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The Emerging Influence of Intestinal Microecological Dynamics on the Pathogenesis and Progression of Hepatic Chronic Pathologies: Current Scientific Perspectives

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Abstract: The intestinal microbiome, often characterized as humanity's "secondary genome," possesses a genetic repertoire that dwarfs the coding capacity of the human genome by orders of magnitude. The essential architecture of this system is constituted by a vast phylogenetic tapestry of luminal microorganisms, whose dynamic symbiosis serves as a critical determinant of intestinal mucosal homeostasis and functional fidelity. The past decade has witnessed a paradigm shift in biomedical sciences, wherein technological breakthroughs in microbial single-cell genomics and spatial metatranscriptomics have unveiled the gut ecosystem's pivotal role in host physiology. Emerging evidence from gut-liver interface research demonstrates how microbial-derived signals, facilitated by the portal circulatory nexus, mechanistically contribute to the initiation and perpetuation of chronic hepatopathies. This review elucidates the pathophysiological mechanisms through which intestinal dysbiosis propagates chronic hepatopathies, with the ultimate objective of informing novel diagnostic paradigms and therapeutic interventions.

Keywords: Viral hepatitis; Alcoholic liver disease; Metabolic-dysfunction associated fatty liver disease; Gut microecology; Fecal microbiota transplantation

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1. Introduction

The clinical entity designated as chronic liver disease constitutes a heterogenous group of persistent hepatic conditions with disparate pathophysiological origins, including hepatotropic virus infections, alcohol-induced damage, drug-induced injury, and immune system disorders. It encompasses a range of chronic liver conditions such as viral hepatitis, alcoholic liver disease (ALD), metabolic-dysfunction associated fatty liver disease (MAFLD), autoimmune liver disease, and drug-induced liver injury (DILI). The course of these diseases typically exceeds six months and can progressively develop into liver fibrosis, cirrhosis, or even hepatocellular carcinoma,

posing a profound jeopardy to human welfare [1]. According to the World Health Organization (WHO), as documented in 2022 global disease surveillance, hepatitis B virus had established chronic infection in an estimated 254 million human hosts across international populations [2]. Despite significant improvements in healthcare conditions, widespread implementation of vaccination programs, and increased awareness of viral hepatitis prevention and treatment—leading to a decline in HBV infection rates—the annual number of deaths attributed to hepatitis B continues to rise [3]. This trend underscores the ongoing challenges in the prevention and treatment of viral hepatitis. Meanwhile, with socioeconomic development and changes in lifestyle and dietary habits, MAFLD has emerged as a rapidly growing global health concern, now ranking as the most common chronic liver disease worldwide. Its incidence, prevalence, and mortality rates have shown a significant upward trend. These evolving epidemiological patterns in chronic hepatopathies, along with changes in prevalence and mortality rates, not only impose a heavy burden on public health and the economy but also present new challenges to healthcare systems worldwide [4].

The intestinal microecosystem is one of the human microecosystems jointly constructed by the normal gut flora and their living environment. As the core component of this system, homeostatic maintenance of commensal gut flora is fundamentally dependent on unimpaired structural and functional parameters of the intestinal epithelium. Under normal circumstances, beneficial bacteria, harmful bacteria, and opportunistic pathogens in the gut maintain a dynamic equilibrium. Within this balance, the gut microbiota performs various functions, such as promoting human growth and development, regulating the body's material and energy metabolism, and providing immune defense, each contributing fundamentally to the preservation of optimal human biological functioning. However, once this dynamic equilibrium is disrupted—characterized by a reduction in the variety and quantity of beneficial bacteria, a relative increase in harmful and opportunistic pathogens, or damage to the cytoarchitectural framework and homeostatic functionality of the gut mucosal defense—such mechanisms can potentiate the initiation and aggravation of multiple gastrointestinal and hepatic pathologies, encompassing functional bowel disorders, chronic intestinal inflammation, metabolic-associated fatty liver disease, and hepatobiliary malignancies [5]. Consequently, maintaining the dynamic stability of gut microbiota and protecting the structure and function of the intestinal mucosa have become key research focuses in the treatment of digestive system diseases in recent years. This scholarly discourse elucidates the pathophysiological contributions and mechanistic underpinnings of enteric microbial networks in chronic hepatopathies, offering translational perspectives to refine diagnostic paradigms and therapeutic interventions.

2. Gut microecosystem and viral hepatitis

Hepatotropic viral infections can trigger inflammatory liver lesions, clinically referred to as viral hepatitis. Pathologically, it is primarily characterized by hepatocyte necrosis, degeneration, and inflammatory reactions, which may progress to severe hepatitis or liver failure. The gut microecosystem harbors an immense number and variety of microorganisms that actively participate in maintaining human health [6]. The paradigmatic construct of bidirectional gut-liver crosstalk initially entered the academic lexicon in the late 20th century (1998). This paradigm exemplifies the dynamic hepatointestinal crosstalk, wherein the liver orchestrates luminal signaling through biliary efflux of regulatory molecules, concurrent with portal venous uptake of intestinally processed bioactive factors. After hepatic metabolism, these substances enter systemic circulation to exert their effects. Studies comparing the gut microbiota structure between hepatitis B virus (HBV)-infected patients and healthy

individuals have found that HBV patients exhibit reduced gut microbiota diversity, with a significant decrease in beneficial bacteria such as *Roseburia*, *Firmicutes*, and *Bifidobacterium*. In contrast, harmful and opportunistic pathogens like *Enterobacteriaceae* and *Enterococcus* are markedly increased [7]. This dysbiosis leads to elevated intestinal toxin production, which enters the liver via the portal vein, increasing the metabolic and detoxification burden on the liver and triggering oxidative stress and inflammatory damage.

However, after entecavir treatment, HBV patients show restored gut microbiota diversity and improved hepatocyte inflammation [8]. Additionally, Current research delineates a virally-mediated dysregulation of microbial community succession during intestinal ecosystem maturation in HBV-infected immature mouse cohorts. When broad-spectrum antibiotics were used to induce gut dysbiosis in adult mice, their ability to clear HBV was impaired, resulting in persistent viral replication similar to that observed in young mice, exacerbating liver damage [9, 10]. Unmethylated CpG DNA, abundant in bacterial families such as *Lactobacillaceae* (including *Bifidobacterium*, *Proteobacteria*, and *Bacteroides*), is subject to recognition by Toll-like receptor 9 (TLR9) expressed on hepatic macrophages. Ligand-receptor binding induces a signaling relay via MyD88-dependent intermediaries (IRAK4, TRAF6, IRAK1), ultimately potentiating NF-κB and MAPK pathway transduction. Such pathways orchestrate the elevated expression of immunomodulatory cytokines and chemokines, culminating in the coordinated enhancement of phagocytic and lymphocytic effector functions [11, 12]. However, in chronic HBV patients, a depletion in the relative abundance of *Lactobacillus* and *Bifidobacterium* taxa correlates with diminished quantities of unmethylated CpG motifs in the intestinal milieu. This suppresses immune responses against HBV, worsening liver damage [13].

In chronic hepatitis C (HCV) patients, the gut microbiota shows a significant increase in *Prevotella* and *Faecalibacterium* but a decrease in *Ruminococcus*, *Bifidobacterium*, and *Clostridium*, along with reduced microbial diversity [14]. Guo found that gut dysbiosis may impair intestinal barrier function, allowing bacterial translocation to the liver. This enhances the expression of programmed cell death-1 (PD-1), which suppresses T-cell-mediated antiviral immunity, aggravating viral hepatitis progression [15]. Although multiple studies have confirmed the reciprocal influence between liver dysfunction in viral hepatitis and gut microbiota disruption, the specific dominant bacterial species involved in different types of viral hepatitis remain incompletely understood. The exact mechanistic paradigms and biological circuits employed by these commensals necessitate more rigorous interrogation.

3. Gut microecosystem and alcoholic liver disease (ALD)

Ethanol-associated hepatic steatosis constitutes a metabolically dynamic liver disorder wherein protracted excessive ethanol intake precipitates reversible triglyceride deposition in parenchymal cells. However, without effective intervention, the disease trajectory can escalate from inflammatory hepatocyte injury (alcoholic hepatitis) to extracellular matrix deposition (fibrosis), and eventually to architecturally disruptive nodular regeneration (cirrhosis). Alcohol metabolism in the liver primarily occurs through two pathways. Alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH)-mediated metabolism. Under chronic alcohol exposure, the microsomal ethanol-oxidizing system (MEOS) becomes significantly activated, particularly cytochrome P450 2E1 (CYP2E1) [16]. Overexpression of CYP2E1 exacerbates liver damage by promoting reactive oxygen species (ROS) generation, leading to oxidative stress or enhancing lipid peroxidation (LPO), which aggravates hepatic inflammation and tissue injury [17].

Recent studies have explored the relationship between the gut microecosystem and ALD, particularly focusing on the hepatoprotective effects of natural polysaccharides. Key findings include alcohol itself suppresses P-glycoprotein and catechin-related antimicrobial peptides while upregulating intestinal miR-122a, which reduces occludin levels. These changes increase intestinal permeability, allowing pro-inflammatory cytokines and endotoxins to leak into the liver and trigger inflammation [18]. Alcohol and its metabolites disrupt gut microbiota balance, reducing microbial diversity and altering species composition [19,20]. Beneficial bacteria (*Lactobacillus*, *Bifidobacterium*) decrease. Harmful bacteria increase, including *Clostridium perfringens* in the ileum and Gram-negative bacteria (*Proteobacteria*, *Campylobacter*, *Helicobacter*) in the cecum. Bacterial translocation through the damaged intestinal barrier allows lipopolysaccharides (LPS) from Gram-negative bacteria to enter the liver via the portal vein.

Through TLR4 ligation, LPS initiates a signaling cascade culminating in NF-κB nuclear import and enhanced synthesis of inflammatory cytokines (IL-6, TNF-α), which collectively potentiate hepatocellular damage [21]. Polysaccharides exhibit anti-lipid peroxidation and hydroxyl radical scavenging properties. In ALD models, polysaccharide supplementation enhances antioxidant enzyme activity, mitigating oxidative stress and inflammation. Restores gut microbiota diversity and structure, improving ALD progression [22]. The collective data establish that stabilization of the gastrointestinal microbiome and maintenance of mucosal barrier competence mediate salutary effects on alcohol-associated hepatic disease progression.

4. The gut microbiome and MAFLD

Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD) represents a clinicopathological entity predominantly defined by aberrant intracellular lipid accumulation and hepatocellular steatosis, now recognized as the predominant etiology of global chronic hepatic morbidity. The pathogenesis of MAFLD is highly complex. Based on multiple basic and clinical studies, the multiple-hit hypothesis has gradually replaced the traditional and classic two-hit hypothesis. This emergent paradigm elucidates the pathogenesis and advancement of MAFLD through a multifactorial nexus, encompassing genetic predisposition, environmental determinants, neuroendocrine perturbations, exacerbated oxidative insult, dysregulated inflammatory cascades, gut microbial dysbiosis, and ectopic lipid deposition, alongside intricate cross-organ and inter-tissue crosstalk [23]. Among these factors, enteric dysbiosis is now implicated as a non-redundant modulator within the polymodal injury hypothesis, with empirical evidence affirming its status as a sui generis risk factor for excessive adipose expansion and ectopic lipid partitioning in mammalian species, irrespective of genomic or dietary covariates [24].

Bacterial metabolite ensembles—spanning aromatic heterocycles (indoles, phenols), nitrogenous intermediates, SCFAs, bile acid analogs, and fermentative alcohols—function as master regulators of metabolic flux, inflammatory tonus, enterocyte tight junctions, chromatin remodeling, and receptor-mediated transduction, thereby contributing to the multifactorial etiology of MAFLD through trans-kingdom interactions [25]. For example, indole-3-propionic acid (IPA), a tryptophan metabolite generated by gut bacteria, can inhibit NF-κB signaling and reduce pro-inflammatory cytokine levels, thereby suppressing liver inflammation and injury [26]. Butyrate, formed by the combination of butyric acid and salt among SCFAs, serves as a critical energy source for intestinal epithelial cells and significantly influences their development [27]. A large-scale meta-analysis delineated distinct dysbiotic signatures within the enteric microbiome of MAFLD patients, featuring pronounced enrichment of *Enterobacteriaceae* (particularly *Escherichia coli*), *Prevotellaceae*, and *Streptococcaceae* taxa, concomitant with substantial depletion of

butyrogenic genera including *Coprococcus*, *Faecalibacterium*, and *Ruminococcus* [28]. Notably, *Faecalibacterium* and *Ruminococcus* are primary butyrate-producing genera [29, 30]. Their depletion reduces butyrate levels, leading to intestinal epithelial dysfunction and compromised barrier integrity. Increased colonization by pathogenic bacteria exacerbated intestinal inflammation and MAFLD progression.

Mechanistically, diminished butyrate downregulates glucagon-like peptide-1 receptor (GLP-1R) expression, aggravating MAFLD [31], impairs G protein-coupled receptor 43 (GPR43) signaling, dysregulating immune responses and promoting inflammation [32]. Key protective effects of Butyrate can activates the LKB1-AMPK-Insig pathway to inhibit sterol regulatory element-binding protein 1c (SREBP-1c) transcription, thereby suppressing lipogenic gene expression and reducing hepatic lipid accumulation [33]. High alcohol-producing Klebsiella pneumoniae (HiAlc Kpn) strains (W14/TH1) utilize the 2,3-butanediol fermentation pathway to convert carbohydrates into endogenous ethanol. At production levels > 20 mmol/L, these strains induce NAFLD in mice within 12 weeks [34]. Ethanol exacerbates liver injury by activating CYP2E1 via the MEOS system, generating acetaldehyde, peroxides, and free radicals that trigger inflammatory cascades [35]. Ethanol increases intestinal permeability, disrupts tight junctions, and enables direct hepatic invasion by endotoxins. Ferroptosis (iron-dependent cell death characterized by lipid peroxidation and ROS accumulation) is implicated in MAFLD progression [36]. MAFLD patients exhibit impaired intestinal barrier function, and allow LPS translocate to the liver. LPS binds TLRs, which can activate MyD88/MAPK/NF-κB pathways to promote further barrier disruption [37]. So, the gut microbiome contributes to MAFLD through multifaceted mechanisms, though the dominant pathways remain unclear. Modulating microbial composition and metabolite production represents a promising therapeutic strategy.

5. Gut microecosystem and hepatic fibrosis/liver cirrhosis

Hepatic fibrosis (HF) is a histopathological manifestation of progressive chronic liver diseases that exceeds the liver's self-repair capacity. Functioning as a harbinger of cirrhotic transformation, this intermediate phase exhibits a strong pathophysiological correlation with the metabolic reprogramming and contractile activation of HSCs, key effectors of extracellular matrix deposition. Early detection and intervention of hepatic fibrosis can significantly improve clinical outcomes in chronic liver disease, and reduce the risk of progression to cirrhosis and hepatocellular carcinoma. Liver cirrhosis, the end-stage manifestation of various liver diseases, is characterized by diffuse hepatic fibrosis and pseudolobule formation. The aforementioned gut microbial dysbiosis is closely linked to hepatic fibrosis and cirrhosis. Studies have confirmed that patients with nonalcoholic steatohepatitis (NASH) exhibit reduced gut microbiota α-diversity compared to healthy individuals, and this diversity further declines in cirrhotic patients [38]. The primary microbial changes include decreased abundances of *Lachnospiraceae*, *Ruminococcaceae*, and *Clostridia*, alongside enrichment of *Enterobacteriaceae* and *Streptococcaceae* [39]. These alterations in microbial composition compromise intestinal barrier structure and function, increasing gut-derived endotoxin production. Through the gut-liver axis, endotoxins translocate to the liver, activating hepatic stellate cells (HSCs) and upregulating TLR-4 expression, which triggers excessive extracellular matrix (ECM) deposition, thereby promoting hepatic inflammation and fibrosis. Thus, the gut microecosystem and hepatic fibrosis/cirrhosis interact bidirectionally. Once gut dysbiosis or liver fibrosis/cirrhosis develops, they can form a vicious cycle, progressively compromising overall health.

6. Conclusion

In summary, a reciprocal pathophysiological interplay exists between enteric dysbiosis and compromised intestinal barrier integrity, collectively exacerbating the initiation and advancement of diverse chronic hepatopathies – spanning viral hepatitis, ethanol-induced liver injury, metabolic-associated steatohepatitis, fibrotic hepatic remodeling, and end-stage cirrhotic transformation. Selective modulation of gut microbial consortia—through enrichment of commensal symbionts and depletion of pathobionts—ameliorates intestinal barrier dysfunction, consequently attenuating hepatic inflammatory cascades and arresting disease trajectory in chronic hepatopathies. In recent years, advances in high-throughput gene sequencing technologies have brought the gut microbiome into the research spotlight. Numerous studies have explored the therapeutic or preventive potential of microbiota modulation via probiotics, pharmaceuticals, or other interventions for conditions such as obesity, constipation, diarrhea, ALD, and MAFLD [40, 41]. Commonly used probiotics (*Bifidobacterium* and *Lactobacillus* strains) face limitations, including restricted microbial diversity and inconsistent efficacy. Fecal microbiota transplantation (FMT), an emerging therapeutic approach, involves transferring processed fecal microbiota from healthy donors into patients' intestines via endoscopy, nasogastric/nasointestinal tubes, or enemas [42]. This method has demonstrated promise in: Restoring gut microbial balance, Repairing intestinal barrier structure and function, Reducing epithelial inflammation and bacterial translocation. Extensive preclinical studies support its efficacy, and ongoing clinical applications have shown encouraging outcomes with minimal adverse effects, highlighting its therapeutic potential [43–45]. Notably, the fungal microbiome—a long-overlooked domain—may also play critical roles in modulating chronic liver diseases [46]. However, key questions remain unresolved, including: Optimal timing for microbiome-targeted interventions, Strain-specific probiotic formulations and dosages for different liver diseases, Treatment duration and efficacy evaluation criteria. Future research should elucidate the precise mechanisms linking the gut microecosystem to chronic liver pathologies, providing a stronger foundation for clinical translation.

Disclosure statement

The author declares no conflict of interest.

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