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Review Article

Metabolic Dysregulation and Metabolite Imbalances in Acute-on-chronic Liver Failure: Impact on Immune Status

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Abstract

Liver failure encompasses a range of severe clinical syndromes resulting from the deterioration of liver function, triggered by factors both within and outside the liver. While the definition of acute-on-chronic liver failure (ACLF) may vary by region, it is universally recognized for its association with multiorgan failure, a robust inflammatory response, and high short-term mortality rates. Recent advances in metabolomics have provided insights into energy metabolism and metabolite alterations specific to ACLF. Additionally, immunometabolism is increasingly acknowledged as a pivotal mechanism in regulating immune cell functions. Therefore, understanding the energy metabolism pathways involved in ACLF and investigating how metabolite imbalances affect immune cell functionality are crucial for developing effective treatment strategies for ACLF. This review methodically examined the immune and metabolic states of ACLF patients and elucidated how alterations in metabolites impact immune functions, offering novel perspectives for immune regulation and therapeutic management of liver failure.

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Introduction

Liver failure, characterized by the rapid deterioration of liver function, is triggered by internal or external stimuli, occurring with or without underlying chronic liver disease.[1] This condition can be classified into acute liver failure (ALF), acute-on-chronic liver failure (ACLF), and acute exacerbation of decompensated cirrhosis. Specifically, ACLF and acute exacerbation of decompensated cirrhosis are key clinical manifestations observed in patients experiencing acute decompensation with a background of chronic liver disease, and their definitions exhibit some overlap.[2] The European Association for the Study of the Liver—Chronic Liver Failure Consortium defines ACLF as a severe form of acute decompensated cirrhosis[3,4] and utilizes the Chronic Liver Failure Consortium Organ Failure scoring system to detect organ failure. This system categorizes patients into non-ACLF and ACLF grades of 1, 2, and 3 based on the type and number of organ failures.[5] Despite regional differences in defining ACLF, particularly regarding the baseline population and types of organ failure, there is broad consensus that multiorgan failure and a high 28-day mortality rate are definitive clinical features of ACLF (Table 1).[3–9]

Additionally, the pathophysiology of ACLF remains under extensive investigation, with systemic inflammatory responses likely playing a critical role in its development.[10] Bacterial infections and acute alcoholic hepatitis are major triggers of systemic inflammation in patients with ACLF.[11,12] Severe hemorrhage can also induce ischemic hepatitis, leading to cell necrosis and the release of proinflammatory mediators.[13] Moreover, patients with HBV-related ACLF experience systemic inflammatory responses and immune dysfunction.[14] Some studies have shown that patients with ACLF display more marked and persistent systemic inflammatory responses—including elevated white blood cell counts and increased levels of C-reactive protein and chemokines—than non-ACLF patients.[4,15,16] The significant increase in the diversity and levels of circulating cytokines among ACLF patients indicates the presence of a "cytokine storm," a condition of intensified inflammatory response.[10] Immunologists believe that this inflammatory response is an immune mechanism aimed at eliminating pathogens or harmful agents.[17] To support the high energy requirements of this inflammatory process, there are substantial metabolic changes in how the body processes nutrients.[18] Recent metabolomic studies of blood and liver samples from ACLF patients have confirmed these findings.[19] Notably, the simultaneous presence of immunodeficiency and systemic inflammation is a crucial factor that impedes pathogen clearance (particularly from the gastrointestinal tract) and perpetuates tissue and organ deterioration.[20–22] The altered metabolic activities of immune cells not only fulfill the increased energy needs of these activated cells but also contribute to the synthesis of essential immune effector molecules, facilitating crucial immune functions—this process is known as immunometabolism.[23,24] Moreover, certain metabolites, such as lactate and lysophosphatidylcholine, can remodel the microenvironment and function as signaling molecules to alter immune cell functions, resulting in immune dysregulation.[25,26] Consequently, exploring changes in energy metabolism during liver failure and examining alterations in circulating metabolites may offer new

Keywords: Acute-on-chronic liver failure; Immunometabolism; Metabolism; Metabolic reprogramming; Metabolomics; Microenvironment.

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Table 1. Characteristics of definitions of ACLF by four different consortia

Characteristics	APASL[7]	EASL-CLIF[3–5]	NACSELD[8]	COSSH[9]
Patient group	Patients with previously diagnosed or undiagnosed chronic liver disease or cirrhosis, excluding those with decompensated cirrhosis	Patients with acute decompensated cirrhosis, regardless of previous decompensation episodes	In patients with infection-related acute decompensated cirrhosis, regardless of whether there has been a previous decompensation episode	In patients with HBV-related liver disease, regardless of the presence or absence of cirrhosis
Triggering factors	Intrahepatic acute injury (sepsis is considered a complication of ACLF rather than a cause)	Intrahepatic or extrahepatic injury factors	Extrahapatic (infectious) injury factors	Intrahepatic or extrahepatic injury factors
Basis of the definition	Liver failure: jaundice, serum bilirubin ≥5 mg/dL (85 μmol/L) Coagulation dysfunction: INR ≥1.5 or prothrombin activity <40% HE may occur	The definition relies on six major organ systems: liver, kidney, brain, coagulation, circulatory, and respiratory	The definition relies on four major organ systems: the brain, kidneys, circulation, and respiration	The definition requires reliance on six major organ systems: liver, kidney, brain, coagulation, circulation, and respiration
ACLF scoring system	Scoring is based on five variables: serum bilirubin, INR, serum lactate, serum creatinine, and HE, with scores of 5–7 indicating Grade I, 8–10 indicating Grade II, and 11-15 indicating Grade III. These correspond to groups with potential for recovery, groups requiring special monitoring, and groups needing immediate intervention to improve outcomes, respectively	Patients with acute cirrhosis are stratified based on the type and number of organ failures: 1. Acute decompensated cirrhosis without ACLF; 2. Grade 1 ACLF patients: A, patients with single renal failure; B, patients with single liver, coagulation, circulatory, or lung failure related to creatinine, with creatinine concentrations ranging from 1.5 mg/dL to 1.9 mg/dL, or with grade 1 or 2 hepatic encephalopathy, or both; C, patients with single brain failure and creatinine levels between 1.5 and 1.9 mg/dL; 3. Grade 2 ACLF patients: patients with failure of two organ systems; 4. Grade 3 ACLF patients: patients with three or more organ systems failure	Cirrhosis patients with two or more organ failures are defined as ACLF	1. Grade 1 ACLF: Patients with isolated renal failure: Patients with a single episode of liver failure with an INR not exceeding 1.5 and/or renal insufficiency and/or Grade I or II hepatic encephalopathy (HE); Patients with a single type of coagulation, circulatory, or respiratory system organ failure and/or renal dysfunction and/or Grade I or II HE; Patients with isolated brain dysfunction plus renal impairment. 2. Grade 2 ACLF: Patients with failure of two organ systems. 3. Grade 2 ACLF: Patients with failure of two organ systems
Comments	Based on the definition of chronic liver disease patients, not limited to those with cirrhosis, but excluding patients with decompensated cirrhosis. This methodology offers an early detection advantage, highlighting the reversible characteristics of ACLF, suggesting that timely intervention could significantly impact the disease trajectory. While the approach is sensitive in predicting early mortality, it does exhibit a lack of specificity	The definition is based on patients with acute decompensated cirrhosis and incorporates organ failure into the diagnostic criteria, which may lead to a later diagnosis and lack the potential for reversibility. Compared to the NACSELD score, this definition and scoring system have a higher sensitivity in predicting 90-day mortality and could potentially be used to prioritize patients for liver transplantation	The definition is based on patients with acute decompensated cirrhosis and incorporates organ failure into the criteria, potentially leading to a later diagnosis time and lacking characteristics that may be reversible. Compared to the EASL-CLIF score, this definition and scoring have a higher specificity for predicting mortality within seven days and may be used to exclude patients for transplantation	The definition is based on patients with chronic liver disease, not limited to those with cirrhosis, and excludes patients with decompensated cirrhosis. It has the advantage of early detection, demonstrating the reversible characteristics of ACLF. Early intervention may alter the course of the disease

ACLF, acute-on-chronic liver failure; APASL, Asian Pacific Association for the Study of the Liver; EASL-CLIF, European Association for the Study of the Liver - Chronic Liver Failure; NACSELD, North American Consortium for the Study of End-stage Liver Disease; COSSH, Chinese Group on the Study of Severe Hepatitis B; HE, hepatic encephalopathy; INR, international normalized ratio.

avenues for modulating immune functions and improving the management of liver failure.

Immune cells in ACLF

Patients with ACLF demonstrate significant alterations in immune cell populations, including an increase in white blood cells (predominantly monocytes) and a decrease in lymphocytes and NK cells.[27] An increase in neutrophils and a decrease in lymphocytes are key characteristics of ACLF. These fluctuations in white blood cell counts are central to the Chronic Liver Failure Consortium ACLF scoring system, which assesses the prognosis and mortality risk of ACLF, with changes correlating directly with disease severity.[2] Severe inflammation combined with immune paralysis is a critical pathological hallmark of ACLF. Alterations in immune cell functions are major contributors to the development and adverse outcomes associated with ACLF.[28]

Neutrophils

Neutrophils, essential components of the circulating immune cells in ACLF patients, show both increased numbers and functional impairments.[21,28] Microarray analysis has revealed that the transcription levels of genes encoding neutrophil granules are specifically increased, along with genes crucial for glycolysis, which activate neutrophils.[27] Additionally, these cells exhibit high expression of CD177, enhancing their adhesion to endothelial cells and significantly increasing their migratory capacity toward tissues. This tendency is exacerbated by endothelial dysfunction and excessive inflammatory damage in ACLF, promoting further neutrophil migration into tissues and worsening tissue damage.[29] Despite the increased number and infiltration of neutrophils, many studies highlight significant deficiencies in these cells, including markedly low expression of Toll-like receptors 2 and 4, and flaws in the phagocytic and oxidative burst functions necessary for bacterial recognition, ingestion, and destruction.[30] Consequently, the ability of neutrophils to eliminate pathogens and damaged cells is severely compromised, leading to adverse outcomes. Furthermore, while neutrophils demonstrate significant deficits in essential clearance functions, their ability to form neutrophil extracellular traps (NETs) is increased, particularly in patients with poor prognoses, further contributing to tissue damage and disease progression.[30]

Monocytes/Macrophages

The liver, one of the organs with the highest density of monocytes/macrophages, contains 20–40% of hepatocytes.[31] These monocytes/macrophages express pattern recognition receptors that identify pathogen-associated molecular patterns and damage-associated molecular patterns, secrete cytokines, and engage in immune responses.[20] Notably, these cells exhibit remarkable plasticity, differentiating into various types after injury to adopt either proinflammatory or reparative roles.[32] Similar to neutrophils, they produce reactive oxygen species with antimicrobial properties.[33] As ACLF progresses, the proportion of monocytes gradually increases, while the proportions of lymphocytes and NK cells decrease. Transcriptomic analysis of monocytes from alcohol-related ACLF patients has revealed upregulation of immunosuppressive markers and impairment in antimicrobial and antigen presentation processes. In HBV-related ACLF patients, an increase in the expression of genes associated with innate immunity and a marked downregulation of genes related to adaptive immune responses (T cells, B cells, and NK cells) were observed. Despite the increased proportion of monocytes, the anti-inflammatory cytokine IL-10 is upregulated. Flow cytometric analysis of monocyte phenotypes in HBV-ACLF patients has revealed an increased frequency of circulating monocytic $CD14^+CD15^+HLA\text{-}DR^-$ myeloid-derived suppressor cells (hereinafter referred to as M-MDSCs), which impair antigen presentation by monocytes and hinder T-cell activation and response. Moreover, M-MDSCs lead to impaired secretion of inflammatory cytokines and bacterial phagocytosis in response to various Toll-like receptor ligands. The expression of scavenger, costimulatory, and phagocytic receptors (e.g., MERTK, CD64, and CD86) is reduced. In ACLF patients, increased expression of CD163 on circulating macrophages promotes shedding, leading to elevated levels of soluble CD163, which is associated with poor prognosis and increased susceptibility to infection.[34–37] Kupffer cells (KCs) are liver-resident macrophages that initiate liver inflammation. They secrete chemokines to recruit circulating neutrophils and monocyte-derived macrophages to the liver, thereby promoting inflammation while also releasing anti-inflammatory cytokines to mitigate excessive hepatic inflammatory responses.[38] In diseased livers, the number of KCs typically decreases, but this can be compensated for by the infiltration of monocyte-derived macrophages, some of which can differentiate into Kupffer-like cells.[39] A metabolomics analysis in HBV-ACLF patients revealed depletion of liver-resident KCs, which are replaced by immunosuppressive monocytes/macrophages, consistent with the immunosuppressive characteristics observed in these patients.[40] Consequently, targeting the immune characteristics of monocytes/macrophages with therapeutic interventions to reverse and enhance their functions could be a crucial strategy for improving the prognosis of ACLF patients.

Other immune cells

In addition to neutrophils and monocytes, which are pivotal in innate immunity, other immune cells such as dendritic cells (DCs), lymphocytes, and NK cells also play crucial roles in the immune response and inflammation in ACLF, though they are less studied. Transcriptional analysis of ACLF patients has revealed the upregulation of genes associated with DCs.[27] Similarly, studies have noted an accumulation of DCs within the liver and a depletion of circulating DCs in ACLF patients.[41,42] Despite these accumulations and genetic upregulations, liver DCs lack mature surface markers such as human leukocyte antigen-DR, CD86, and CD54. They respond poorly to classical activation molecules such as IL-4 and IFN-γ, leading to functional deficiencies.[43–45] Suboptimal maturation and insufficient cytokine secretion by DCs impact the maturation and distribution of T-cell subsets, diminishing the secretion of proinflammatory cytokines. This reduction in DC functionality can increase susceptibility to infections, where severe infections can trigger overactivation of immune functions, resulting in immune exhaustion and further disease progression.

A reduction in lymphocytes is a defining feature of the circulatory changes observed in ACLF, contributing to an immunosuppressive environment. Prospective studies have indicated that reductions in lymphocytes and NK cells occur early in the development of cirrhosis, along with the induction of costimulatory factors and immune checkpoint inhibitors, suggesting that immune damage may be a factor in ACLF onset.[46] Additionally, ACLF is characterized by an immune imbalance between Th17 and Treg cells, characterized by an asynchronous increase in Th17 cells and a decrease in Treg cells. A lower Treg/Th17 ratio is correlated with a poorer prognosis.[47] Targeting immune therapy to reverse these im-

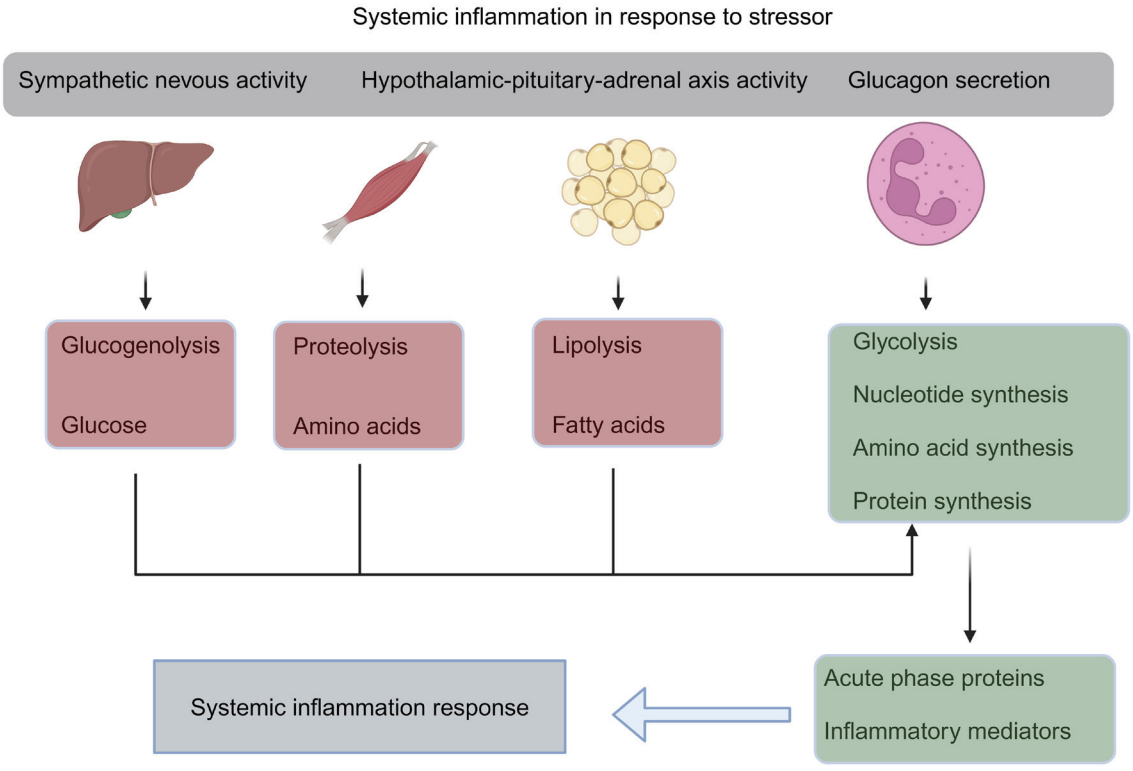

Fig. 1. Major changes in energy metabolism levels in ACLF (acute-on-chronic liver failure) include: (1) High levels of inflammation activate the body's neurohumoral response axis, regulating the catabolic metabolism of peripheral organ systems (such as the liver, muscle, and adipose tissue) to provide sufficient energy for immune cells; (2) Immune cells undergo metabolic reprogramming with increased levels of glycolysis, focusing primarily on anabolic metabolism to produce adequate nucleotides and proteins. These are used to secrete cytokines, acute-phase proteins, and chemokines, which further enhance the inflammatory response and assist in pathogen clearance.

mune dysfunctions can effectively improve ACLF outcomes, making it a critical focus for ACLF immune therapy.[48,49]

Metabolism in ACLF

Patients with liver failure undergo metabolic reprogramming across various functional cells to adapt to the body's intense inflammatory response. In immune cells, this inflammatory response drives metabolic reprogramming, predominantly shifting toward anabolic metabolism to accommodate their elevated energy demands. This shift facilitates the production and secretion of essential inflammatory cytokines and chemokines,[50] which aligns with the observed accumulation of nucleotide synthesis-related metabolites in the blood. Conversely, in nonimmune cells, the inflammatory response reallocates energy resources through neurohumoral adjustments, prioritizing catabolic metabolism to sustain the energy needs required for supporting immune cell functions (Fig. 1).[51]

Metabolic reprogramming in immune cells

Metabolic research on peripheral blood mononuclear cells has revealed that in patients with ACLF, mitochondrial oxidative phosphorylation (OXPHOS) is markedly suppressed. The primary site of glucose metabolism shifts from the mitochondria to the cytoplasm, favoring energy generation via extramitochondrial pathways. This shift is characterized by increased activity in glycolysis, the pentose phosphate pathway (PPP), and glycogenolysis, indicating a metabolic realignment from energy production to biosynthesis (Fig. 2).[52] Notably, the activated PPP[34] not only supplies abundant substrates for nucleotide synthesis, which are crucial for immune cell activation and balancing glucose metabolism, but also enhances the production of proinflammatory cytokines, contributing to a systemic inflammatory response.[53] Furthermore, NADPH, a major source of reactive oxygen species, triggers oxidative stress responses and partially inhibits mitochondrial OXPHOS.[54] NADPH also provides substrates for NOX enzymes, facilitating the release of NETs, which may be linked to the high levels of NETs observed in ACLF, further intensifying inflammation and organ damage.[30,55] Furthermore, impaired cellular mitochondrial function significantly contributes to the reduction in mitochondrial OXPHOS. Most studies indicate that mitochondrial dysfunction begins during the decompensated stage of cirrhosis and becomes more severe during the ACLF stage.[56] However, mitochondrial dysfunction is not a complete "shutdown" but rather involves selective damage within the tricarboxylic acid (TCA) cycle.[57] Mitochondrial function tests have shown that peripheral blood mononuclear cells and neutrophils in ACLF patients share a common breakpoint in the upper part of the TCA cycle, from citrate to succinate. This breakpoint may lead to the accumulation of upstream intermediates, such as cis-aconitate, which can be converted into itaconate with immunoregulatory functions.[58] Itaconate, upregulated during immune activation, has strong immunosuppressive properties and can exert anti-inflammatory and immunosuppressive effects by regulating transcription factors and affecting protein levels and metabolic enzyme activities.[59–61] The immunosuppressive effect of itaconate may contribute to recurrent infections and poor prog-

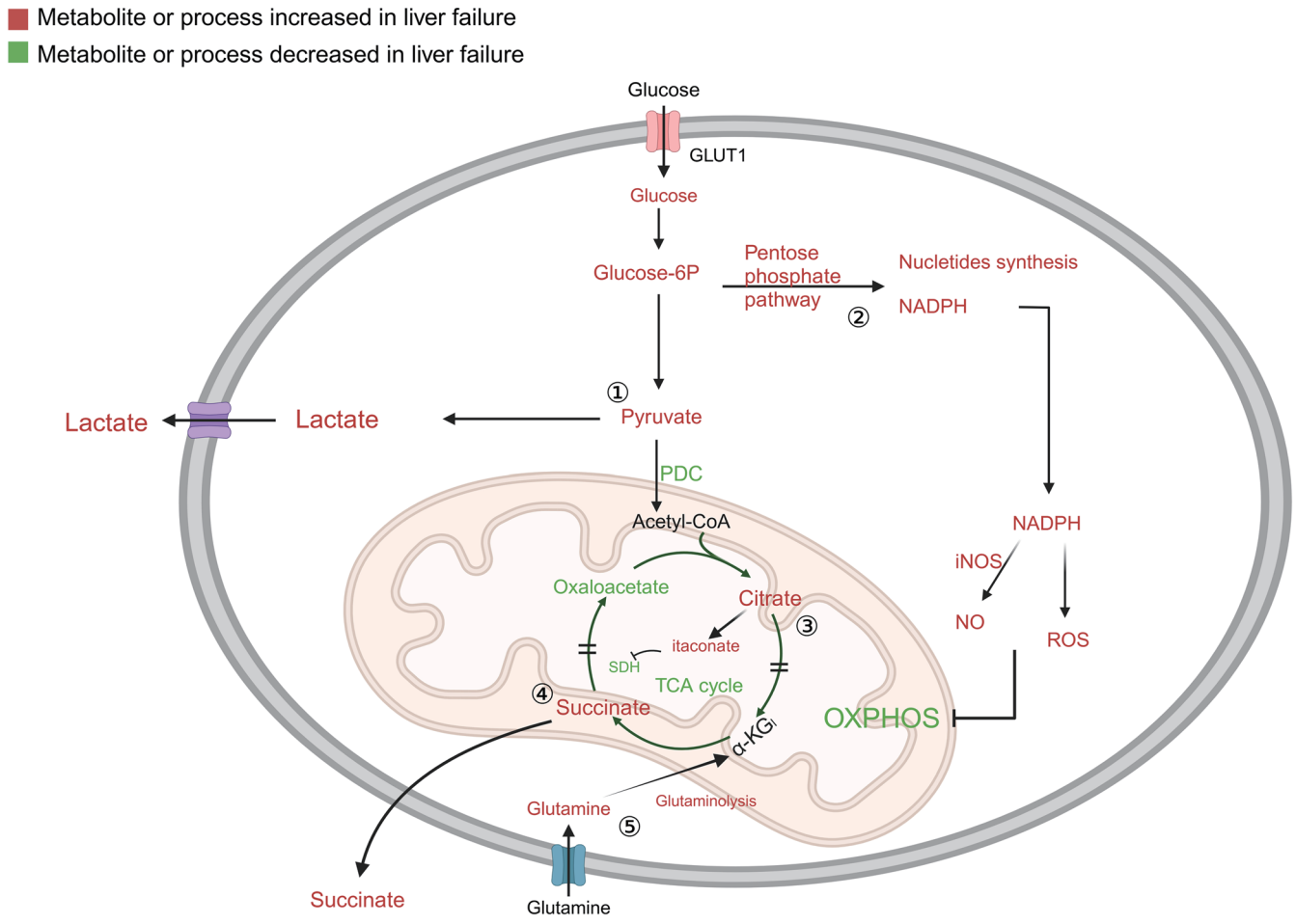

Fig. 2. Alterations in glucose metabolism and key metabolites during liver ACLF (acute-on-chronic liver failure) in immune cells. ① The glycolysis pathway is strengthened in the early stages, with increased concentrations of lactate and pyruvate both intracellularly and in serum; ② During liver failure, the rate of the pentose phosphate pathway accelerates, leading to increased nucleotide biosynthesis and NADPH (nicotinamide adenine dinucleotide phosphate) production, which promotes subsequent pathways; ③ Mitochondrial are inhibited to varying degrees, disrupting the TCA (citric acid) cycle and causing the accumulation of citrate and itaconate; ④ The accumulation of itaconate can inhibit succinate dehydrogenase (SDH), triggering a secondary breakpoint in the TCA cycle and promoting disturbances in mitochondrial pathways; ⑤ The replenishment pathway of glutamine is increased. ROS, reactive oxygen species; NO, nitric oxide; iNOS, inducible nitric oxide synthase

nosis in ACLF patients.

In addition to shifts in carbohydrate metabolism, amino acid metabolism in ACLF patients tends toward anabolic processes. An analysis of blood metabolite data from the CANONIC study revealed coordinated activation of aerobic glycolysis, the PPP, and one-carbon metabolism (Fig. 3), which is essential for the synthesis and salvage of purines and the synthesis of pyrimidines—crucial for managing the severe inflammatory response in patients and associated with adverse outcomes.[62] The activation and accumulation of the methionine cycle in ACLF suggest increased nucleotide synthesis. Moreover, the connection between methionine and the trans-sulfuration pathway via homocysteine plays a role in maintaining cellular redox balance, with the activated trans-sulfuration pathway in the blood indicating ongoing antioxidative processes. Transcriptional analysis of peripheral blood mononuclear cells from HBV-ACLF patients revealed significant disruptions predominantly in the PPAR and mTOR pathways, indicating substantial lipid metabolic dysregulation during liver failure.[14] Further metabolic profiling revealed impaired mitochondrial β-oxidation[63] and a shift in fatty acid metabolism toward synthetic pathways.

Intense peripheral catabolic metabolism

Patients with ACLF undergo metabolic alterations driven by the central nervous system. The heightened inflammatory state associated with ACLF activates the hypothalamic-pituitary-adrenal axis, leading to the secretion of hormones that promote extensive catabolic metabolism. This process predominantly involves glycogenolysis, proteolysis, and lipolysis, which release nutrients crucial for supporting the energy-intensive activation of the innate immune response.[64,65] Elevated levels of 4-hydroxy-3-methoxyphenylglycol sulfate in the blood of ACLF patients—an indicator of increased sympathetic nervous activity—support these metabolic shifts.[66] Furthermore, the increase in circulating amino acids mainly results from muscle protein breakdown, contributing to the frequent occurrence of muscle wasting in ACLF patients.[67] High levels of acylcarnitines and unsaturated fatty acids in the circulation reflect substantial peripheral lipolysis, providing essential nutrients for the high-energy demands of immune organs.[68] These findings also indicate a reduction in mitochondrial β-oxidation and overall mitochondrial dysfunction in liver failure.[52] The inability to metabolize fatty acids through β-oxidation, coupled with systemic inflammation-

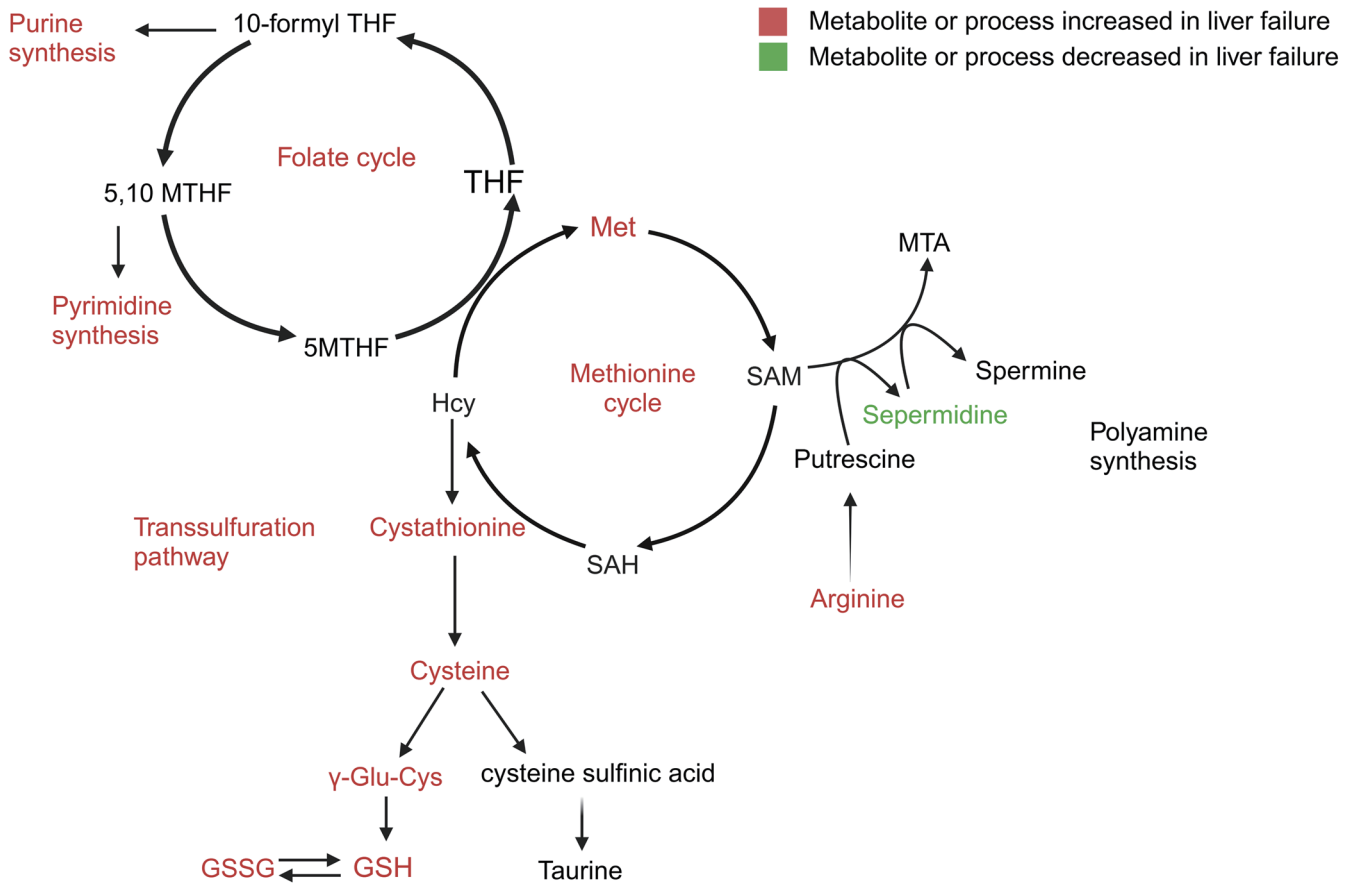

Fig. 3. Alterations in amino acid metabolism during ACLF (acute-on-chronic liver failure). THF, tetrahydrofolate; 5MTHF, 5-methyltetrahydrofolate; 10-formyl THF, 10-formyltetrahydrofolate; Met, methionine; SAM, S-adenosylmethionine; SAH, S-adenosyl-L-homocysteine; Hcy, homocysteine; MTA, 5′-deoxy-5′-(methylthio) adenosine.

induced reactive oxygen species, further leads to mitochondrial damage, exacerbating the progression of failure in peripheral organs.

Metabolites influence immune cell function

The redistribution of nutrients is a critical metabolic change driven by inflammatory responses, designed to provide the body with sufficient energy to eliminate pathogens. However, this adaptive mechanism also depletes peripheral tissues of vital energy sources, potentially leading to damage and failure in peripheral organs. A study demonstrated that peripheral blood mononuclear cells from healthy individuals, when cultured in ACLF plasma, exhibited an immunosuppressive phenotype.[40] This highlights the significant impact of the circulating microenvironment on immune function and disease progression. Thus, intense peripheral catabolic metabolism, coupled with the metabolic reprogramming of immune cells, creates a metabolic microenvironment that may contribute to immune paralysis and adverse outcomes in ACLF patients. Table 2 compiles relevant metabolomic data on ACLF metabolic markers and discusses several critical metabolites in detail.[56,66,69–75]

Lactate

Previous studies have shown that hyperlactatemia is a common feature of liver failure, with an elevated lactate-to-albumin ratio serving as a predictive biomarker for in-hospital mortality in ACLF patients.[76,77] The accumulation of lactate in the blood reflects a shift in metabolic programming, where pyruvate from glucose breakdown is preferentially converted to lactate, facilitating rapid energy production. Although lactate has traditionally been considered a mere byproduct of glucose metabolism, it is now recognized for its multiple regulatory functions, particularly in immune modulation.[78–80] In tumor immunology, a high lactate environment reshapes immune function to create an immunosuppressive microenvironment that supports cancer cell proliferation.[81] High lactate concentrations can inhibit the key glycolytic enzyme PFK-1, leading to its degradation into a less active dimer form, thereby diminishing glycolytic flux in monocytes and impacting their immune functions and differentiation. During acute inflammation, lactate promotes the transition of macrophages from a proinflammatory to an anti-inflammatory phenotype.[82,83] In sepsis, accumulated lactate inhibits inflammatory pathways in hypertrophied cells through MCT1, reduces inflammatory cytokine production, decreases glycolysis, and decreases ATP production, contributing to the transition from the inflammatory phase to secondary immune suppression.[84] Conversely, in chronic inflammation, accumulated lactate enhances immune cell infiltration in inflamed areas, prolonging inflammation and activating macrophages with a fibrotic phenotype.[85–88] ATP production from glycolysis through lactate is crucial for maintaining neutrophil

Table 2. Biomarkers (bold) from liver failure and their main biological characteristics

Study	Diagnosis or prediction	Study population	Research sample	Research Methods	Biomarkers	Biomarker characteristics and functions
Thomas, 2017[72]	Diagnosis	Prospective study based on patients with cirrhosis (Patients hospitalized at the Medical University Vienna)	serum	HPLC	Total serum **bile acid** levels are associated with AD and ACLF, and can serve as an additional marker for risk stratification of new onset AD and ACLF in patients with cirrhosis	**Bile acids**: proinflammatory action
Clària, 2019[69]	prediction	Prospective study (patients included in the CANONIC study)	serum	LC-MS	Higher **KP activity** can independently predict the mortality of patients with AD and ACLF	**Tryptophan:** antioxidant action; **KYN**: pro-oxidant action; **AA**: anti-inflammatory action; **Canine urine acid** (likely a mistranslation, possibly should be uric acid or another compound): anti-inflammatory action, immunosuppressive action
Clària, 2021[70]	Diagnosis	Cohort study based on patients with acute decompensated cirrhosis (patients included in the CANONIC study)	serum	LC-MS	**Sphingomyelin** serves as a metabolic fingerprint for decompensated cirrhosis; **cholesteryl esters and LPC** form unique metabolic markers for ACLF	**Sphingolipid**: Sphingolipids and their derivatives have immunomodulatory functions, promoting the differentiation of immune cells. Their reduced levels may be associated with immunosuppression. **Cholesteryl ester**: Reduced levels are associated with impaired liver function, renal failure, refractory shock, and high mortality. **LPC**: Possesses immunomodulatory properties, identified as a group of pro-inflammatory lipids capable of activating immune responses and enhancing immune cell function. The reduction in levels in ACLF may also be related to impaired immune function
Cristina, 2020[73]	Diagnosis	119 patients with ACLF (patients included in the CANONIC study)	plasma	LC-MS	**LTE_4** and **12-HHT** can serve as biomarkers for ACLF patients; **LTE_4** levels can differentiate grade 3 ACLF from grade 1 and 2 ACLF, and are positively correlated with markers of inflammation and non-apoptotic cell death; **LTE_4** and **LXA_5** are associated with short-term mortality	These biomarkers all originate from bioactive **lipid mediators** produced by unsaturated fatty acids, involved in immunomodulation. The accumulation of unsaturated fatty acids and their derivatives is associated with the formation of immunosuppression
Jasmohan, 2020[74]	prediction	602 patients in NACSELD consortium sites	serum	LC-MS	**Microbial metabolism**-related products (such as bile acids, aromatic amino acid metabolites, xenobiotics, and choline metabolism) as well as **lipid metabolism** products are associated with the occurrence of ACLF and 30-day mortality rate	**Bile acids**: pro-inflammatory action. **Aromatic amino acid metabolites**: Indole and its various derivatives play an important role in maintaining intestinal barrier and immune homeostasis and have anti-inflammatory effects. Choline metabolites: **Common metabolic** products such as methylamine and TMAO maintain gut microbiota diversity, protect liver function, and are markers of liver health. On the other hand, TMAO also has pro-inflammatory functions

(continued)

Table 2. *(continued)*

Study	Diagnosis or prediction	Study population	Research sample	Research Methods	Biomarkers	Biomarker characteristics and functions
Richard, 2020[56]	Diagnosis	650 AD patients; 181 ACLF patients; 43 compensated cirrhosis patients; 29 healthy controls (patients included in the CANONIC study)	serum	LC-MS	Including **acylcarnitine, the pentose phosphate pathway**, **lactate**, and other 38 metabolites are associated with ACLF and related to systemic inflammation, but not related to the type of organ failure	**Acylcarnitine**: The accumulation in ACLF is associated with mitochondrial dysfunction, which further damages mitochondria, causes systemic inflammation, and is related to peripheral organ failure
Yan Zhang, 2023[75]	Diagnosis and prediction	367 ACLF and 657 non-ACLF (The patients were enrolled in the prospective 14-center CATCH-LIFE studies)	plasma	LC-MS	Identified and validated an ACLF prognosis model composed of **pipecolate**, **NAAG**, and **ureidopropionate**. Identified and validated a pre-ACLF diagnostic model composed of **pipecolate** and **γ-CEHC**	**Pipecolate**: Associated with the severity of liver damage. **NAAG**: Can hydrolyze to produce glutamate, related to the grading of hepatic encephalopathy. **Ureidopropionate**: An increase in levels is associated with psychomotor retardation; it is also a strong indicator related to mortality in cirrhosis. **γ-CEHC**: A metabolite of vitamin E, can act as an antioxidant
Jiangshan Lian, 2016[71]	Diagnosis	76 ACLF, 56 chronic liver failure (CLF), 20 healthy controls (in the First Affiliated Hospital of Zhejiang University School of Medicine)	serum	UPLC-MS	Identified that bile acids, **LPC, PC**, and **acylcarnitine** can serve as biomarkers to distinguish ACLF from the healthy group and the CLF group	**PC**: A major component of cell membrane phospholipids, it can maintain cell membrane integrity; it can also act as a signaling molecule involved in cell proliferation. When cleaved into **LPC** (Lysophosphatidylcholine) by phospholipase A2, it can enhance immune cell function and participate in immunomodulation
Emmanuel, 2023[66]	prediction	Based on data from the CANONIC and PREDICT cohort study	serum	LC-MS	Identified **4-hydroxy-3-methoxyphenylglycol sulfate**, **hexanoylcarnitine**, and **galacturonic acid** as key biomarkers associated with mortality, and incorporated them with common clinical indicators to construct a prognostic model	**4-hydroxy-3-methoxyphenylglycol sulfate**: a terminal metabolite of norepinephrine, involved in immunoregulation and inflammatory responses. **Hexanoylcarnitine**: An intermediate product of fatty acid metabolism, an important indicator of mitochondrial dysfunction. **Galacturonic acid**: A metabolite of sugar, has immunomodulatory functions, and plays a pro-inflammatory role

HPLC, high performance liquid chromatography; LC-MS, liquid chromatography mass spectrometry; UPLC, ultra performance liquid chromatography; AD, acute decompensation; ACLF, acute-on-chronic liver failure; CLF, chronic liver failure; KP, kynurenine pathway; KYN, kynurenine; AA, Anthranilic acid; LPC, lysophosphatidylcholine; LTE4, leukotriene E4; 12-HHT, 12-hydroxyheptadecatrienoic acid; LXA5, Lipoxin A5; TMAO, trimethylamine N-oxide; NAAG, N-acetyl-aspartyl-glutamate; γ-CEHC, gamma-carboxyethyl hydroxychroman; PC, phosphatidylcholine.

function. Lactate has been reported to induce the expression of neutrophil mobilizers such as CXCL1 and CXCL2, and by increasing bone marrow vascular permeability, it drives neutrophil migration and enhances infiltration.[89] Additionally, accumulated lactate can trigger the formation of NETs, further damaging tissue functionality.[90] Overall, lactate accumulation plays diverse immune-modulatory roles in both acute and chronic inflammation, suppressing the proinflammatory phenotype and cytokine secretion of macrophages, promoting chronic inflammation, and damaging tissues and organs. The lactate-rich microenvironment may contribute to the high levels of inflammation and immune suppression observed in ACLF patients.

Recent research has revealed that lactylation of histones and nonhistone lysines is an innovative epigenetic modification stemming from lactate. Numerous studies have demonstrated that lactate accumulation, induced by conditions such as hypoxia, interferon-γ, lipopolysaccharide, or bacterial stimuli, can cause histone lysine lactylation at gene promoters, directly regulating gene expression.[91] P300 is a well-known histone acetyltransferase, and subsequent studies have identified p300 and its homolog CBP as potential writers of histone lactylation.[92,93] In models of pulmonary fibrosis, lactate within macrophages induces histone lactylation at the promoters of profibrotic genes, thereby promoting their expression and contributing to the progression of pulmonary fibrosis.[94] Moreover, studies have shown that histone lactylation can influence macrophage phenotype transformation, leading to increased expression of Arg1 and other wound-healing-related genes, thereby promoting a shift to an immunosuppressive M2 macrophage phenotype and facilitating immune suppression.[95]

Elevated circulating lactate and histone lactylation have been shown to regulate immune cell functions and cytokine secretion during the onset and progression of inflammation. High lactate levels in circulation may be linked to immune dysfunction in ACLF patients. Importantly, lactate accumulation correlates with poor prognosis in ACLF patients, and when combined with NK cell frequency, it can predict survival rates in ALF patients.[96] Consequently, research focusing on targeted lactate metabolism therapies offers promising prospects for improving ACLF outcomes. In cancer therapy research, combining lactate production with tumor immunotherapy has been shown to significantly enhance antitumor immunity and inhibit tumor growth.[97]

Tryptophan-kynurenine pathway (KP)

In a prospective study examining blood levels of tryptophan, kynurenine, kynurenic acid, and quinolinic acid in patients with ACLF, the activity of the KP was found to be significantly elevated, correlating with systemic inflammation. Additionally, KP activity levels were linked to the overall severity of cirrhosis, suggesting its involvement in the development and progression of ACLF. This pathway is also closely associated with the onset of renal inflammation and hepatic encephalopathy, making it a potential independent predictor of short-term mortality in ACLF patients.[62]

Tryptophan, an essential amino acid known for its potent antioxidant properties, is metabolized through the KP into a set of metabolites that serve various functions, including oxidation, antioxidation, neurotoxicity, neuroprotection, and immune modulation. This pathway can be activated by both acute and chronic immune responses and plays a role in the pathogenesis and progression of diverse diseases, including cancer, immune disorders, neurodegenerative diseases, and psychiatric conditions.[98,99] The occurrence of neurotoxicity and hepatic encephalopathy in ACLF may be related to KP activation. Importantly, the KP also participates in body-wide immune regulation. Kynurenine and kynurenic acid modulate immune responses by interacting with the aryl hydrocarbon receptor and the G protein-coupled receptor GPR35 in immune cells. Moreover, the activation of indoleamine 2,3-dioxygenase, a crucial enzyme in the KP, acts as an effective immunosuppressive signal, increasing the release of IL-10.[100] Recent findings indicate that ACLF patients not initially admitted for infections are particularly vulnerable to hospital-acquired infections, underscoring a prevalent state of immune suppression. Research has shown that ACLF patients who develop hospital infections exhibit higher baseline KP activity levels compared to those without infections, suggesting that the KP contributes to an immunosuppressive environment. This, in turn, plays a role in the systemic inflammation and organ failure observed in ACLF patients.[69]

Lysophosphatidylcholine (LPC)

LPC is a lipid with notable immunomodulatory properties.[101] It is produced through the cleavage of phosphatidylcholine (PC) by phospholipase A2 or via the action of lecithin-cholesterol acyltransferase, which transfers fatty acids to free cholesterol, resulting in saturated LPC. Additionally, in the presence of acetyl-CoA, LPC can be converted back into PC by lysophosphatidylcholine acyltransferase, thereby replenishing the body's PC stores.[102] LPC can also be converted by autotaxin into biologically active lysophosphatidic acid, which similarly influences immune function.[103] Excessive LPC, particularly when enriched with oxidized low-density lipoprotein, is associated with the onset of atherosclerosis, inflammatory diseases, and diabetes.[104]

A nontargeted lipidomics study has shown that LPC levels decline systematically in cirrhosis patients as disease severity increases, suggesting its potential as a prognostic biomarker for patient survival.[70,71] Previous studies have demonstrated that circulating LPC induces immune cell chemotaxis and enhances immune responses.[105] Notably, LPC facilitates the expression of TGF-β and Foxp3 in regulatory T cells through the G2A-JNK pathway, thereby enhancing their immunoregulatory capabilities.[106] LPC also amplifies the activity of activated $CD8^+$ T cells and supports memory T-cell populations, enhancing secondary immune responses.[107]

In addition to its effects on T cells, LPC enhances macrophage chemotaxis and phagocytic activity, and stimulates the production of proinflammatory factors.[108] Therefore, the observed systemic decrease in circulating LPC during the progression of ACLF may be closely associated with the immunosuppressive state characteristic of liver failure. Given the reduced LPC levels in other liver diseases, such as cirrhosis and hepatocellular carcinoma, investigating the role of LPC and its metabolites in the pathogenesis and progression of ACLF is critically important.

Ketone bodies

Ketone bodies are short-chain fatty acids produced by the liver when glucose availability is limited. They result from the oxidation of fatty acids and ketogenic amino acids and include β-hydroxybutyrate, acetoacetate, and acetone. These compounds are crucial for maintaining energy homeostasis within the body. In ACLF, peripheral organs undergo intense catabolic metabolism due to a heightened inflammatory state. This leads to insufficient nutrient supply and significantly reduced energy utilization.[65] Consequently, alternative nonglucose energy sources become crucial for sustaining peripheral tissue function.

In ACLF, there is a notable accumulation of free fatty acids and acylcarnitines in the blood, indicating impaired mi-

tochondrial fatty acid β-oxidation and ATP synthesis. This highlights a deficiency in fatty acid ketogenic metabolism.[52] Additionally, increased catabolism of ketogenic amino acids such as phenylalanine, tyrosine, tryptophan, and lysine leads to a buildup of their metabolic byproducts in the blood without a corresponding rise in ketone body levels.[62] These findings suggest a significant inhibition and dysfunction in the amino acid-to-ketone body conversion pathway in ACLF, depriving peripheral tissues of a critical energy source and contributing to organ failure.

Ketone bodies are increasingly recognized not only as alternative metabolic fuels during glucose scarcity but also as signaling molecules. They exhibit anti-inflammatory effects, inhibit histone deacetylases, suppress NF-κB, and regulate immune functions.[109] Similar to succinate and lactate, ketone bodies play dual roles in immune cells as both metabolic substrates and signaling molecules, crucial for regulating macrophage and T-cell functions.[110,111] For example, β-hydroxybutyrate directly increases cytokine production and cytolytic activity in $CD8^+$ T cells. Ketone bodies also enhance T-cell functions by promoting oxidative phosphorylation or ketolysis, thus providing immune protection. Furthermore, conditional removal of ketolysis in macrophages has been shown to increase liver fibrosis in mice fed a high-fat diet. Therefore, ketone bodies are vital for maintaining immune functions, and deficiencies in their production may be linked to the immunosuppressive state observed in ACLF patients. Increasing ketone body levels through exogenous supplementation or stimulating ketogenic mechanisms could be viable therapeutic strategies for managing ACLF.

Current status of research on targeted metabolic regulation

Currently, there is no specific treatment for ACLF; management primarily focuses on supportive care, addressing precipitating factors, preventing complications, and providing organ support, including liver transplantation. Given the key pathophysiological features of ACLF—namely, systemic inflammatory response and immune dysfunction—emerging therapeutic approaches are actively being explored.

Immunotherapy

Immunotherapy represents a revolutionary breakthrough in tumor treatment, and abnormal immune cell function, along with the aberrant secretion of cytokines, plays an increasingly important role in the pathogenesis of liver failure. Consequently, research on improving liver failure by regulating immune function has intensified. One notable area of interest is the regulation of immune cell function through mesenchymal stem cells (MSCs) to promote liver regeneration and mitigate liver disease injury.[112] MSCs are multipotent stem cells capable of regenerating and differentiating into various cell types, including hepatocytes, and they possess immunomodulatory properties.[113] Exogenous MSCs have also been utilized in clinical trials for cirrhosis, with reported effectiveness in most completed clinical trials.[114] However, clinical trials are still ongoing, and further research is needed to establish the clinical application of MSC therapy for treating ACLF.

Additionally, granulocyte colony-stimulating factor (G-CSF) is an important approach for targeting persistent inflammation and immune cell depletion. G-CSF can stimulate the proliferation and differentiation of neutrophil progenitor cells, potentially improving immune system function in ACLF.[115] However, the results of clinical trials involving G-CSF have been inconsistent. In patients with HBV-related ACLF, G-CSF treatment improved liver function and three-month survival rates.[116] Conversely, another prospective, open-label phase II study indicated that G-CSF did not improve liver function scores or reduce the incidence of infections.[117] Therefore, further trials are necessary to validate the clinical application of G-CSF.

Targeted metabolic therapy

Other methods for modulating immune cell function still need exploration. The use of metabolic modulators as adjuvants in immunotherapy has shown great promise in tumor therapy, potentially playing a synergistic role in the immunotherapeutic process.[118]

As previously described, elevated lactate levels are a common characteristic of liver failure and can also serve as a predictive marker for in-hospital mortality in ACLF patients. Treatments targeting lactate have been extensively explored in cancer therapy. Additionally, a study has shown that blocking lactate levels with lactate inhibitors can act as an immunomodulator and improve the prognosis of COVID-19 patients.[119] Targeting lactate synthesis, transport, and related signaling pathways, such as the mTOR pathway, to regulate lactate levels in the microenvironment holds promise as an important approach for treating and mitigating the progression of ACLF.

The gut microbiota plays a significant role in liver cirrhosis, ACLF, and related complications. Increased gut permeability, the release of metabolic products (such as short-chain fatty acids), and endotoxins can all act as triggers for the progression to ACLF.[120] Omics analyses have revealed that the gut microbiota in cirrhotic patients differs from that of healthy controls.[121] Fecal microbiota transplantation from healthy donors, aimed at alleviating gut dysbiosis and immune dysfunction, may be an important method to influence the course of liver disease, and this approach is currently undergoing clinical trials.[122,123] In addition to fecal microbiota transplantation, rifaximin, an orally administered, nonsystemic antibiotic, is currently used to prevent recurrent encephalopathy in cirrhotic patients. Previous studies suggest that rifaximin may influence the course of cirrhosis by modulating the gut microbiota and affecting the gut-liver axis.[124] Moreover, oral magnesium has been found to attenuate acetaminophen-induced ALF by modulating changes in gut microbial metabolism.[125]

Lipid mediators may also be significantly associated with the development of ACLF. Lipid-targeted modulators, used in therapeutic studies of inflammatory diseases, have been shown to modulate neutrophil recruitment and cytophagy, and can be protective against colitis.[126] Furthermore, LPC modulates immunoregulatory checkpoints in peripheral monocytes, regulates the monocyte phenotype *in vitro*, and influences immune cell function during the development of liver failure.[127]

Therefore, exploring metabolic modulators to safely and rationally regulate the microenvironment of ACLF metabolites is expected to improve immune cell function, enhance ACLF progression, and promote hepatic regenerative function.

Conclusions

Changes in immune metabolism can reprogram immune cell function, and similarly, changes in metabolite levels due to alterations in metabolism can also influence immune cell function. Just as with the tumor microenvironment, cytokines and metabolites can create a distinct metabolic microenvironment during the development of liver failure, continually affecting both the patient's immune system and organ state.

Studies have shown that culturing peripheral blood mononuclear cells from healthy individuals with the plasma of ACLF patients results in a phenotype and function similar to those of ACLF patients. Therefore, targeting the metabolic microenvironment of liver failure is an important strategy for improving patient immune function and alleviating symptoms. Metabolomic approaches offer strong evidence for changes in metabolic pathways and metabolites in liver failure. This review primarily discusses the impact of significant metabolite changes on immune function from the perspective of energy metabolism changes in liver failure, providing new directions for research in this area.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Data retrieval and collection (DZ, ZG), writing of the manuscript (DZ), generation of data tables and graphs (JG, YW), review and editing of the manuscript (CS), and obtaining and monitoring of funding (ZG). All authors have approved the final version and publication of the manuscript.

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