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Study on the Association Between Gut Microbiota Dysbiosis and the Risk of Alcoholic Hepatitis

Bingxin Wu, Liyan Bai*

School of Life Sciences, Yunnan University, Kunming, Yunnan, 650091, China

ABSTRACT
Based on alcohol-induced gut microbiota imbalance, this study analyzes its relationship with the risk of alcoholic hepatitis. It elucidates the role of microbial homeostasis in maintaining gut-liver axis function, detailing the processes of reduced microbiota diversity, increased barrier permeability, and amplified inflammatory signaling under alcoholic conditions. By examining changes in key bacterial genera and metabolites, the study explores their roles in lipid metabolism disorders and immune activation. Results indicate that dysbiosis promotes alcoholic hepatitis formation through coupled metabolic and inflammatory pathways, revealing its microbiome-mediated pathogenic mechanism.

KEYWORDS
Gut microbiota; Alcoholic hepatitis; Gut-liver axis; Metabolites; Inflammatory pathways

1 Introduction

Alcoholic hepatitis, representing the acute progression stage of alcoholic liver disease, involves multiple mechanisms including metabolic imbalance, oxidative stress, and immune dysregulation [1]. Recent years have seen growing attention on the role of the gut-liver axis in this disease. Evidence indicates that gut microbiota not only participates in detoxifying ethanol metabolites and energy conversion but also influences hepatic homeostasis by regulating intestinal barrier integrity and inflammatory signaling. Chronic alcohol exposure reshapes the microbial ecosystem, reducing short-chain fatty acid-producing bacteria while promoting overgrowth of opportunistic pathogens and endotoxin-producing bacteria. This increases intestinal mucosal permeability, allowing enteric metabolites and inflammatory signals to enter the liver via the portal vein system, triggering a cascade of lipid deposition and immune activation. Current research on alcoholic hepatitis predominantly focuses on hepatic metabolic mechanisms, while the inducing role of dysbiosis in disease initiation and its signaling pathways remain poorly understood [2-3]. This study adopts gut microbiota ecological shifts as its entry point, comprehensively examining how dysbiosis induces intestinal barrier disruption, metabolic pathway disturbance, and amplified inflammatory responses. It reveals the microbiological mechanisms underpinning the progression of alcoholic hepatitis from functional metabolic impairment to structural damage, aiming to provide theoretical support and a research framework for prevention and treatment strategies at the gut-liver axis level.

2 Physiological mechanisms of gut microbiota homeostasis

Gut microbiota homeostasis is the cornerstone for maintaining normal gut-liver axis function. Under healthy conditions, trillions of microorganisms in the gut regulate energy absorption and bile acid recycling by metabolizing short-chain fatty acids (SCFAs), thereby sustaining host energy balance and hepatic metabolic stability [4]. Microbiota metabolic activity can be expressed by the following equation:

$$M = \sum_{i=1}^{n} \left(C_i \cdot R_i \right) \tag{1}$$

Where:M represents overall metabolic activity,C_i denotes microbial abundance, andR_i indicates its metabolic rate [5].

Under microbial homeostasis, Firmicutes and Bacteroidetes maintain an optimal ratio. Metabolites like butyrate and propionate enhance energy supply to the intestinal epithelium and increase expression of tight junction proteins (ZO-1, Occludin, Claudin), forming a robust physical barrier. Concurrently, IgA and antimicrobial peptides (e.g., Reg3γ) constitute an immune defense against pathogenic adhesion and invasion [6]. Intestinal epithelial cells, immune cells, and microbial metabolites collectively construct a multilayered synergistic barrier, maintaining intestinal low permeability and immune tolerance (Figure 1). Disruption of this homeostasis directly leads to endotoxin entering the liver via the portal venous system, potentially initiating alcoholic hepatitis.

* **Corresponding Author:** Liyan Bai, bailiyan99@163.com

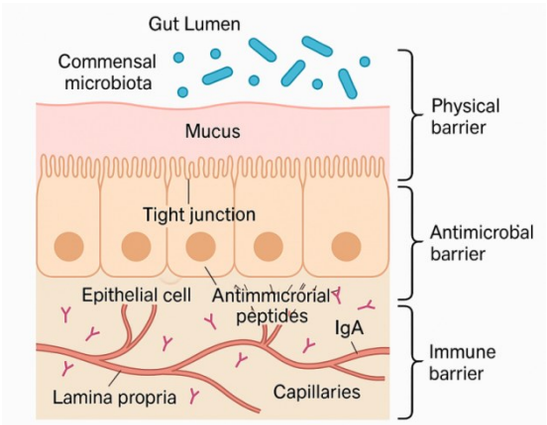

Figure 1 Schematic diagram of normal intestinal barrier structure

3 Microbial community structural changes under alcohol exposure

3.1 Trends in microbial abundance and diversity

Alcohol exerts persistent disruption on the intestinal ecosystem, most notably characterized by dual declines in microbial abundance and diversity [7] Chronic alcohol consumption induces niche contraction in the gut microbiota, characterized by a decrease in Firmicutes and a significant expansion of Bacteroidetes and Proteobacteria. This shifts the overall microbial profile from a "metabolic homeostasis type" to an "inflammation-prone type." This loss of diversity weakens complementary effects among microbes, reduces short-chain fatty acid (SCFA) -producing bacteria, and simultaneously diminishes the energy supply to the intestinal epithelium and its immune regulatory capacity [8]. Certain opportunistic pathogens, such as Streptococcus and Enterococcus, proliferate excessively in the intestinal lumen, secreting endotoxins and activating mucosal inflammatory responses, further compromising barrier function [9]. The transition from a diverse ecosystem to a monotonous community represents a key precursor mechanism for alcohol-related intestinal barrier vulnerability.

3.2 Intestinal barrier damage and increased permeability

Alcohol consumption disrupts the multi-layered defense structure of the intestinal barrier, causing a synergistic imbalance in physical, chemical, and immune barriers [10]. The expression of tight junction proteins ZO-1, Occludin, and Claudin-1 is significantly reduced by acetaldehyde and reactive oxygen species, while the thinning of the mucus layer exposes the intestinal epithelium directly to microbial metabolites and lipopolysaccharides (LPS). Increased permeability can be approximated by a transmembrane diffusion model:

$$P_t = K_p \cdot \frac{A_m}{d_m} \cdot (\Delta C) \tag{2}$$

Where:P_t represents intestinal permeability rate,K_p denotes permeability coefficient,A_m indicates effective epithelial area, d_m signifies barrier thickness, andΔC represents the concentration gradient across the lumen. At an ethanol concentration of 30 mmol/L,K_p increases from 0.12 cm/h to 0.34 cm/h, indicating an approximately 1.8-fold enhancement in barrier permeability [11]. Increased permeability allows LPS-acetyl-L-alanine adducts to enter the liver via the portal venous system, activating Kupffer cells to release TNF- α and IL-6, thereby amplifying inflammatory signaling. The decline in intestinal barrier integrity is not only a direct consequence of dysbiosis but also a critical physiological trigger for the onset of alcoholic hepatitis.

3.3 Characteristics of microbial composition shift

Alcohol exposure leads to profound alterations in the composition and functionality of gut microbiota, reflected in a reduction of ecological diversity and metabolic flexibility. The disturbance of microbial balance alters the relative distribution of dominant bacterial phyla, weakening the cooperative metabolic network that supports intestinal and hepatic homeostasis [12]. The decline of beneficial taxa within the Firmicutes group and the loss of butyrate-producing genera, such as Faecalibacterium prausnitzii and Roseburia, diminish the production of short-chain fatty acids, which are essential for epithelial energy metabolism and barrier maintenance. In contrast, an expansion of Proteobacteria and other facultative anaerobes introduces a microbial environment enriched in endotoxin-producing and inflammation-associated species.

The proliferation of opportunistic pathogens, including Streptococcus, Enterococcus, and Escherichia, disrupts redox balance within the intestinal lumen through the excessive release of acetaldehyde and lipopolysaccharides, which heighten oxidative stress and compromise mucosal integrity. These compositional shifts reprogram microbial metabolic

pathways from energy-yielding to pro-inflammatory states, transforming the gut ecosystem into an unstable, inflammation-prone environment. Such ecological remodeling not only impairs intestinal resilience but also facilitates the continuous translocation of microbial signals to the liver through the portal circulation, thereby linking dysbiosis to the initiation of hepatic inflammation and injury.

4 Liver Pathological responses induced by dysbiosis

4.1 Hepatocyte lipid accumulation and metabolic dysregulation

Gut microbiota dysbiosis profoundly alters hepatic energy metabolism by transmitting disordered metabolic signals through the portal circulation. The decline in short-chain fatty acid (SCFA) availability weakens mitochondrial β-oxidation and reduces acetyl-CoA utilization, disturbing the equilibrium between lipid synthesis and degradation [13]. Ethanol metabolism intensifies this imbalance by elevating the NADH/NAD^+ ratio, shifting hepatocellular redox homeostasis toward an anabolic state that favors triglyceride accumulation and lipid droplet formation. Simultaneously, the translocation of gut-derived lipopolysaccharides (LPS) and acetaldehyde adducts activates Kupffer cells and hepatic stellate cells, releasing inflammatory mediators that further suppress AMPK signaling and enhance SREBP-1c activity. As a result, lipid biosynthesis proceeds under sustained activation, leading to excessive storage of neutral lipids within hepatocytes. The expansion of lipid droplets provokes endoplasmic reticulum stress and promotes reactive oxygen species generation, initiating lipid peroxidation and mitochondrial dysfunction. These metabolic disturbances constitute a hallmark of early alcoholic liver injury, linking microbial dysbiosis to hepatic steatosis through the convergence of impaired oxidation, disrupted signaling, and inflammatory amplification. Collectively, the interaction between microbial metabolites, oxidative imbalance, and transcriptional regulation establishes a pathogenic feedback loop that underlies the transition from adaptive hepatic metabolism to progressive alcoholic hepatitis.

4.2 Inflammatory factors and immune activation characteristics

Gut microbiota dysbiosis initiates a cascade of hepatic immune activation through the translocation of lipopolysaccharides (LPS) and other bacterial products into the portal circulation. Upon reaching hepatic sinusoids, LPS engages Toll-like receptor 4 (TLR4) on Kupffer cells, triggering the rapid activation of downstream NF-κB and MAPK signaling pathways that orchestrate the release of pro-inflammatory cytokines [14]. These mediators amplify the hepatic inflammatory response, creating a complex network of interactions between resident macrophages, infiltrating neutrophils, and hepatic stellate cells. The sustained activation of these immune pathways disrupts hepatic redox homeostasis, leading to reactive oxygen and nitrogen species accumulation and mitochondrial dysfunction.

Within this inflammatory microenvironment, cytokines such as TNF-α, IL-6, and IL-1β regulate lipid peroxidation, acute-phase protein synthesis, and hepatocyte apoptosis, respectively, forming an interdependent signaling loop that reinforces hepatic injury. Kupffer cell activation also promotes chemokine expression, particularly CXCL2, facilitating neutrophil recruitment and extending inflammatory foci beyond initial lesions [15]. This persistent immune stimulation transforms a localized response into systemic inflammation, bridging metabolic stress and structural hepatic damage. The interplay between microbial products, cytokine signaling, and oxidative stress therefore represents a central mechanism driving the progression of alcoholic hepatitis from metabolic dysregulation toward irreversible tissue injury.

4.3 Manifestations of tissue injury induced by microbial translocation

The disruption of intestinal barrier integrity enables bacterial translocation, which represents a pivotal pathological event linking gut dysbiosis to hepatic tissue injury. Under sustained permeability increase, enteric microorganisms such as Streptococcus, Enterococcus, and Escherichia coli can traverse the mucosal layer and enter the liver through the portal circulation. Within hepatic sinusoids, these microbial components encounter endothelial cells and Kupffer cells, where excessive phagocytic activity leads to immune overload and reduced clearance efficiency [16]. The accumulation of bacterial fragments and endotoxins in the central lobular zone promotes the formation of localized inflammatory foci, accompanied by the activation of macrophages and neutrophil infiltration [17].

Histopathological observations consistently describe hepatocellular necrosis and lipid droplet coalescence within damaged parenchyma, indicating the coexistence of metabolic and inflammatory injury. Persistent exposure to microbial ligands, particularly lipopolysaccharides, sustains Kupffer cell activation and cytokine secretion, including TNF-α, IL-6, and chemokines that recruit additional immune cells [18]. This continuous inflammatory signaling disrupts the hepatic microvascular structure, leading to sinusoidal dilation, mitochondrial swelling, and disorganization of hepatic cords. Concurrent oxidative stress diminishes the liver's antioxidant defenses, intensifying lipid peroxidation and cellular apoptosis [19].

Beyond the liver, microbial translocation can extend to extrahepatic organs through circulating microbial DNA and inflammatory mediators, promoting a systemic inflammatory milieu [20]. This low-grade but chronic activation of immune pathways contributes to multiorgan metabolic stress and accelerates hepatic decompensation. The progression from

localized hepatic inflammation to systemic immune activation reflects a critical pathogenic transition, marking the evolution of alcoholic hepatitis from reversible metabolic imbalance toward irreversible structural and cellular destruction.

5 Research on pathogenic mechanisms of key microbiota

5.1 Analysis and identification of characteristic microbiota differences

Functional differentiation within the gut microbiota represents a pivotal mechanism underlying the transition from intestinal imbalance to hepatic inflammation in alcoholic hepatitis [21]. Under chronic ethanol exposure, the gut microbial ecosystem undergoes a shift from an anaerobic, energy-producing environment toward a facultative anaerobic state dominated by pro-inflammatory taxa. This ecological remodeling results in a pronounced functional segregation between metabolic and immune-related bacterial communities. Beneficial taxa that synthesize short-chain fatty acids, such as Faecalibacterium and Roseburia, decline substantially, leading to decreased butyrate availability, reduced epithelial energy metabolism, and delayed mucosal repair. The weakening of these commensal populations disrupts the metabolic stability of the intestinal barrier, compromising its regenerative and protective capacities.

Conversely, opportunistic and endotoxin-producing bacteria, including Streptococcus, Enterococcus, Escherichia, and Klebsiella, expand markedly under high-ethanol and oxidative conditions. Their metabolic byproducts—lipoteichoic acid, lipopolysaccharides, and peptidoglycan fragments—serve as potent ligands for Toll-like receptor activation, sustaining inflammatory signaling along the gut–liver axis. The loss of metabolic buffering by beneficial microbes, combined with the persistent presence of inflammation-associated genera, establishes a self-reinforcing state of immune activation. From an ecological perspective, this functional bifurcation between metabolic and immunogenic bacterial groups signifies a breakdown of cooperative microbial networks and the emergence of a pathogenic steady state [22]. Such microbial restructuring not only reveals the inherent fragility of the intestinal ecosystem under alcohol stress but also defines key microbial targets for understanding the pro-inflammatory mechanisms that drive alcoholic liver disease progression.

5.2 Speculation on streptococcus inflammatory mechanisms and signaling pathways

Against the backdrop of dysbiosis, abnormal proliferation of Streptococcus species is considered one of the key triggers of the inflammatory cascade in alcoholic hepatitis [23]. The release of lipoteichoic acid (LTA) and peptidoglycan, major components of its cell wall, increases approximately 2.3-fold in high-ethanol environments. These substances directly stimulate TLR2/TLR6 complexes on the surface of hepatic sinusoidal macrophages, triggering activation of the NF-κB signaling pathway. Following receptor binding, the MyD88-dependent pathway mediates IKK complex phosphorylation, promoting nuclear translocation of the p65 subunit and inducing elevated expression of IL-6, TNF-α, and IL-1β. Concurrently, enhanced activation of p38 and JNK within the MAPK pathway boosts the activity of the inflammatory transcription factor AP-1, sustaining high expression of pro-inflammatory genes.

Furthermore, metabolites secreted by Streptococcus, such as lactic acid and hydrogen peroxide, alter intestinal pH and redox status, disrupting the competitive niche of probiotics and further expanding the ecological advantage of inflammatory microbiota. The bacterial outer membrane enzymes (e.g., hemolysin and proteases) can damage hepatic sinusoidal endothelial cells, increasing local leakage and facilitating greater entry of LPS-aldehyde adducts into the hepatic parenchyma [24]. Stimulated hepatocytes release CXCL2 to recruit neutrophils, exacerbating tissue inflammation. At the signaling level, the TLR2/NF-κB and p38-MAPK pathways synergistically form a continuously amplified positive feedback loop, causing IL-6 concentrations to rise 2–3-fold in phases after exposure and establishing a chronic inflammatory maintenance state. The streptococcal-driven inflammatory pathway is illustrated in Figure 2.

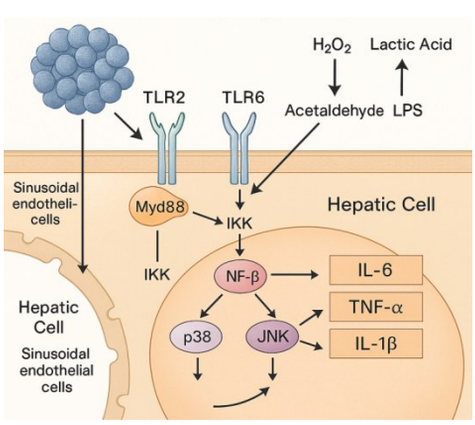

Figure 2 Schematic diagram of streptococcus-hepatitis inflammatory signaling pathway

5.3 Regulatory role of microbiome metabolites in hepatic responses

Gut microbial metabolites constitute a complex signaling network that bridges intestinal ecological stability and hepatic physiological function. In the context of chronic alcohol exposure, alterations in microbial composition induce extensive metabolic remodeling, shifting the balance from protective to injurious biochemical pathways. A decline in short-chain fatty acids (SCFAs), particularly butyrate and propionate, reduces activation of energy-sensing pathways such as AMPK, thereby weakening lipid oxidation and impairing mitochondrial efficiency in hepatocytes [25]. This metabolic attenuation diminishes the liver ' s ability to maintain redox equilibrium and to regenerate following oxidative challenge.

Simultaneously, increased production of toxic intermediates—including acetaldehyde and secondary bile acids—amplifies oxidative stress and disrupts bile acid homeostasis. Excess acetaldehyde promotes aberrant protein acetylation and reactive oxygen species accumulation, while secondary bile acids interfere with farnesoid X receptor (FXR) signaling, attenuating feedback inhibition in bile acid synthesis and promoting hepatocellular membrane instability [26]. These processes collectively disturb intracellular metabolism, compromising both energy utilization and structural integrity.

Another vital regulatory pathway involves microbial indole derivatives, which act through the aryl hydrocarbon receptor (AhR) to modulate anti-inflammatory cytokine synthesis. Reduction in these indole compounds leads to suppressed IL-22 production and impaired hepatic repair capacity, linking microbial metabolic insufficiency to weakened immune tolerance [27].

At the oxidative interface, interactions among acetaldehyde, bile acids, and reactive oxygen intermediates initiate lipid peroxidation and inhibit antioxidant enzymes, perpetuating redox imbalance. The cumulative effect of these metabolic perturbations shifts the liver from an adaptive metabolic phase toward a state of persistent oxidative and inflammatory stress. This transition exemplifies how altered microbial metabolism drives the chronic progression of alcoholic hepatitis, integrating metabolic, immunological, and oxidative dimensions into a unified pathological framework.

6 Conclusion

Dysbiosis in alcoholic hepatitis progresses from metabolic disruption to immune activation. The gut microbiota shifts toward an inflammation-prone profile, where reduced short-chain fatty acids and proliferating pathogens jointly elevate intestinal permeability. Enteric toxins entering the liver induce lipid deposition and amplify inflammation. Streptococci promote inflammation via the TLR2/NF-κB pathway, while their metabolites interfere with AMPK, FXR, and AhR signaling. This exacerbates metabolic stress and tissue damage, forming a pathological network of dysbiosis-metabolism-immunity imbalance.

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