged by chronic alcohol consumption. Sulfatide-mediated activation of Type II NKT cells can be considered to effectively halt alcoholic liver disease progression [61].

3.5. MCs

The presence of mast cells (MCs) expressing tryptase and chymase is strongly linked to the magnitude of fibrosis [62]. The number of MCs in the liver increase in the circumstance of alcoholic cirrhosis. These cells may contribute to the development of hepatic fibrosis indirectly via the release of substances facilitating cirrhosis or directly by secreting proteins to form the extracellular matrix [63]. In the liver, MCs can exhibit immunomodulatory effects on other immune cells, thereby enhancing or suppressing the initiation, magnitude, and/or duration of immune activities within the liver, preventing diminished hepatobiliary functions during disease progression, or by acting as a first effector cell in an innate response to encounter antigens [64,65] (Figure 3).

3.6. T Cells

During alcohol-induced liver injury, T cell proliferation and activation are considerably impaired, particularly with an increase in the proportion of regulatory T cells (Tregs), which weakens the anti-inflammatory response. Concurrently, the function of CD4+ and CD8+ T cells is to some extent compromised, diminishing the liver's ability

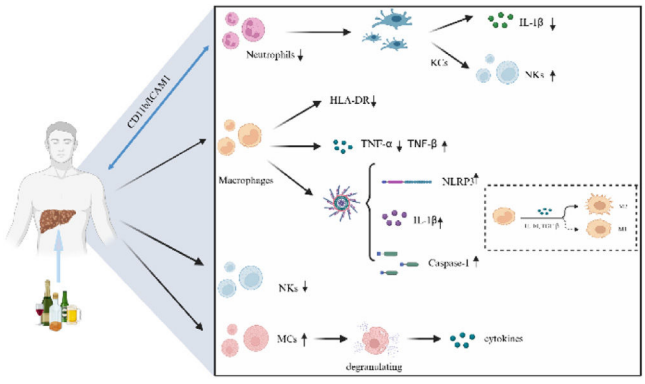

Figure 3. Innate immune system. Including reduced neutrophil counts and impaired formation of neutrophil extracellular traps, monocyte dysfunction, the assembly of inflammasomes, reduced NK cells activity alongside decreased NK cell numbers, and an increase in the number of MCs. NKs: natural killer cells; MCs: mast cells; KCs: Kupffer cells; HLA-DR: human leukocyte antigen.

to eliminate infections. Unlike the innate immune response, which can be triggered by any antigen, adaptive immunity is specific to certain antigen. Tregs limit and suppress immune responses to prevent excessive immune activation and autoimmune reactions [66,67]. T helper cells (CD4+) regulate the activity of other immune cells by generating and secreting various cytokines. Th1 cells activate macrophages or CD8+ cells to instigate a cell-mediated immune response against intracellular pathogens, primarily exerting their influences through the release of IFN-γ [68]. Th2 cells, on the other hand, are responsible for a humoral immune response against extracellular pathogens through proteins produced by B cells, primarily mediated by a range of interleukins, some of which have anti-inflammatory properties [69]. Additionally, Th17 cells, a subset of T helper cells, are characterized by their production of interleukin-17 and primarily functioning to defend against pathogens at epithelial and mucosal barriers [70].

3.7. B Cells

In patients with alcoholic cirrhosis, B cell dysfunction gives rise to insufficient antibody production, negatively impacting the body's defense against bacterial and viral infections, thereby increasing the risk of spontaneous bacterial peritonitis (SBP). The B cell populations are significantly reduced in the context of alcoholic cirrhosis [71–74], resulting in diminished antigen-specific antibody responses [60], although total levels of IgA, IgG, and IgM are elevated overall [75,76].

3.8. MALT cells

In cirrhosis, the gut-associated lymphoid tissue is highly active due to sustained bacterial translocation from the gut on account of increased intestinal permeability [77]. Local inflammation alters intestinal tight junction protein expression and barrier function [78–80]. Intestinal microbial dysbiosis and bacterial translocation are also expanded by depressed expression of antimicrobial peptides, including regenerating islet-derived 3 beta and gamma [81–84]. Mucosa-associated lymphoid tissue (MALT) cells are reduced in number, hyperactivated, and exhibit functional defects concerning antimicrobial cytokine and cytotoxic responses [17,85]. These alterations are exacerbated in patients experiencing alcoholic cirrhosis, which is in alignment with the dynamic course of CAID.

Immune system imbalance in alcoholic cirrhosis impairs the ability of organ to clear harmful metabolic byproducts, such as ammonia, leading to its accumulation in the bloodstream and subsequent effects on the central nervous system, triggering hepatic encephalopathy [86]. Ammonia impairs neutrophil function by reducing chemotaxis and phagocytosis while increasing spontaneous oxidative burst, which has been linked to 3-month and 1-year mortality among patients with cirrhosis [85,87]. Alcoholic cirrhosis is connected with reduced neutrophil counts, elevated CD8+ T cell levels, reduced steatosis, and impaired NK cell function. Additionally, an increase in LOX-1+ myeloid-derived suppressor cells, which exhibit immunosuppressive characteristics, has been observed in Child-Pugh C patients with alcoholic cirrhosis [88]. Several studies have reported a slight increase in PD-1 and/or TIM-3 lymphocyte expression in the circumstance of acute alcoholic hepatitis/cirrhosis, leading to the inhibition of the second signal required for T cell activation [89–92].

Furthermore, decompensated liver cirrhosis gives rise to a state of functional immunosuppression, and often presents with hypergammaglobulinemia (HGG) [92–94]. The inability of patients with advanced cirrhosis to mount protective antibody responses despite concurrent HGG is based on dysregulation of Tfh cells response [95]. Importantly, systemic C3c and IgG1 levels seem to be remarkable biomarkers indicative of CAID [8]. Concordantly, Massonnet et al. suggested that the upregulation of IgA production in cirrhosis is related to activation of TLR pathways [73]. The prognostic value of IL-6 and

IgG1 likely underline the clinical significance of a proinflammatory state [96]. The finding of increased IgG-4 levels which is considered as a mediator of anti-inflammatory effects or even of immunotolerance in other context [97] support the concept that both inflammation and immunocompromise are intimate features of CAID [8,66]. Alpha-2-macroglobulin (A2M) functions as a protease inhibitor and may scavenge cytokines and other proinflammatory mediators [98]. The mechanistic implications caused by dysregulation of A2M may further contribute to immune dysfunction [98].

4. Potential treatment opportunity

Patients with alcoholic cirrhosis often present with a spectrum of immune-related complications, the most common being spontaneous bacterial peritonitis (SBP), hepatic encephalopathy, and hepatocellular carcinoma. The immune dysfunction associated with alcoholic cirrhosis leverages significant challenges on clinical practice. Targeting systemic inflammation increases the risk of infections, while stimulating the inflammatory response may exacerbate detrimental immune reactions and associated injuries. Mounting evidence suggests that certain interventions, which have recently gained increasing attention, may be beneficial.

4.1. Gut microbiota modulation

Probiotics and prebiotics reduce LPS and TNF-α levels, decrease bacterial overgrowth, and accelerate the repair of alcohol-induced cirrhosis, thereby lowering the incidence of bacterial infections. Obeticholic acid, a farnesoid X receptor agonist, contributes to restore the intestinal homeostasis and prevent intestinal vascular barrier dysfunction [51,99]. Additionally, fecal microbiota transplantation capsules have exhibited therapeutic potentials in enhancing microbial diversity with respect to the duodenal mucosa and intestines, increasing antimicrobial peptide expression, and reducing LPS-binding protein levels, representing a promising non-antibiotic therapeutic strategy [100].

4.2. Anti-infection therapy

Rifaximin-α can promote the intestinal microenvironment rich in TNF-α and interleukin-25, enhance the antibacterial response to invading pathogens, and promote the repair of intestinal barrier [86,99]. In a multicenter double-blind randomized trial conducted in 291 patients with advanced cirrhosis, Norfloxacin decreased 6-month mortality in patients with ascites fluid protein concentrations of less than 15 g/L [101]. A beneficial effect of norfloxacin could be related to a decrease in systemic inflammation through direct “off-label” anti-inflammatory effects of the antibiotic in immune cells [102]. It can not only reduce the recurrence of overt hepatic encephalopathy, but also favorably manage the intestinal microbiota [103,104]. However, long-term use of antibiotics in patients with liver cirrhosis can reduce the diversity of intestinal bacteria [105].

Nonantibiotic strategies should be implemented to prevent infections in the context of cirrhosis. Beta-blockers and long-term use of albumin were proved to decrease intestinal permeability, bacterial translocation, and magnitude of released inflammatory cytokines [106]. Statins exhibits anti-inflammatory and antifibrotic effects, and are shown to decrease the portal pressure in patients with cirrhosis, as well as improving survival in those with variceal hemorrhage [23]. A non-antibiotic gut decontaminating product CARBALIVE, known as a novel engineered orally ingested macroporus carbon bead, is capable of binding toxins [107]. This has the potential to ameliorate systemic and gut inflammation.

4.3. Immune enhancement therapy

There are few publications with respect to emerging immunotherapeutic approaches. G-CSF induces the mobilization of hematopoietic stem cells into the peripheral blood in response to neutrophil activation. This is thought to overcome functional immune paresis in patients with advanced cirrhosis and CAID [108]. Probiotics, metformin and their combination can promote M2 polarization and inhibit M1 polarization, partially contributing to the amelioration concerning alcoholic liver injury [109]. Branched-chain amino acid (BCAA) granules have been addressed as potential novel therapeutic agents for patients with cirrhosis experiencing CAID along with effectiveness [110]. BCAAs are integrated by immune cells. Studies have shown that BCAA granules significantly restore phagocytic activity across various stages of cirrhosis [108]. They activate the mTOR pathway, a central signaling pathway of the immune microenvironment [111,112]. A translational study demonstrated that BCAAs reduce bacterial translocation, lipopolysaccharide-binding protein expression, TLR-4 activation [81], and significantly improve neutrophil phagocytic capacity [94]. Activation of TLRs induces a significant impairment of neutrophil function (phagocytosis and oxidative rupture) [93], a decrease in the ability of T cells to produce IFN-γ, and an increase in serum levels of immunosuppressive receptors such as PD1 and TIM3 [89]. Endotoxin removal blocks TLR and restores the antimicrobial activity of neutrophils and T cell [89].

Both steroids and TNF-α inhibitors suppress inflammation, but they also repress liver regeneration and increase bacterial infection rates, indicative of the main reason regarding poor efficacy of current treatments. IL-22 has antibacterial effect and promotes liver regeneration [113]. It is feasible to administer IL-22 to treat alcoholic cirrhosis absence of liver cancer, but it cannot be used in patients with precancerous cirrhosis or liver cancer [113]. It has also been demonstrated that visceral sympathectomy causes an increase in *E. coli* phagocytosis [114]. A recent study has reported that microRNA (miR)-223 inhibits IL-6 expression within neutrophils, and mitigates ROS production [115,116]. However, the presence of a hepatic mitochondrial deoxyribonucleic acid/TLR-9/miR-223 axis mediates negative feedback loop bringing susceptibility to progressive liver injury [115,116].

5. Conclusions

Immune dysfunction in alcoholic cirrhosis is a key mechanism underlying disease progression and the development of complications, involving both the innate and adaptive immune systems. By exploring the molecular mechanisms of alcoholic cirrhosis and developing targeted interventions, this narrative review summarizes the primary research directions and therapeutic advances related to immune dysfunction in alcoholic cirrhosis. Therapeutic strategies targeting immune dysregulation, including cytokine modulation and macrophage polarization, hold promise for improving outcomes in these patients. Various cell types comprising the intestinal barrier contribute to mucosal dysfunction associated with the severity of liver disease. Therefore, multi-targeted and personalized therapies appear to be the most viable approach to effectively manage these patients. These approaches may offer promising strategies for patients with alcoholic cirrhosis in hopes of improving their prognosis and quality of life.

Author contributions

Mingyu Sun and Ziyang Yang – Writing – original draft; Fei Tang, Fenghui Li and Qing Ye – Data curation; Jing Liang and Chao Sun – Writing – review & editing; all authors read and approved the final manuscript.

Declaration of interests

None.

Funding

This work was supported by the Natural Science Foundation of Tianjin Science and Technology Bureau, China, No. 23KPHDRC00350.

References

[1] Global status report on alcohol and health 2018. Geneva: World Health Organization; 2018 Licence: CC BY-NC-SA 3.0 IGO.
[2] Manthey J, Shield KD, Rylett M, Hasan OSM, Probst C, Rehm J. Global alcohol exposure between 1990 and 2017 and forecasts until 2030: a modelling study. Lancet 2019;393(10190):2493–502. https://doi.org/10.1016/s0140-6736(18)32744-2.
[3] Bala S, Marcos M, Gattu A, Catalano D, Szabo G. Acute binge drinking increases serum endotoxin and bacterial DNA levels in healthy individuals. PLoS One 2014;9(5):e96864. https://doi.org/10.1371/journal.pone.0096864.
[4] Rehm J, Taylor B, Mohapatra S, Irving H, Baliunas D, Patra J, et al. Alcohol as a risk factor for liver cirrhosis: a systematic review and meta-analysis. Drug Alcohol Rev 2010;29(4):437–45. https://doi.org/10.1111/j.1465-3362.2009.00153.x.
[5] Julien J, Ayer T, Bethea ED, Tapper EB, Chhatwal J. Projected prevalence and mortality associated with alcohol-related liver disease in the USA, 2019-40: a modelling study. Lancet Public Health 2020;5(6):e316–23. https://doi.org/10.1016/s2468-2667(20)30062-1.
[6] Mathurin P, Lucey MR. Management of alcoholic hepatitis. J Hepatol 2012;56 (Suppl 1):S39–45. https://doi.org/10.1016/s0168-8278(12)60005-1.
[7] Ghassemi S, Garcia-Tsao G. Prevention and treatment of infections in patients with cirrhosis. Best practice & research. Clinic Gastroenterol 2007;21(1):77–93. https://doi.org/10.1016/j.bpg.2006.07.004.
[8] Albillos A, Martin-Mateos R, Van der Merwe S, Wiest R, Jalan R, Álvarez-Mon M. Cirrhosis-associated immune dysfunction. Nat Rev Gastroenterol Hepatol 2022;19(2):112–34. https://doi.org/10.1038/s41575-021-00520-7.
[9] Albillos A, Lario M, Álvarez-Mon M. Cirrhosis-associated immune dysfunction: distinctive features and clinical relevance. J Hepatol 2014;61(6):1385–96. https://doi.org/10.1016/j.jhep.2014.08.010.
[10] Martin-Mateos R, Alvarez-Mon M, Albillos A. Dysfunctional immune response in acute-on-chronic liver failure: it takes two to tango. Front Immunol 2019;10:973. https://doi.org/10.3389/fimmu.2019.00973.
[11] Leclercq S, Matamoros S, Cani PD, Neyrinck AM, Jamar F, Stärkel P, et al. Intestinal permeability, gut-bacterial dysbiosis, and behavioral markers of alcohol-dependence severity. Proc Natl Acad Sci U S A 2014;111(42):E4485–93. https://doi.org/10.1073/pnas.1415174111.
[12] Jandhyala SM, Talukdar R, Subramanyam C, Vuyyuru H, Sasikala M, Nageshwar Reddy D. Role of the normal gut microbiota. World J Gastroenterol 2015;21(29):8787–803. https://doi.org/10.3748/wjg.v21.i29.8787.
[13] Parlesak A, Schäfer C, Schütz T, Bode JC, Bode C. Increased intestinal permeability to macromolecules and endotoxemia in patients with chronic alcohol abuse in different stages of alcohol-induced liver disease. J Hepatol 2000;32(5):742–7. https://doi.org/10.1016/s0168-8278(00)80242-1.
[14] Nolan JP, DeLissio MG, Camara DS, Feind DM, Gagliardi NC. IgA antibody to lipid A in alcoholic liver disease. Lancet 1986;1(8474):176–9. https://doi.org/10.1016/s0140-6736(86)90652-5.
[15] Nolan JP. Intestinal endotoxins as mediators of hepatic injury—an idea whose time has come again. Hepatology 1989;10(5):887–91. https://doi.org/10.1002/hep.1840100523.
[16] Yang AM, Inamine T, Hochrath K, Chen P, Wang L, Llorente C, et al. Intestinal fungi contribute to development of alcoholic liver disease. J Clin Invest 2017;127(7):2829–41. https://doi.org/10.1172/jci90562.
[17] Bajaj JS, Heuman DM, Hylemon PB, Sanyal AJ, White MB, Monteith P, et al. Altered profile of human gut microbiome is associated with cirrhosis and its complications. J Hepatol 2014;60(5):940–7. https://doi.org/10.1016/j.jhep.2013.12.019.
[18] Szabo G. Clinical trial design for alcoholic hepatitis. Semin Liver Dis 2017;37(4):332–42. https://doi.org/10.1055/s-0037-1608788.
[19] Bukong TN, Iracheta-Vellve A, Saha B, Ambade A, Satishchandran A, Gyongyosi B, et al. Inhibition of spleen tyrosine kinase activation ameliorates inflammation, cell death, and steatosis in alcoholic liver disease. Hepatology 2016;64(4):1057–71. https://doi.org/10.1002/hep.28680.
[20] Ji X, Li L, Lu P, Li X, Tian D, Liu M. NLRP6 exerts a protective role via NF-kB with involvement of CCL20 in a mouse model of alcoholic hepatitis. Biochem Biophys Res Commun 2020;528(3):485–92. https://doi.org/10.1016/j.bbrc.2020.05.171.
[21] Luu K, Shao Z, Schwarz H. The relevance of soluble CD137 in the regulation of immune responses and for immunotherapeutic intervention. J Leukoc Biol 2020;107(5):731–8. https://doi.org/10.1002/jlb.2mr1119-224r.
[22] Tu TH, Kim CS, Kang JH, IS Nam-Goong, Nam CW, Kim ES, et al. Levels of 4-1BB transcripts and soluble 4-1BB protein are elevated in the adipose tissue of human obese subjects and are associated with inflammatory and metabolic parameters. Int J Obes 2014;38(8):1075–82. https://doi.org/10.1038/ijo.2013.222.
[23] Weigand K, Peschel G, Grimm J, Luu K, Schacherer D, Wiest R, et al. Soluble CD137 is a novel serum marker of liver cirrhosis in patients with hepatitis C and alcohol-associated disease etiology. Eur J Immunol 2022;52(4):633–45. https://doi.org/10.1002/eji.202149488.
[24] Hopfner KP, Hornung V. Molecular mechanisms and cellular functions of cGAS-STING signalling. Nat Rev Mol Cell Biol 2020;21(9):501–21. https://doi.org/10.1038/s41580-020-0244-x.
[25] Racanelli V, Rehermann B. The liver as an immunological organ. Hepatology 2006;43(Suppl 1):S54–62. https://doi.org/10.1002/hep.21060.
[26] Petrasek J, Iracheta-Vellve A, Csak T, Satishchandran A, Kodys K, EA Kurt-Jones, et al. STING-IRF3 pathway links endoplasmic reticulum stress with hepatocyte apoptosis in early alcoholic liver disease. Proc Natl Acad Sci U S A 2013;110(41):16544–9. https://doi.org/10.1073/pnas.1308331110.
[27] Lei Z, Deng M, Yi Z, Sun Q, Shapiro RA, Xu H, et al. cGAS-mediated autophagy protects the liver from ischemia-reperfusion injury independently of STING. Am J Physiol Gastrointest Liver Physiol 2018;314(6):G655–67. https://doi.org/10.1152/ajpgi.00326.2017.
[28] Sun L, Wu J, Du F, Chen X, Chen ZJ. Cyclic GMP-AMP synthase is a cytosolic DNA sensor that activates the type I interferon pathway. Science 2013;339(6121):786–91. https://doi.org/10.1126/science.1232458.
[29] Chen Q, Sun L, Chen ZJ. Regulation and function of the cGAS-STING pathway of cytosolic DNA sensing. Nat Immunol 2016;17(10):1142–9. https://doi.org/10.1038/ni.3558.
[30] Chen R, Du J, Zhu H, Ling Q. The role of cGAS-STING signalling in liver diseases. JHEP Rep 2021;3(5):100324. https://doi.org/10.1016/j.jhepr.2021.100324.
[31] Zhang X, Tachibana S, Wang H, Hisada M, Williams GM, Gao B, et al. Interleukin-6 is an important mediator for mitochondrial DNA repair after alcoholic liver injury in mice. Hepatology 2010;52(6):2137–47. https://doi.org/10.1002/hep.23909.
[32] Hong F, Radaeva S, Pan HN, Tian Z, Veech R, Gao B. Interleukin 6 alleviates hepatic steatosis and ischemia/reperfusion injury in mice with fatty liver disease. Hepatology 2004;40(4):933–41. https://doi.org/10.1002/hep.20400.
[33] Wang H, Lafdil F, Kong X, Gao B. Signal transducer and activator of transcription 3 in liver diseases: a novel therapeutic target. Int J Biol Sci 2011;7(5):536–50. https://doi.org/10.7150/ijbs.7.536.
[34] Miller AM, Wang H, Bertola A, Park O, Horiguchi N, Ki SH, 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):846–56. https://doi.org/10.1002/hep.24517.
[35] Kaminski TW, Ju EM, Gudapati S, Vats R, Arshad S, Dubey RK, et al. Defenestrated endothelium delays liver-directed gene transfer in hemophilia A mice. Blood Adv 2022;6(12):3729–34. https://doi.org/10.1182/bloodadvances.2021006388.
[36] van Albada ME, Shah P, Derks TGJ, Fuchs S, Jans JJM, McLin V, et al. Abnormal glucose homeostasis and fasting intolerance in patients with congenital portosystemic shunts. Front Endocrinol 2023;14:1190473. https://doi.org/10.3389/fendo.2023.1190473.
[37] Petagine L, Zariwala MG, Patel VB. Alcoholic liver disease: current insights into cellular mechanisms. World J Biol Chem 2021;12(5):87–103. https://doi.org/10.4331/wjbc.v12.i5.87.
[38] Xu W, Wu M, Chen B, Wang H. Myeloid cells in alcoholic liver diseases: mechanism and prospect. Front Immunol 2022;13:971346. https://doi.org/10.3389/fimmu.2022.971346.
[39] Carpenter R, Oh HJ, Ham IH, Kim D, Hur H, Lee J. Scaffold-assisted ectopic transplantation of internal organs and patient-derived tumors. ACS Biomater Sci Eng 2019;5(12):6667–78. https://doi.org/10.1021/acsbiomaterials.9b00978.
[40] Tritto G, Bechlis Z, Stadlbauer V, Davies N, Francés R, Shah N, et al. Evidence of neutrophil functional defect despite inflammation in stable cirrhosis. J Hepatol 2011;55(3):574–81. https://doi.org/10.1016/j.jhep.2010.11.034.
[41] Fiuza C, Salcedo M, Clemente G, Tellado JM. In vivo neutrophil dysfunction in cirrhotic patients with advanced liver disease. J Infect Dis 2000;182(2):526–33. https://doi.org/10.1086/315742.
[42] Sreeramkumar V, Adrover JM, Ballesteros I, Cuartero MI, Rossaint J, Bilbao I, et al. Neutrophils scan for activated platelets to initiate inflammation. Science 2014;346(6214):1234–8. https://doi.org/10.1126/science.1256478.
[43] Pitchford SC, Momi S, Giannini S, Casali L, Spina D, Page CP, et al. Platelet P-selectin is required for pulmonary eosinophil and lymphocyte recruitment in a murine model of allergic inflammation. Blood 2005;105(5):2074–81. https://doi.org/10.1182/blood-2004-06-2282.
[44] Guyer DA, Moore KL, Lynam EB, Schammel CM, Rogelj S, McEver RP, et al. P-selectin glycoprotein ligand-1 (PSGL-1) is a ligand for L-selectin in neutrophil aggregation. Blood 1996;88(7):2415–21.
[45] Rajkovic IA, Williams R. Abnormalities of neutrophil phagocytosis, intracellular killing and metabolic activity in alcoholic cirrhosis and hepatitis. Hepatology 1986;6(2):252–62. https://doi.org/10.1002/hep.1840060217.
[46] Gomez F, Ruiz P, Schreiber AD. Impaired function of macrophage Fc gamma receptors and bacterial infection in alcoholic cirrhosis. N Engl J Med 1994;331(17):1122–8. https://doi.org/10.1056/nejm199410273311704.
[47] Lin CY, Tsai IF, Ho YP, Huang CT, Lin YC, Lin CJ, et al. Endotoxemia contributes to the immune paralysis in patients with cirrhosis. J Hepatol 2007;46(5):816–26. https://doi.org/10.1016/j.jhep.2006.12.018.
[48] O'Brien AJ, Fullerton JN, Massey KA, Auld G, Sewell G, James S, et al. Immunosuppression in acutely decompensated cirrhosis is mediated by prostaglandin E2. Nat Med 2014;20(5):518–23. https://doi.org/10.1038/nm.3516.
[49] China L, Maini A, Skene SS, Shabir Z, Sylvestre Y, Colas RA, et al. Albumin counteracts immune-suppressive effects of lipid mediators in patients with advanced

liver disease. Clinic Gastroenterol Hepatol 2018;16(5):738–47 e7. https://doi.org/10.1016/j.cgh.2017.08.027.
[50] Bernsmeier C, Pop OT, Singanayagam A, Triantafyllou E, Patel VC, Weston CJ, et al. Patients with acute-on-chronic liver failure have increased numbers of regulatory immune cells expressing the receptor tyrosine kinase MERTK. Gastroenterology 2015;148(3):603–15 e14. https://doi.org/10.1053/j.gastro.2014.11.045.
[51] Wasmuth HE, Kunz D, Yagmur E, Timmer-Stranghöner A, Vidacek D, Siewert E, et al. Patients with acute on chronic liver failure display "sepsis-like" immune paralysis. J Hepatol 2005;42(2):195–201. https://doi.org/10.1016/j.jhep.2004.10.019.
[52] Gadd VL, Patel PJ, Jose S, Horsfall L, Powell EE, Irvine KM. Altered peripheral blood monocyte phenotype and function in chronic liver disease: implications for hepatic recruitment and systemic inflammation. PLoS ONE 2016;11(6):e0157771. https://doi.org/10.1371/journal.pone.0157771.
[53] Lee J, French B, Morgan T, French SW. The liver is populated by a broad spectrum of markers for macrophages. In alcoholic hepatitis the macrophages are M1 and M2. Exp Mol Pathol 2014;96(1):118–25. https://doi.org/10.1016/j.yexmp.2013.09.004.
[54] Xia T, Fu S, Yang R, Yang K, Lei W, Yang Y, et al. Advances in the study of macrophage polarization in inflammatory immune skin diseases. J Inflamm 2023;20(1):33. https://doi.org/10.1186/s12950-023-00360-z.
[55] Lee JH, Shim YR, Seo W, Kim MH, Choi WM, Kim HH, et al. Mitochondrial double-stranded RNA in exosome promotes interleukin-17 production through toll-like receptor 3 in alcohol-associated liver injury. Hepatology 2020;72(2):609–25. https://doi.org/10.1002/hep.31041.
[56] Cho YE, Yu LR, Abdelmegeed MA, Yoo SH, Song BJ. Apoptosis of enterocytes and nitration of junctional complex proteins promote alcohol-induced gut leakiness and liver injury. J Hepatol 2018;69(1):142–53. https://doi.org/10.1016/j.jhep.2018.02.005.
[57] Zhang K, Fan X, Wang X, Zhang X, Zeng L, Li N, et al. Alterations in circadian rhythms aggravate Acetaminophen-induced liver injury in mice by influencing Acetaminophen metabolization and increasing intestinal permeability. Bioengineered 2022;13(5):13118–30. https://doi.org/10.1080/21655979.2022.2079255.
[58] Thurman II RG. Alcoholic liver injury involves activation of Kupffer cells by endotoxin. Am J Physiol 1998;275(4):G605–11. https://doi.org/10.1152/ajpgi.1998.275.4.G605.
[59] Hao L, Zhong W, Woo J, Wei X, Ma H, Dong H, et al. Conventional type 1 dendritic cells protect against gut barrier disruption via maintaining Akkermansia muciniphila in alcoholic steatohepatitis. Hepatology 2023;78(3):896–910. https://doi.org/10.1097/hep.0000000000000019.
[60] Laso FJ, Vaquero JM, Almeida J, Marcos M, Orfao A. Chronic alcohol consumption is associated with changes in the distribution, immunophenotype, and the inflammatory cytokine secretion profile of circulating dendritic cells. Alcohol Clinic Exp Res 2007;31(5):846–54. https://doi.org/10.1111/j.1530-0277.2007.00377.x.
[61] Maricic I, Sheng H, Marrero I, Seki E, Kisseleva T, Chaturvedi S, et al. Inhibition of type I natural killer T cells by retinoids or following sulfatide-mediated activation of type II natural killer T cells attenuates alcoholic liver disease in mice. Hepatology 2015;61(4):1357–69. https://doi.org/10.1002/hep.27632.
[62] Matsunaga Y, Terada T. Mast cell subpopulations in chronic inflammatory hepatobiliary diseases. Liver 2000;20(2):152–6. https://doi.org/10.1034/j.1600-0676.2000.020002152.x.
[63] Matsunaga Y, Kawasaki H, Terada T. Stromal mast cells and nerve fibers in various chronic liver diseases: relevance to hepatic fibrosis. Am J Gastroenterol 1999;94(7):1923–32. https://doi.org/10.1111/j.1572-0241.1999.01232.x.
[64] Grizzi F, Di Caro G, Laghi L, Hermonat P, Mazzola P, Nguyen DD, et al. Mast cells and the liver aging process. Immun Ageing 2013;10(1):9. https://doi.org/10.1186/1742-4933-10-9.
[65] Tolefree JA, Garcia AJ, Farrell J, Meadows V, Kennedy L, Hargrove L, et al. Alcoholic liver disease and mast cells: what's your gut got to do with it? Liver Res 2019;3(1):46–54. https://doi.org/10.1016/j.livres.2019.02.002.
[66] Márquez M, Fernández-Gutiérrez C, Montes-de-Oca M, Blanco MJ, Brun F, Rodríguez-Ramos C, et al. Chronic antigenic stimuli as a possible explanation for the immunodepression caused by liver cirrhosis. Clin Exp Immunol 2009;158(2):219–29. https://doi.org/10.1111/j.1365-2249.2009.04005.x.
[67] Devière J, Denys C, Schandene L, Romasco F, Adler M, Wybran J, et al. Decreased proliferative activity associated with activation markers in patients with alcoholic liver cirrhosis. Clin Exp Immunol 1988;72(3):377–82.
[68] Perrin D, Bignon JD, Beaujard E, Cheneau ML. Populations of circulating T lymphocytes in patients with alcoholic cirrhosis. Gastroenterol Clin Biol 1984;8(12):907–10.
[69] Morita K, Fukuda Y, Nakano I, Katano Y, Hayakawa T. Peripheral lymphocyte subsets vary with stage of hepatitis C virus-associated liver disease. Hepatogastroenterology 2005;52(66):1803–8.
[70] McGovern BH, Golan Y, Lopez M, Pratt D, Lawton A, Moore G, et al. The impact of cirrhosis on CD4+ T cell counts in HIV-seronegative patients. Clinic Infect 2007;44(3):431–7. https://doi.org/10.1086/509580.
[71] Cook RT, Waldschmidt TJ, Cook BL, Labrecque DR, McLatchie K. Loss of the CD5+ and CD45RAhi B cell subsets in alcoholics. Clin Exp Immunol 1996;103(2):304–10. https://doi.org/10.1046/j.1365-2249.1996.d01-621.x.
[72] Laso FJ, Madruga JI, López A, Ciudad J, Alvarez-Mon M, San Miguel J, et al. Distribution of peripheral blood lymphoid subsets in alcoholic liver cirrhosis: influence of ethanol intake. Alcohol Clinic Exp Res 1996;20(9):1564–8. https://doi.org/10.1111/j.1530-0277.1996.tb01700.x.
[73] Massonnet B, Delwail A, Ayrault JM, Chagneau-Derrode C, Lecron JC, Silvain C. Increased immunoglobulin A in alcoholic liver cirrhosis: exploring the response of B cells to Toll-like receptor 9 activation. Clin Exp Immunol 2009;158(1):115–24. https://doi.org/10.1111/j.1365-2249.2009.04004.x.
[74] Doi H, Iyer TK, Carpenter E, Li H, Chang KM, Vonderheide RH, et al. Dysfunctional B-cell activation in cirrhosis resulting from hepatitis C infection associated with disappearance of CD27-positive B-cell population. Hepatology 2012;55(3):709–19. https://doi.org/10.1002/hep.24689.
[75] Mili F, Flanders WD, Boring JR, Annest JL, DeStefano F. The associations of alcohol drinking and drinking cessation to measures of the immune system in middle-aged men. Alcohol Clin Exp Res 1992;16(4):688–94. https://doi.org/10.1111/j.1530-0277.1992.tb00662.x.
[76] Smith Jr. WI, Van Thiel DH, Whiteside T, Janoson B, Magovern J, Puet T, et al. Altered immunity in male patients with alcoholic liver disease: evidence for defective immune regulation. Alcohol Clin Exp Res 1980;4(2):199–206. https://doi.org/10.1111/j.1530-0277.1980.tb05635.x.
[77] Muñoz L, José Borrero M, Ubeda M, Lario M, Díaz D, Francés R, et al. Interaction between intestinal dendritic cells and bacteria translocated from the gut in rats with cirrhosis. Hepatology 2012;56(5):1861–9. https://doi.org/10.1002/hep.25854.
[78] Assimakopoulos SF, Tsamandas AC, Tsiaoussis GI, Karatza E, Triantos C, Vagianos CE, et al. Altered intestinal tight junctions' expression in patients with liver cirrhosis: a pathogenetic mechanism of intestinal hyperpermeability. Eur J Clin Invest 2012;42(4):439–46. https://doi.org/10.1111/j.1365-2362.2011.02609.x.
[79] Pijls KE, Koek GH, Elamin EE, de Vries H, Masclee AA, Jonkers DM. Large intestine permeability is increased in patients with compensated liver cirrhosis. Am J Physiol Gastrointest Liver Physiol 2014;306(2):G147–53. https://doi.org/10.1152/ajpgi.00330.2013.
[80] Du Plessis J, Vanheel H, Janssen CE, Roos L, Slavik T, Stivaktas PI, et al. Activated intestinal macrophages in patients with cirrhosis release NO and IL-6 that may disrupt intestinal barrier function. J Hepatol 2013;58(6):1125–32. https://doi.org/10.1016/j.jhep.2013.01.038.
[81] Yan AW, Fouts DE, Brandl J, Stärkel P, Torralba M, Schott E, et al. Enteric dysbiosis associated with a mouse model of alcoholic liver disease. Hepatology 2011;53(1):96–105. https://doi.org/10.1002/hep.24018.
[82] Hartmann P, Chen P, Wang HJ, Wang L, McCole DF, Brandl K, et al. Deficiency of intestinal mucin-2 ameliorates experimental alcoholic liver disease in mice. Hepatology 2013;58(1):108–19. https://doi.org/10.1002/hep.26321.
[83] Teltschik Z, Wiest R, Beisner J, Nuding S, Hofmann C, Schoelmerich J, et al. Intestinal bacterial translocation in rats with cirrhosis is related to compromised Paneth cell antimicrobial host defense. Hepatology 2012;55(4):1154–63. https://doi.org/10.1002/hep.24789.
[84] Sun C, Wang X, Hui Y, Fukui H, Wang B, Miwa H. The potential role of REG family proteins in inflammatory and inflammation-associated diseases of the gastrointestinal tract. Int J Mol Sci 2021;22(13). https://doi.org/10.3390/ijms22137196.
[85] Shawcross DL, Wright GA, Stadlbauer V, Hodges SJ, Davies NA, Wheeler-Jones C, et al. Ammonia impairs neutrophil phagocytic function in liver disease. Hepatology 2008;48(4):1202–12. https://doi.org/10.1002/hep.22474.
[86] Fernández J, Acevedo J, Castro M, Garcia O, de Lope CR, Roca D, et al. Prevalence and risk factors of infections by multiresistant bacteria in cirrhosis: a prospective study. Hepatology 2012;55(5):1551–61. https://doi.org/10.1002/hep.25532.
[87] Taylor NJ, Manakkat Vijay GK, Abeles RD, Auzinger G, Bernal W, Ma Y, et al. The severity of circulating neutrophil dysfunction in patients with cirrhosis is associated with 90-day and 1-year mortality. Aliment Pharmacol Ther 2014;40(6):705–15. https://doi.org/10.1111/apt.12886.
[88] Gao M, Huang A, Sun Z, Sun Y, Chang B, Zhang JY, et al. Granulocytic myeloid-derived suppressor cell population increases with the severity of alcoholic liver disease. J Cell Mol Med 2019;23(3):2032–41. https://doi.org/10.1111/jcmm.14109.
[89] Markwick LJ, Riva A, Ryan JM, Cooksley H, Palma E, Tranah TH, et al. Blockade of PD1 and TIM3 restores innate and adaptive immunity in patients with acute alcoholic hepatitis. Gastroenterology 2015;148(3):590–602 e10. https://doi.org/10.1053/j.gastro.2014.11.041.
[90] Lebossé F, Gudd C, Tunc E, Singanayagam A, Nathwani R, Triantafyllou E, et al. CD8(+)T cells from patients with cirrhosis display a phenotype that may contribute to cirrhosis-associated immune dysfunction. EBioMedicine 2019;49:258–68. https://doi.org/10.1016/j.ebiom.2019.10.011.
[91] Riva A, Palma E, Devshi D, Corrigall D, Adams H, Heaton N, et al. Soluble TIM3 and its ligands galectin-9 and CEACAM1 are in disequilibrium during alcohol-related liver disease and promote impairment of anti-bacterial immunity. Front Physiol 2021;12:632502. https://doi.org/10.3389/fphys.2021.632502.
[92] Fadriquela A, Kim CS, Lee KJ, Kang SH, Lee JH. Characteristics of immune checkpoint regulators and potential role of soluble TIM-3 and LAG-3 in male patients with alcohol-associated liver disease. Alcohol 2022;98:9–17. https://doi.org/10.1016/j.alcohol.2021.10.002.
[93] Thomas HC, MacSween RN, White RG. Hyperglobulinaemia in liver disease. Lancet 1973;2(7820):104–5. https://doi.org/10.1016/s0140-6736(73)93308-4.
[94] Berger SR, Helms RA, Bull DM. Cirrhotic hyperglobulinemia: increased rates of immunoglobulin synthesis by circulating lymphoid cells. Dig Dis Sci 1979;24(10):741–5. https://doi.org/10.1007/bf01317205.
[95] Basho K, Zoldan K, Schultheiss M, Bettinger D, Globig AM, Bengsch B, et al. IL-2 contributes to cirrhosis-associated immune dysfunction by impairing follicular T helper cells in advanced cirrhosis. J Hepatol 2021;74(3):649–60. https://doi.org/10.1016/j.jhep.2020.10.012.
[96] Simbrunner B, Hartl L, Jachs M, Bauer DJM, Scheiner B, Hofer BS, et al. Dysregulated biomarkers of innate and adaptive immunity predict infections and disease progression in cirrhosis. JHEP Rep 2023;5(5):100712. https://doi.org/10.1016/j.jhepr.2023.100712.

[97] Crescioli S, Correa I, Karagiannis P, Davies AM, Sutton BJ, Nestle FO, et al. IgG4 characteristics and functions in cancer immunity. Curr Allergy Asthma Rep 2016;16(1):7. https://doi.org/10.1007/s11882-015-0580-7.
[98] Vandooren J, Itoh Y. Alpha-2-macroglobulin in inflammation, immunity and infections. Front Immunol 2021;12:803244. https://doi.org/10.3389/fimmu.2021.803244.
[99] Patel VC, Lee S, McPhail MJW, Da Silva K, Guilly S, Zamalloa A, et al. Rifaximin-α reduces gut-derived inflammation and mucin degradation in cirrhosis and encephalopathy: RIFSYS randomised controlled trial. J Hepatol 2022;76(2):332–42. https://doi.org/10.1016/j.jhep.2021.09.010.
[100] Bass NM, Mullen KD, Sanyal A, Poordad F, Neff G, Leevy CB, et al. Rifaximin treatment in hepatic encephalopathy. N Engl J Med 2010;362(12):1071–81. https://doi.org/10.1056/NEJMoa0907893.
[101] Moreau R, Elkrief L, Bureau C, Perarnau JM, Thevenot T, Saliba F, et al. Effects of long-term norfloxacin therapy in patients with advanced cirrhosis. Gastroenterology 2018;155(6):1816–27 e9. https://doi.org/10.1053/j.gastro.2018.08.026.
[102] Zapater P, Caño R, Llanos L, Ruiz-Alcaraz AJ, Pascual S, Barquero C, et al. Norfloxacin modulates the inflammatory response and directly affects neutrophils in patients with decompensated cirrhosis. Gastroenterology 2009;137(5):1669–79 e1. https://doi.org/10.1053/j.gastro.2009.07.058.
[103] Yang W, Guo G, Sun C. Therapeutic potential of rifaximin in liver diseases. Biomed Pharmacother 2024;178:117283. https://doi.org/10.1016/j.biopha.2024.117283.
[104] Reiberger T, Ferlitsch A, Payer BA, Mandorfer M, Heinisch BB, Hayden H, et al. Non-selective betablocker therapy decreases intestinal permeability and serum levels of LBP and IL-6 in patients with cirrhosis. J Hepatol 2013;58(5):911–21. https://doi.org/10.1016/j.jhep.2012.12.011.
[105] Abraldes JG, Villanueva C, Aracil C, Turnes J, Hernandez-Guerra M, Genesca J, et al. Addition of simvastatin to standard therapy for the prevention of variceal rebleeding does not reduce rebleeding but increases survival in patients with cirrhosis. Gastroenterology 2016;150(5):1160–70 e3. https://doi.org/10.1053/j.gastro.2016.01.004.
[106] Caraceni P, Abraldes JG, Ginès P, Newsome PN, Sarin SK. The search for disease-modifying agents in decompensated cirrhosis: From drug repurposing to drug discovery. J Hepatol 2021;75(Suppl 1):S118–34. https://doi.org/10.1016/j.jhep.2021.01.024.
[107] Pomier-Layrargues G, Huet PM, Richer G, Marleau D, Viallet A. Hyperglobulinemia in alcoholic cirrhosis. Relationship with portal hypertension and intrahepatic portal-systemic shunting as assessed by Kupffer cell uptake. Dig Dis Sci 1980;25(7):489–93. https://doi.org/10.1007/bf01315210.
[108] Chamroonkul N, Rujeerapaiboon N, Sripongpun P, Kaewdech A, Piratvisuth T. The efficacy of branched-chain amino acid granules to restore phagocytic activity in cirrhosis patients, a randomized controlled trial. Front Nutr 2023;10:1142206. https://doi.org/10.3389/fnut.2023.1142206.
[109] Powell JD, Pollizzi KN, Heikamp EB, Horton MR. Regulation of immune responses by mTOR. Annu Rev Immunol 2012;30:39–68. https://doi.org/10.1146/annurev-immunol-020711-075024.
[110] Nakamura I. Impairment of innate immune responses in cirrhotic patients and treatment by branched-chain amino acids. World J Gastroenterol 2014;20(23):7298–305. https://doi.org/10.3748/wjg.v20.i23.7298.
[111] Eguchi A, Iwasa M, Tamai Y, Tempaku M, Takamatsu S, Miyoshi E, et al. Branched-chain amino acids protect the liver from cirrhotic injury via suppression of activation of lipopolysaccharide-binding protein, toll-like receptor 4, and signal transducer and activator of transcription 3, as well as Enterococcus faecalis translocation. Nutrition 2021;86:111194. https://doi.org/10.1016/j.nut.2021.111194.
[112] Nakamura I, Ochiai K, Imai Y, Moriyasu F, Imawari M. Restoration of innate host defense responses by oral supplementation of branched-chain amino acids in decompensated cirrhotic patients. Hepatol Res 2007;37(12):1062–7. https://doi.org/10.1111/j.1872-034X.2007.00166.x.
[113] Gao B. Hepatoprotective and anti-inflammatory cytokines in alcoholic liver disease. J Gastroenterol Hepatol 2012;27(Suppl 2):89–93. https://doi.org/10.1111/j.1440-1746.2011.07003.x.
[114] Tilg H, Day CP. Management strategies in alcoholic liver disease. Nat Clin Pract Gastroenterol Hepatol 2007;4(1):24–34. https://doi.org/10.1038/ncpgasthep0683.
[115] He Y, Feng D, Li M, Gao Y, Ramirez T, Cao H, et al. Hepatic mitochondrial DNA/Toll-like receptor 9/MicroRNA-223 forms a negative feedback loop to limit neutrophil overactivation and acetaminophen hepatotoxicity in mice. Hepatology 2017;66(1):220–34. https://doi.org/10.1002/hep.29153.
[116] Ren R, He Y, Ding D, Cui A, Bao H, Ma J, et al. Aging exaggerates acute-on-chronic alcohol-induced liver injury in mice and humans by inhibiting neutrophilic sirtuin 1-C/EBPα-miRNA-223 axis. Hepatology 2022;75(3):646–60. https://doi.org/10.1002/hep.32152.