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The role of immune effector cell dysregulation in acute and chronic liver failure and its upstream mechanism of the gut–liver axis

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Abstract: *Acute-on-chronic liver failure (ACLF) is one of the most severe clinical syndromes in patients with chronic liver disease, particularly cirrhosis, and is associated with extremely high short-term mortality. Emerging evidence indicates that ACLF is not merely the terminal aggravation of decompensated cirrhosis, but an independent disease state driven by systemic inflammation, multi-organ dysfunction, and immune dysregulation. Disruption of gut–liver axis homeostasis is regarded as a key upstream mechanism: portal hypertension, gut microbiota dysbiosis, and intestinal barrier dysfunction promote bacterial translocation and the entry of pathogen-associated molecular patterns (PAMPs) into the portal circulation, which subsequently activate hepatic innate immune responses through Toll-like receptors (TLRs) and amplify systemic inflammation. At the same time, innate immune cells such as monocytes, macrophages, and neutrophils become persistently hyperactivated, whereas adaptive immune cells including T cells and natural killer (NK) cells gradually develop functional exhaustion and immunosuppression, resulting in a unique immunopathological state characterized by the coexistence of "hyperinflammation" and "immune paralysis." The Two-to-tango model provides a useful framework to explain the simultaneous occurrence of high infection rates, organ failure, and short-term mortality in ACLF. This review summarizes the evolution of the ACLF concept, gut–liver axis imbalance, amplification of systemic inflammation, and dysregulation of immune effector cells, and discusses potential therapeutic strategies based on gut–liver axis intervention and immune stratification, with the aim of providing insights for mechanistic research and precision treatment of ACLF.*

Keywords: *Acute-on-Chronic Liver Failure (ACLF); Gut–Liver Axis; Systemic Inflammation; Immune Effector Cells; Bacterial Translocation (BT); Two-to-Tango Model*

1. Introduction

Acute-on-chronic liver failure (ACLF) is one of the most severe clinical events in chronic liver disease, especially in patients with cirrhosis. Its main feature is the rapid onset of intrahepatic or extrahepatic organ failure on the basis of acute decompensation, accompanied by a significantly increased risk of short-term death. Previous studies have shown that ACLF is not simply the terminal exacerbation of decompensated cirrhosis, but a syndrome with an independent clinical phenotype, dynamic course, and high short-term mortality. It accounts for a certain proportion of hospitalized cirrhosis patients, and the disease often rapidly transmigrates within a short period [1]. Further research shows that ACLF and general acute decompensation differ significantly in clinical manifestations, disease severity, and prognosis, with core features being the occurrence of organ failure and a marked increase in short-term mortality risk.

For a long time, liver failure-related research has focused on hepatocellular injury, hepatic dysfunction, and portal hypertension-related complications. While this "liver-centered" framework helps explain the evolution of cirrhosis from compensated to decompensated, it is difficult to fully elucidate the complex links among inflammatory response intensity, immune abnormalities, and multiple organ failure in ACLF [2]. As research continues to deepen, systemic inflammation is gradually being recognized as the core pathological process driving the occurrence and progression of ACLF. Clinical studies show that inflammatory markers such as white blood cell count and C-reactive protein are not only closely related to disease severity but also positively correlated with short-term mortality

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risk [3].

On this basis, the gut–liver axis has gradually been proposed as an important upstream perspective for understanding the pathogenesis of ACLF. Related studies suggest that the interaction between gut bacterial translocation, innate immune abnormalities, and circulatory dysfunction forms an important bridge connecting local liver injury and uncontrolled systemic inflammation[4]. Based on these insights, this article will review the evolution of the ACLF concept, gut-liver axis imbalance, systemic inflammation amplification, and immune effector cell dysregulation, and further explore the implications of the Two-to-tango model for mechanistic research and therapeutic strategy transformation.

2. Evolution of the ACLF concept and a research perspective on the gut–liver axis

2.1 ACLF as an independent clinical syndrome

The concept of acute-on-chronic liver failure (ACLF) was proposed based on ongoing recognition of the heterogeneity of clinical outcomes in patients with acute decompensated cirrhosis. Traditional natural history of cirrhosis usually only distinguishes between compensated and decompensated periods, but as clinical research has deepened, scholars have gradually found that some patients can rapidly progress to intrahepatic or extrahepatic organ failure in a short period on top of acute decompensation, accompanied by a significantly increased risk of short-term death. This process can no longer be explained simply by "decompensated aggravation." Based on the CANONIC prospective multicenter study conducted by the European Alliance for the Study of Chronic Liver Failure (EASL-CLIF), Moreau et al. pointed out that among cirrhosis patients hospitalized due to acute decompensation, those with organ failure have significantly increased in-hospital mortality and short-term mortality risks, and should therefore be regarded as a new clinical syndrome [5]. Subsequently, further analysis by Arroyo, Moreau, Jalan, and Ginès found that ACLF patients not only had a higher 28-day mortality rate, but their risk of death also increased significantly with the number of organ failures, clarifying the clinical features of ACLF defined by acute decompensation, organ failure, and high short-term mortality [6].Compared to the relatively stable course of simple acute decompensation, ACLF is more prominently characterized by rapidly appearing multi-organ dysfunction against a background of systemic inflammation. The relevant review further emphasizes that the core of ACLF is not acute decompensation itself, but rather the unique disease severity represented by organ failure and high short-term mortality [8]. Epidemiological studies also support this understanding, with about one-third of hospitalized decompensated cirrhosis patients meeting ACLF criteria upon admission, and their 90-day mortality rate approaching 60%[7]. Therefore, ACLF should be regarded as an independent clinical syndrome occurring in the context of chronic liver disease, triggered by acute decompensation, characterized by systemic inflammation and multiple organ failure, and accompanied by high short-term mortality.

2.2 AD → ACLF Continuous Spectra and Definition Systems

Based on ACLF being identified as an independent clinical syndrome, researchers further recognize that acute decompensation (AD) and ACLF are not separate but should be understood as different stages within the same disease progression spectrum. AD typically presents as complications such as ascites, hepatic encephalopathy, gastrointestinal bleeding, or bacterial infections. Its occurrence marks the accelerated clinical progression of cirrhosis, but outcomes vary significantly among different patients: some maintain a relatively stable decompensated state, while others rapidly progress to ACLF under ongoing inflammatory stimulation and organ dysfunction, even reaching the pre-ACLFstage [9]. Within this continuum framework, ACLF is not an emergency independent of AD, but rather the clinical phenotype with the most severe illness and highest risk of short-term death among decompensated patients.

With this understanding, multiple ACLF diagnostic systems have been established, sharing the common goal of identifying patients in the high-risk stage of the AD-ACLF continuum spectrum and stratifying short-term prognosis. The European Chronic Liver Failure Research Consortium has proposed the CLIF-SOFA scoring system based on the CANONIC study, which grades ACLFs and predicts short-term mortality risk by assessing the functional status of organs such as liver, kidneys, brain, circulatory, respiratory, and blood coagulation. Dhiman et al. showed that ACLF patients identified by CLIF-SOFA had higher 28-day mortality rates, with the risk increasing with ACLF

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grading [10]. Meanwhile, APASL places greater emphasis on liver failure caused by acute liver injury, while EASL-CLIF and NACSELD pay more attention to extrahepatic organ failure and its relationship with short-term mortality [11]. The Kyoto Consensus further proposed that the definition of ACLF should comprehensively consider acute triggers, the degree of organ failure, and the risk of short-term death [12].

2.3 The gut-liver axis as an explanatory framework

Against the backdrop of ongoing research on chronic liver disease and its complications, the gut–liver axis has gradually been proposed as an important integrative framework for understanding the pathogenesis of ACLF. Arab, Martin-Mateos, and Shah pointed out that the gut epithelial barrier, gut microbiome, and hepatic immune system together form a key network maintaining host homeostasis. Gut microbes and their metabolites can enter the liver via the portal vein and are recognized by intrahepatic immune cells, thereby creating a dynamic balance between immune tolerance and inflammatory response[13]. Under normal conditions, the intestinal barrier restricts bacteria and their products from entering the portal vein circulation through the mucus layer, epithelial cells, and tightly connected structures; When microecological imbalance or barrier function is compromised, enterogenous substances can enter the liver in large quantities and induce immune activation. In the context of cirrhosis, portal hypertension is considered a key step in breaking this steady state. Simbrunner, Mandorfer, and Reiberger pointed out that portal hypertension can increase intestinal permeability and promote the entry of bacteria and their products into the portal vein system by altering intestinal microcirculation, affecting mucosal blood flow and barrier structure[14]. Trebicka, Reiberger, and Laleman further proposed that the interaction among portal hypertension, changes in gut microbiota, and barrier dysfunction sustainably activates the immune system and induces systemic inflammatory responses, forming an important mechanism linking intestinal abnormalities and multiple organ failure[15]. Meanwhile, integrative studies also show that pathogen-related molecules derived from the intestines can be recognized by liver immune cells through pattern recognition receptors, thereby activating inflammatory signaling pathways and amplifying immune responses[4]. Therefore, the gut-liver axis can be regarded as a key bridge connecting intestinal barrier damage, inflammatory signal input, and multi-organ dysfunction, providing a unified perspective for subsequent mechanistic analysis from the perspectives of intestinal microecological imbalance, bacterial translocation, and immune recognition.

3. Disruption of Enterohepatic Axis Homeostasis: The vulnerable basis of ACLF

3.1 Normal gut–liver axis and homeostasis maintenance

The homeostasis of the normal gut–liver axis depends on the dynamic balance network formed among the gut barrier, symbiotic microbiota, and host immune system. The gut is not only a digestive organ but also a highly complex ecosystem, with numerous symbiotic microorganisms colonizing the intestinal lumen over time, participating in nutritional metabolism, immune development, and inflammation regulation[16]. In this steady state, the intestinal mucosal barrier forms the first line of defense restricting intestinal microbes and their products from entering the portal vein circulation. It consists of tight junctions, epithelial cell layers, and mucus layers, as well as chemical barriers like antimicrobial peptides, lysozyme, and Reg3 family proteins, which spatially separate microbes from the host immune system and prevent excessive inflammatory activation[17]. Intestinal epithelial cells not only serve as mechanical barriers but also sense microbes and their metabolites, secreting cytokines, chemokines, and antimicrobial molecules, exerting bidirectional regulation between symbiotic bacteria and the host immune system[18]. Meanwhile, symbiotic bacteria enhance barrier integrity and suppress excessive inflammatory responses by competing for colonization sites, stimulating secretion of mucus and antimicrobial molecules, and producing metabolites such as short-chain fatty acids[19]. At the immune level, innate immune cells such as dendritic cells, macrophages, and monocytes in the gut lamina propria continuously interact with symbiotic bacteria, maintaining a balance between anti-infection defense and immune tolerance[20]. Therefore, the essence of a normal gut-liver axis is not the existence of a single structure, but rather the result of barrier integrity, microecological stability, and immune regulatory capacity maintained together.

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3.2 Vulnerable intestinal condition against the background of cirrhosis

As chronic liver disease progresses to cirrhosis, the homeostasis of the gut–liver axis is gradually disrupted, and the intestine shifts from a stable barrier state to a highly vulnerable pathological state. Existing studies indicate that portal hypertension is a key driver of this process. As intrahepatic vascular resistance increases and sinus structure abnormalities form, portal vein pressure continues to rise, not only promoting decompensation of cirrhosis but also altering intestinal barrier function by affecting mesenteric circulation and mucosal blood supply. Simbrunner et al. pointed out that portal hypertension can lead to intestinal microcirculation disorders, angiogenesis, and increased mucosal permeability, thereby weakening the intestinal epithelial barrier and promoting the entry of enteric substances into the portal venous system[14]. Nicoletti et al. further pointed out that mucosal hemodynamic abnormalities and local inflammatory responses caused by portal hypertension can lead to disordered tight junction protein expression and damage to epithelial cell structure, ultimately increasing intestinal permeability and making it easier for bacterial components, toxins, and metabolic products to cross the intestinal barrier[21]. Meanwhile, cirrhosis patients often experience excessive growth of gut microbiota and reduced local immune defenses. These changes further exacerbate intestinal barrier fragility and promote the transfer of bacteria and their products from the intestinal lumen to mesenteric lymph nodes and the portal vein system[22]. In addition to hemodynamic factors, metabolic inflammations such as lipotoxicity, oxidative stress, and inflammatory factor release further damage the intestinal barrier and amplify hepatic immune activation by promoting endotoxin entry vein circulation[23]. Engelmann et al.'s summary also indicates that portal hypertension, circulatory dysfunction, systemic inflammation, and metabolic abnormalities promote mutually promoting relationships, collectively driving the intestine from steady state to a highly permeable, highly responsive vulnerable state[24]. Therefore, intestinal injury in the context of cirrhosis is not caused by a single factor, but is the result of long-term accumulation of portal hypertension, barrier structure damage, microbiota imbalance, and metabolic inflammation. It is precisely on this basis that gut-derived stimulation can more easily break through local defenses and promote subsequent bacterial translocation and inflammation amplification.

4. Gut microecological imbalance and bacterial translocation: initiation of signals from intestinal inflammation

4.1 Gut microbiota imbalance

Gut microbiota homeostasis is a crucial foundation for maintaining the physiological balance of the gut-liver axis, with its core being the stability of microbial community structure, coordination of metabolic functions, and dynamic balance with the host immune system. As chronic liver disease progresses to the stage of cirrhosis, this homeostasis is gradually disrupted, resulting in dysbiosis characterized mainly by decreased microbiota diversity, remodeling of community structure, and an increase in potential pathogens. Chronic liver disease, alcohol consumption, dietary changes, and drug exposure can all disrupt this ecosystem, shifting the gut from a homeostasis maintenance microenvironment to one focused on inflammation promotion [25]. Trebicka et al., after integrating studies from NACSELD, CANONIC, and PREDICT, proposed that as the disease progresses from the compensated to decompensated phases, the diversity of gut microbes significantly decreases, often accompanied by excessive bacterial growth in the small intestine, slowed intestinal transport, and metabolic dysfunction; Meanwhile, potential pathogens such as Proteobacteria, Enterococcaceae, and Streptococcaceae increased, while important symbiotic bacteria maintaining intestinal homeostasis, such as Lachnospiraceae, Ruminococcaceae, and Roseburia, significantly decreased [26]. A systematic review by Liu et al. also showed that cirrhosis patients generally have a tendency to have a relative decrease in Bacteroidetes and increased Proteobacteria and Enterobacteriaceae [27]. The significance of these changes is not just about "strain changes," but more so that reducing butyric acid-producing symbiotic bacteria weakens short-chain fatty acid production and nutritional support for intestinal epithelium, while the expansion of pathogenic bacteria more easily promotes local inflammation and barrier dysfunction [25]. Therefore, imbalance of cirrhosis-related microbiota is essentially an overall shift in microecological structure, metabolite spectrum, and immune regulatory capacity, gradually transforming the intestine into a key source of persistent inflammatory stimulation.

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4.2 Leaky Gut and Bacterial Translocation

The integrity of the intestinal barrier is a crucial prerequisite for maintaining gut-liver axis homeostasis. However, during chronic liver disease and its decompensation stages, structural and functional damage to this barrier often occurs, manifesting as increased intestinal permeability, known as the "leaky gut"; On this basis, the process by which bacteria or their products cross the intestinal mucosa and enter mesenteric lymph nodes, portal veins, or even systemic circulation is called bacterial translocation (BT). Research shows that patients with chronic liver disease often experience decreased expression of tight junction proteins and increased intestinal epithelial permeability, making it easier for bacteria and their metabolites in the intestinal lumen to enter the portal vein circulation and reach the liver[22]. Chen and others further concluded that tightly junction proteins such as occludin, claudin, and ZO-1 are especially crucial for restricting bacterial access to by-cell pathways; When factors such as chronic inflammation, alcohol, lipid metabolism disorders, or portal hypertension are present, these structures become disrupted, making it easier for bacteria and their antigens to cross the mucosal barrier and enter the portal vein system[28]. From the perspective of ACLF mechanisms, BT is not merely a passive result of intestinal barrier disruption, but a key mediator for translating local barrier damage into persistent inflammatory input. Zhang et al. pointed out that in patients with cirrhosis or liver failure, when the intestinal mucosal immune barrier is damaged, lipopolysaccharides, lipophosphate (lipophosphate wallic acid), and bacterial DNA more easily enter mesenteric lymph nodes and portal vein systems, continuously delivering inflammatory stimulation to the liver[29]. Giannelli et al. also pointed out that gut leak and BT in cirrhosis patients are not only associated with complications such as hepatic encephalopathy and hepatorenal syndrome, but also closely linked to increased susceptibility to infection and systemic inflammation[30]. Therefore, leaky gut provides a pathway, and bacterial translocation forms a continuous source of stimulation; together, they form a key transition step in gut-liver axis imbalance from "barrier damage" to "inflammatory input."

4.3 PAMP/DAMP–TLR Immunorecognition

In the context of gut-liver axis imbalance, enterogenic microbes entering the portal vein circulation and their metabolites need to be recognized and converted into inflammatory signals by the host's innate immune system, with pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) serving as the core sources of stimulation for this process. PAMPs mainly include lipopolysaccharides, bacterial DNA, and peptidoglycans among microbial components, while DAMPs originate from endogenous risk signals released by damaged cells. These two molecules together drive the liver immune system from steady-state tolerance to inflammatory activation [31]. In this recognition process, Toll-like receptors (TLRs) are among the most important pattern recognition receptors. Among these, TLR4 is the most critical for LPS derived from Gram-negative bacteria; After LPS binds to TLR4, with the involvement of coordinators such as CD14, MD2, and lipopolysaccharide-binding proteins, it can activate MyD88-dependent or non-dependent signaling pathways, further initiating the NF-κB and MAPK cascade, and inducing the release of inflammatory factors such as TNF-α, IL-1β, and IL-6 [31]. Brandl and Schnabl also pointed out that when gut microbiota imbalance and barrier damage coexist, the opportunity for microbial products such as LPS and bacterial DNA to enter the portal venous system increases significantly, and can promote liver inflammation through signaling pathways like TLR4 and TLR9 [32]. Within the liver, Kupffer cells, hepatocytes, sinusoidal endothelial cells, and hepatic stellate cells can all express TLRs. Among them, Kupffer cells, after recognizing gut-derived PAMPs and DAMPs, rapidly released inflammatory mediators and recruited more inflammatory cells, while hepatic stellate cells, stimulated by TLR signaling, promoted extracellular matrix deposition, further linking inflammatory responses to fibrotic progression [31]. Giannelli et al.'s review further suggests that persistent bacterial translocation and microbial antigen import in cirrhosis patients exposes the liver to prolonged inflammatory stimulation and provides a mechanistic basis for subsequent systemic inflammation amplification [30].

5. From Enterogenous Inflammation to Systemic Inflammation: The Inflammatory Amplification Network of ACLF

5.1 Systemic Inflammation Hypothesis

Systemic inflammation is considered one of the core pathological mechanisms driving the

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development of acute decompensated cirrhosis and acute-chronic liver failure (ACLF). With the deepening understanding of the immunopathology of cirrhosis, more and more studies have found that persistent systemic inflammatory responses are not only important markers of disease progression but also key drivers of organ dysfunction and multiple organ failure. Dirchwolf and Ruf noted in their review that cirrhosis patients often exhibit a marked systemic inflammatory state. This inflammatory response, together with immune dysfunction, forms the "cirrhosis-associated immune dysfunction syndrome," characterized by coexistence of excessive inflammatory response and immunodeficiency, which dynamically evolves with disease progression[33]. Multiple clinical studies have also shown that in patients with decompensated cirrhosis and ACLF, inflammatory markers such as white blood cell count, C-reactive protein, and procalcitonin are significantly elevated, and are closely related to disease severity and short-term prognosis.

Based on this background, Arroyo, Angeli, Moreau, and Jalan proposed the "systemic inflammation hypothesis," suggesting that systemic inflammation is a common driving mechanism linking acute decompensation with multiple organ failure. This view builds on large prospective cohort studies such as CANONIC and PREDICT, which show that patients in the acute decompensated phase often already have significant inflammatory activation, manifested as elevated levels of inflammatory factors like IL-6 and TNF-α and immune cell activation, while ACLF patients exhibit a higher inflammatory burden [34]. Laleman et al. also pointed out that the intensity of inflammatory responses is positively correlated with ACLF severity, with white blood cell counts and CRP levels increasing as ACLF grades rise, suggesting that inflammatory imbalance is not merely a comorbid phenomenon but an important factor determining organ failure and short-term mortality risk [3].

From the perspective of inflammation, imbalance in gut microbiota and bacterial translocation cause lipopolysaccharides and other PAMPs to continuously enter the circulatory system, while DAMPs released by necrotic hepatocytes can jointly activate immune cells, creating sustained inflammatory stimulation [34]. Once these signals are recognized by pattern recognition receptors, they can induce activation of pathways such as NF-κB, promote the release of inflammatory factors, and further trigger vasodilation, circulatory dysfunction, metabolic reprogramming, and immune-mediated tissue damage. Research by Martínez-Esparza and others also confirmed that inflammatory mediators such as TNF-α, IL-1β, and IL-6 are continuously elevated in cirrhosis patients. These molecules not only participate in local liver inflammation but also act on distant organs via the circulatory system [35]. Therefore, the significance of the systemic inflammation hypothesis lies in its integration of enteric stimulation, host damage signals, immune activation, and organ failure within the same explanatory framework, making ACLF more likely to be understood as a systemic syndrome driven by uncontrolled inflammation.

5.2 Inflammatory–Circulatory–Metabolic–Organ Failure Network

During the development of ACLF, systemic inflammation does not exist in isolation but interacts with circulatory dysfunction, metabolic reprogramming, and multi-organ dysfunction, forming a continuously amplified pathophysiological network. Engelmann et al. pointed out that portal hypertension, circulatory dysfunction, systemic inflammation, and metabolic abnormalities are not independent but reinforce each other during disease progression, jointly driving disease progression[24]. Within this network, systemic inflammation is a key initial driving force. Clària, Arroyo, and Moreau proposed that inflammatory mediators such as cytokines and lipid mediators can induce large amounts of nitric oxide in visceral arteries, leading to significant vasodilation and hyperdynamic circulation, which further reduce peripheral vascular resistance, decrease effective arterial volume, and insufficient organ perfusion[36]. At the same time, inflammatory responses can promote neutrophil migration into tissues and release reactive oxygen species and proteases, causing vascular endothelial damage and microcirculation disorders; Microthrombosis and decreased local perfusion further weaken tissue oxygen supply, making organs such as the kidneys, brain, and circulatory system more prone to functional decompensation.

Clinical studies also support this view. Prospective studies by Solé et al. showed that multiple inflammatory mediators in ACLF patients were significantly elevated and closely related to leukocyte migration and monocyte chemotactic pathways, suggesting that inflammatory responses not only reflect disease severity but also directly participate in organ injuryprocesses [37]. In addition to circulatory disorders, inflammation accelerates organ failure through metabolic pathways. Clària et al. pointed out that inflammatory responses are essentially highly energy-consuming processes. When immune cells are activated, they require large amounts of glucose, fatty acids, and amino acids, which prioritizes the body's limited energy resources for redistribution to the immune system, while other

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organs face relative energy deficiencies[36]. Against this backdrop, mitochondrial dysfunction, decreased oxidative phosphorylation, and insufficient ATP production can cause peripheral organs to enter a low-energy state, making the already fragile kidney, brain, and circulatory systems more prone to failure.

Cycle anomalies in turn will worsen this energy crisis. Premkumar and Anand pointed out that portal hypertension triggers systemic hemodynamic abnormalities by activating the renin-angiotensin-aldosterone system and the sympathetic nervous system, which can reduce renal perfusion and trigger hepatorenal syndrome, as well as worsen brain metabolic disorders[38]. Romero-Gómez and others further pointed out that hyperammonemia and systemic inflammation have a synergistic effect at the nervous system level, jointly exacerbating brain dysfunction and increasing the risk of death[39]. Therefore, in ACLF, inflammation, circulation, and metabolism are not just several parallel pathological events, but a continuous process that drives and amplifies each other: inflammation triggers hemodynamic abnormalities and microcirculation disorders, circulatory disorders worsen tissue hypoxia and metabolic imbalance, and metabolic crises weaken organs' ability to maintain function, ultimately forming a vicious cycle of organ failure. This network model not only helps explain the systemic characteristics of multi-organ dysfunction in ACLF but also suggests that future intervention strategies should not be limited to single inflammatory suppression but should also focus on circulatory support and immune metabolic remodeling.

6. Immune effector cell dysregulation and its therapeutic targeting: Two-to-tango model

6.1 Overactivation of innate immunity

In the immunopathological processes of acute decompensated cirrhosis and acute-chronic liver failure (ACLF), overactivation of the innate immune system is considered an important mechanism driving systemic inflammatory responses and organ damage. Current research shows that signaling molecules released by enterogenic microbial products and tissue damage enter the circulation and rapidly activate innate immune cells such as monocytes, macrophages, and neutrophils, enabling them to release inflammatory mediators, chemokines, and oxidative molecules to form sustained inflammatory amplification responses[40]. Among them, monocytes and macrophages occupy the core positions. Triantafyllou and others pointed out that Kupffer cells and macrophages differentiated from bone marrow-derived monocytes are important effector cells mediating hepatic inflammatory responses; When DAMPs and PAMPs are recognized by pattern recognition receptors on their surfaces, they can rapidly activate inflammatory pathways such as NF-κB, induce the release of inflammatory factors like TNF-α and IL-1β, and further recruit circulating monocytes into the liver, resulting in sustained amplification of local and systemic inflammation[41]. Macrophage polarization imbalance further enhances pro-inflammatory effects; pro-inflammatory macrophages can produce large amounts of TNF-α, IL-6, and other inflammatory mediators, thereby worsening hepatocyte damage[42]. Meanwhile, neutrophils, as important inflammatory amplification cells, are also significantly activated in ACLF. Casulleras et al. pointed out that ACLF patients exhibit significant leukocyte activation and neutrophil recruitment. Neutrophils release reactive oxygen species, proteases, and inflammatory lipid mediators, directly damaging vascular endothelium and the tissue microenvironment, and forming a positive feedback inflammatory amplification loop[43]. Clinical studies also support this view. Satsangi et al. found that ACLF patients had significantly elevated plasma inflammatory factors, accompanied by abnormal monocyte HLA-DR expression and neutrophil dysfunction, suggesting that the innate immune system is in a highly active yet dysfunctional state during disease progression[44]. Therefore, the key significance of overactivation of innate immunity lies in its ability to rapidly convert gut-derived stimuli and host damage signals into systemic inflammation and multi-organ dysfunction.

6.2 Immunosuppression and Immune Paralysis

Alongside innate immune overactivation is the progressively worsening immunosuppression and immune paralysis in ACLF. The concept of "cirrhosis-associated immune dysfunction syndrome" (CAIDS), proposed in recent years, is precisely used to describe this abnormal state where "high inflammatory load" and "low immune efficacy" coexist. Hasa, Hartmann, and Schnabl pointed out that as cirrhosis progresses from the compensated phase to the decompensated stage and even ACLF, inflammatory factors continue to rise in patients, accompanied by decreased function-effector of immune cells. This long-term inflammatory stimulus can gradually shift the immune system from overreactive to functional exhaustion [45]. Clinical studies show that monocyte HLA-DR expression in

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ACLF patients is significantly reduced, while neutrophil oxidative burst capacity is abnormally enhanced, suggesting that although the body is in an inflammatory activation state, antigen presentation and effective immune response capacity are significantly impaired [44]. HLA-DR downregulation is considered an important marker of the ACLF immunosuppressive phenotype. Sipeki, Antal-Szalmas, and Papp further pointed out that patients with cirrhosis may also exhibit widespread immune abnormalities during disease progression, including decreased neutrophil phagocytosis and bactericidal functions, weakened monocyte chemotactic ability, reduced natural killer cell activity, and decreased T cell number and proliferation capacity [46]. This immune hyporeactivity is not a simple substitute for inflammation, but rather a functional imbalance formed against a background of ongoing inflammation. As pro-inflammatory factors increase, anti-inflammatory factors such as IL-10 also increase, indicating that the body has activated compensatory immunosuppressive mechanisms; The result, however, is a decline in anti-infection defense, making patients more susceptible to bacterial and fungal infections, which in turn further exacerbate systemic inflammation and organ dysfunction [45].

6.3 Two-to-tango Model

Immunological research at ACLF has gradually shown that this syndrome is not driven by a single inflammatory response or a single state of immunosuppression, but rather by a complex immune imbalance where both coexist and interact. The recently proposed "Two-to-tango" model is precisely used to explain the pathological mechanisms by which systemic inflammatory responses and immune paralysis coexist in ACLF. This model emphasizes that during disease onset and progression, excessive inflammation and immunosuppression are not two interchangeable stages, but rather two intertwined, dynamically coexisting immune processes that together shape the unique immunopathological state of ACLF[47]. Mechanistically, PAMPs and DAMPs continuously entering the portal vein and systemic circulation continuously activate monocytes, macrophages, and neutrophils, inducing the release of inflammatory factors such as TNF-α, IL-6, and IL-1β; On the other hand, long-term inflammatory stimulation can trigger compensatory anti-inflammatory responses, manifested as monocyte HLA-DR downregulation, MERTK upregulation, and immunosuppressive myelinoid cell expansion, thereby gradually promoting immune tolerance and functional exhaustion[47]. Clinical studies also support this understanding. Rueschenbaum et al. found that as the disease progresses, the numbers of T cells, B cells, and NK cells gradually decrease, T cells' ability to produce IFN-γ and TNF-α weakens, while Torque teno virus replication levels increase, indicating a continued decline in immune surveillance function. Tyc et al. also pointed out that the immunopathology of ACLF essentially manifests as a dual disorder characterized by systemic inflammation and immunosuppression: the former drives tissue damage and organ failure, while the latter increases susceptibility to infection and weakens pathogen clearing ability. The two are not linearly relational but mutually promote and jointly worsen clinical outcomes[48]. Therefore, the value of the Two-to-tango model lies not only in describing the "inflammatory and suppressive" immune phenomenon of ACLFs, but also in its ability to uniformly explain why high inflammatory burden, high infection rates, and high mortality coexist.

6.4 Treatment Strategies and Future Directions

At the treatment level of ACLF, current clinical management still focuses on trigger removal, organ support, and infection control, but as understanding of the "gut–hepatic axis–systemic inflammation–immune dysregulation" continuous pathological chain deepens, treatment approaches are gradually shifting from purely supportive treatment to mechanism-oriented intervention. Reviews have pointed out that there is still a lack of recognized specific treatments for liver failure. Clinical practice mainly relies on comprehensive medical treatment, artificial liver support systems, and liver transplantation. However, due to limitations such as donor sources, medical costs, and timing of application, the overall mortality rate remains high [49][50].

From the gut–liver axis perspective, weakening the input of gut-derived inflammation may be a promising upstream intervention pathway. Engelmann et al. found in ACLF animal models that recombinant alkaline phosphatase can significantly reduce liver function damage, cerebral edema, cytokine release, and hepatocyte death by reducing LPS bioactivity and attenuating TLR4-related signaling, suggesting that targeting the LPS-TLR4 axis may block the inflammatory amplification loop driven by intestinal stimulation [51]. Interventions centered on gut microecology also have theoretical appeal, restoring microbial homeostasis, regulating microbial metabolites, and improving intestinal barrier integrity, which may reduce liver vulnerability by reducing endotoxin load and inflammatory signal input [52].

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In terms of immune regulation, glucocorticoids remain one of the most discussed intervention methods. Ye, Li, and Zhang pointed out that glucocorticoids can theoretically alleviate overly strong inflammatory responses by inhibiting macrophage activation, reducing the release of inflammatory factors, and intervening in related signaling pathways[49]. However, its efficacy is unstable and highly dependent on etiology, timing of use, and the patient's immune status. Xue and Meng further pointed out that glucocorticoids are essentially a "double-edged sword": they may offer some benefits in the early stages dominated by inflammatory responses, while continued use during the stage when immune paralysis is already more pronounced may further increase the risk of infection[50]. Therefore, ACLF immunotherapy should not be limited to the binary judgment of "anti-inflammatory" but should be based on disease stage and immune classification.

Looking ahead, ACLF treatment should no longer be limited to passive organ support, but should gradually shift toward personalized interventions based on immune stratification. The key is not to find a single "universal drug," but to identify the dominant pathological state in the patient: whether the inflammatory storm is predominant, immune paralysis predominates, or both are intertwined. Research based on single-cell sequencing, transcriptomics, and metabolomics is helping to identify dynamic changes in different immune cell subpopulations and their key molecular targets, laying the foundation for more precise immunotherapy and gut–hepatic axis interventions in the future[47]. Therefore, ACLF's treatment strategy should be based on pathological mechanism stratification, organically combining gut-liver axis intervention, inflammation control, immune remodeling, and supportive care, promoting the shift of treatment models from "passive rescue" to "mechanism-oriented precision intervention."

7. Summary and Outlook

Acute-on-chronic liver failure (ACLF) is not simply a terminal exacerbation of decompensated cirrhosis, but rather an independent clinical syndrome characterized by systemic inflammatory responses, multiple organ failure, and high short-term mortality [1][53][54]. Based on existing research, it can be concluded that the occurrence and development of ACLF result from disruption of the gut-liver axis homeostasis, continuous input of gut-derived inflammatory signals, amplification of systemic inflammation, and immune dysfunction [4]. Among them, the Two-to-tango model effectively explains the clinical features of high inflammatory burden, increased infection susceptibility, and high mortality in ACLF patients. Future research should further focus on the dynamic changes in immune cell functional remodeling at different disease stages, combining multi-omics techniques, single-cell sequencing, and clinical stratification tools to identify key molecules and immune phenotypes; At the same time, intervention research targeting the gut-liver axis, inflammatory pathways, and immune remodeling should be strengthened, promoting ACLF treatment from traditional supportive care to mechanism-oriented and precisely stratified intervention.

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