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Review Article

The Gut–Liver Axis in Liver Diseases: From Dysbiosis Mechanisms to Precision Niche Remodeling

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Abstract

The gut microbiota engages in a complex, bidirectional dialogue with the liver via the gut–liver axis, and its dysbiosis plays a central role in the initiation and progression of various liver diseases. This review comprehensively integrates recent advances in the common features and etiology-specific patterns of gut microbial dysbiosis in liver diseases, signal decoding of key microbial metabolite axes, gut–liver immune crosstalk mechanisms, the accelerating role of gut barrier disruption, and recent progress in the use of the microbiome as diagnostic and prognostic biomarkers. We focus on analyzing the common patterns of reduced diversity, depletion of beneficial bacteria, and enrichment of pathogenic bacteria associated with gut flora dysbiosis across different liver diseases, ranging from nonalcoholic fatty liver disease and alcoholic liver disease to cirrhosis and hepatocellular carcinoma, as well as their unique etiology-related characteristics. Core findings reveal that microbial metabolites act as key chemical messengers that precisely drive liver disease progression by modulating host metabolic, immune, and inflammatory pathways. Meanwhile, the translocation of microbes and their products resulting from disruption of gut barrier integrity serves as a key accelerator, exacerbating liver injury and related complications. Based on these mechanisms, this review further explores ecological niche remodeling strategies targeting the gut microbiota, including the existing evidence and limitations of fecal microbiota transplantation and probiotics/prebiotics, as well as the prospects of emerging precision interventions such as phage therapy, microbial enzyme inhibitors, and engineered bacteria. Finally, we emphasize the potential and personalized implementation pathways of synergistically integrating microbiota modulation with existing therapies such as antivirals, antifibrotics, immunotherapy, and metabolic surgery. Future research must focus on promoting the translation of microbiome research from association studies to clinical applications through multi-omics integration and prospective clinical trials, ultimately achieving precise prevention and treatment of liver diseases based on gut–liver axis regulation.

Keywords: Liver disease; Gut–liver axis; Gut microbial dysbiosis; Microbial metabolites; Gut barrier; Ecological niche remodeling; Therapeutics; Multi-omics.

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Introduction

Liver diseases are one of the leading causes of death and disability worldwide, with a broad spectrum ranging from metabolic dysfunction–associated steatotic liver disease (MASLD)/nonalcoholic fatty liver disease (NAFLD), alcoholic liver disease (ALD), and viral hepatitis to cirrhosis and hepatocellular carcinoma (HCC). These diseases not only impose a heavy burden on global public health systems but also constitute major clinical challenges due to their high incidence, complex pathogenesis, and limited treatment options.[1–3] In recent years, with the deepening of microbiome research, the core role of the gut microbiota as a key hub connecting the environment, genetics, and host health in the development of liver diseases has become increasingly prominent. Ample evidence indicates that gut microbial dysbiosis is a common pathological

feature of various liver diseases. Through the gut–liver axis, a bidirectional communication network, dysbiotic flora and their metabolic products continuously influence the liver's immune, metabolic, and repair processes, thereby driving disease progression.[4–6] Therefore, deeply analyzing the role of the gut microbiota in liver diseases is not only crucial for understanding the nature of the disease but also provides unprecedented opportunities for developing novel diagnostic markers and therapeutic strategies. It is important to note that a recent multi-society Delphi consensus updated the disease nomenclature from NAFLD to MASLD, and from nonalcoholic steatohepatitis (NASH) to metabolic dysfunction-associated steatohepatitis (MASH). Because much of the cited literature in this review used earlier nomenclature, the terms NAFLD, NASH, and metabolic dysfunction–associated fatty liver disease (MAFLD) are retained when referring to specific original studies to maintain historical and methodological accuracy. Otherwise, the updated MASLD/MASH terminology is used throughout the manuscript where appropriate.

Current research has comprehensively depicted the common patterns and etiology-specific characteristics of liver disease–related gut microbial dysbiosis. Commonly, patients with liver disease exhibit reduced α-diversity and shifted β-diversity in gut flora. The core features include the depletion of beneficial bacteria that produce short-chain fatty acids (SCFAs) (such as Lachnospiraceae and Ruminococcaceae) and the enrichment of potential pathogens with pro-inflammatory potential (such as Enterobacteriaceae and Streptococcaceae).[4,7] This imbalance disrupts gut barrier integrity, leading to the translocation of microbes and their products (such as lipopolysaccharides (LPS)), which triggers and sustains inflammation by activating hepatic innate immunity.[8,9] Simultaneously, the remodeling of microbial metabolite axes, including bile acids, SCFAs, and tryptophan derivatives, has been confirmed as a key mechanism regulating intrahepatic signaling. For example, microbes remodel the bile acid pool through bile salt hydrolases (BSH) and 7α-dehydroxylases, affecting farnesoid X receptor (FXR) signaling, thereby regulating hepatic lipid metabolism and inflammation[10,11]; SCFAs like butyrate exert anti-inflammatory and metabolic homeostasis–maintaining effects by inhibiting histone deacetylases (HDACs) and activating G-protein–coupled receptors[12]; tryptophan metabolites finely tune hepatic immune balance by activating the aryl hydrocarbon receptor (AhR).[13] These studies collectively construct a framework of "altered microbial composition—metabolic dysfunction—hepatic pathological response," positioning the gut microbiota as a core regulator of liver disease progression.

Despite significant progress, critical knowledge gaps and challenges remain in this field. First, while most studies reveal strong correlations, establishing causality between gut microbial changes and liver disease progression remains challenging. Although intervention studies like fecal microbiota transplantation (FMT) provide some causal evidence, the immense heterogeneity of the microbiome between individuals makes it difficult to draw universal conclusions.[14] Second, existing studies mostly focus on bacterial communities, while little is known about the roles of the gut mycobiome, virome, and their cross-kingdom interactions with bacteria in liver diseases, limiting our understanding of the full picture of gut microecology.[15,16] Furthermore, there is a bottleneck in translating microbiome features into clinical applications. Although diagnostic tools based on machine learning models show high accuracy, their robustness across different populations, regions, and etiologies of liver disease awaits validation in large-scale prospective cohorts.[17,18] More importantly, existing ecological niche remodeling strategies, such as broad-spectrum probiotics, prebiotics, or FMT, exhibit significant individual differences and uncertainty in efficacy and may even produce harmful results, highlighting the urgent necessity of shifting from "broad-spectrum" interventions to "precision" targeting.[19,20]

Therefore, this review aims to comprehensively integrate the latest evidence regarding the role of the gut microbiota in liver diseases, moving beyond simple flora–disease association descriptions to deeply dissect its core mechanisms as an "accelerator" of liver disease progression, and to critically evaluate its translational potential as non-invasive biomarkers and novel therapeutic targets. By critically analyzing the efficacy and limitations of existing niche remodeling strategies and looking forward to the future direction of precision targeting strategies (such as specific strains, phage therapy, and microbial enzyme inhibitors), this review aims to provide a theoretical basis and roadmap for constructing a new paradigm of multidimensional, personalized liver disease management based on the gut–liver axis, ultimately promoting a paradigm shift in liver disease diagnosis and treatment from "targeting the liver" to "regulating the intestinal niche" (Fig. 1).

Common features and etiology-specific patterns of gut microbial dysbiosis in liver diseases

Common features of gut microbial dysbiosis in liver diseases

Various liver diseases, including NAFLD/MASLD, ALD, viral hepatitis, cirrhosis, and HCC, all exhibit common characteristics of gut microbial dysbiosis (Table 1).[4,5,7,21–62] The core manifestation is a systemic reduction in microbial diversity and disruption of specific flora structures. Studies consistently find that, compared with healthy controls, the α-diversity (e.g., Shannon index, Chao1 index) of gut flora in liver disease patients is significantly reduced, and β-diversity (community structure) shifts significantly, indicating that the gut microbial ecosystem tends toward simplification and disorder in disease states.[4,5,7,21] This common pattern of dysbiosis typically manifests as the depletion of "beneficial bacteria" and the enrichment of "harmful bacteria." Specifically, SCFA-producing bacteria, such as *Faecalibacterium prausnitzii*, *Roseburia*, and *Butyricicoccus* within the Lachnospiraceae and Ruminococcaceae families, are universally reduced in liver disease patients.[7,22,23] Conversely, bacterial taxa with pro-inflammatory potential significantly increase, such as Enterobacteriaceae (e.g., *Escherichia-Shigella*, *Klebsiella*), Streptococcaceae, and *Veillonella* within the Proteobacteria phylum.[4,5,23] This imbalance pattern of "reduced protective flora—increased pathogenic flora" disrupts gut barrier function, increases the translocation of endotoxins like LPS, and continuously drives liver inflammation and injury through the gut–liver axis, constituting the common microbial background for the occurrence and development of various liver diseases.[24,25] For example, in patients with NAFLD, the reduction in gut flora α-diversity is negatively correlated with the severity of hepatic steatosis,[26] while gut flora dysbiosis in cirrhosis patients is closely related to the occurrence of complications such as portal hypertension and hepatic encephalopathy (HE).[27]

Microbial characteristics of MASLD/NAFLD

Gut flora dysbiosis in MASLD has distinct characteristics closely linked to obesity, insulin resistance, and hepatic steatosis. A significant change in the gut flora of MASLD patients is an elevated Firmicutes/Bacteroidetes (F/B) ratio, which is typically associated with increased energy absorption and metabolic disorders.[28,29] At

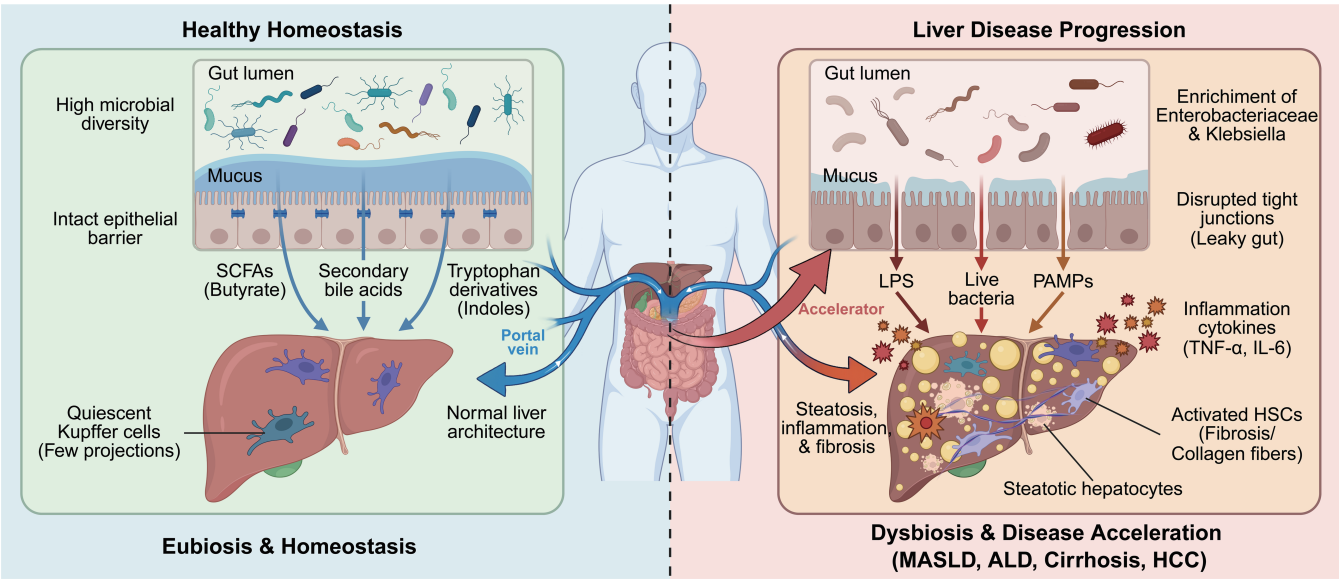

Fig. 1. The Gut–liver axis: Dysbiosis as an accelerator of liver disease progression. This figure illustrates the transition from healthy homeostasis to liver disease progression mediated by the gut–liver axis. The left panel depicts a healthy state characterized by high microbial diversity, an intact epithelial barrier, and the production of beneficial metabolites like SCFAs that maintain normal liver architecture. The right panel shows the progression of liver diseases (MASLD, ALD, cirrhosis, HCC), marked by gut dysbiosis with reduced diversity and the enrichment of pathogenic taxa such as Enterobacteriaceae and Klebsiella. This imbalance disrupts tight junctions (causing a "leaky gut"), facilitating the translocation of microbes and products like lipopolysaccharide (LPS) to the liver. Acting as an "accelerator," these translocated signals activate hepatic innate immunity (e.g., Kupffer cells via TLR4/NF-κB), driving steatosis, inflammation, and fibrosis. This figure was created with BioRender (https://biorender.com/). ALD, alcoholic liver disease; HCC, hepatocellular carcinoma; HSCs, hepatic stellate cells; IL-6, interleukin-6; LPS, lipopolysaccharides; MASLD, metabolic dysfunction-associated steatotic liver disease; NF-κB, nuclear factor kappa B; PAMPs, pathogen-associated molecular patterns; SCFAs, short-chain fatty acids; TLR4, Toll-like receptor 4; TNF-α, tumor necrosis factor-alpha.

the genus level, changes in specific flora are related to disease severity. For instance, the abundance of *Blautia*, *Ruminococcus*, and *Dorea* is often elevated in MASLD patients and positively correlated with liver fat content and inflammatory markers.[30–32] Conversely, *Akkermansia muciniphila*, a bacterium capable of improving gut barrier function and metabolic health, is significantly reduced in MASLD patients, and its abundance is negatively correlated with the degree of hepatic steatosis.[33–35] Furthermore, MASLD, especially its more severe form, nonalcoholic steatohepatitis (NASH), is also associated with gut mycobiome dysbiosis, characterized by the enrichment of fungi such as *Candida* and *Mucor*.[15,32] These microbial characteristics are not only related to disease phenotypes, but microbial signatures constructed based on machine learning models can also distinguish MASLD patients from healthy individuals with high precision and even predict the severity of hepatic steatosis and fibrosis.[36–38] For example, a study found that the ability of the gut microbiome alone to predict liver disease risk is comparable to traditional risk factors, while combining microbiome features with traditional risk factors can significantly improve prediction performance.[39] Specific metabolites, such as gut flora-derived acetate entering the liver to fuel tumor growth, may represent a potential mechanism for gut microbe-mediated early recurrence of HCC.[40] Additionally, gut flora dysbiosis is associated with the occurrence of metabolic diseases such as NAFLD, and regulating the gut microbiome through drugs, prebiotics, probiotics, and FMT may become a feasible method for treating NAFLD.[41,63]

Microbial characteristics of ALD

Gut flora dysbiosis in ALD presents a unique pattern directly related to alcohol metabolism and toxicity. Long-term alcohol intake causes drastic changes in gut flora, characterized by a significant enrichment of Proteobacteria, especially Enterobacteriaceae bacteria, which exacerbates gut barrier damage and endotoxemia.[8,9] A specific increase in the abundance of Fusobacteria is also observed in the stages of alcoholic hepatitis and cirrhosis.[8] Functionally, the gut microbial metabolic profile of ALD patients undergoes profound changes, highlighted by the depletion of SCFAs (such as butyrate and propionate) and anti-inflammatory microbial metabolites (such as indole-3-propionic acid (IPA)), alongside increased production of microbially derived ethanol and endotoxins.[8,42] Notably, specific bacteria carrying virulence factors are associated with poor prognosis in ALD. For example, *Escherichia coli* carrying the capsular polysaccharide synthesis gene *kpsM* can evade hepatic immune clearance and aggravate liver injury, while the activity of trimethylamine (TMA)-producing microbes is enhanced, and their inhibitors could be potential therapeutic targets.[43,44] These characteristics make the microbial profile of ALD not only valuable for diagnosis but also provide a basis for developing precise microbial-targeted therapies. Gut flora imbalance in mice with ALD also leads to reduced vitamin B6 synthesis, thereby affecting hepatic amino acid metabolism and glutathione synthesis, exacerbating the disease process.[45] In addition, FGF-19 dysregulation during alcohol consumption, and the resulting changes in bile acid synthesis and composition, may be contributing factors to ALD and gut flora dysbiosis.[46]

Microbial characteristics of viral hepatitis and cirrhosis

Chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection and the resulting cirrhosis are accompanied by progressively worsening gut flora dysbiosis, the degree of which parallels disease progression. In chronic HBV infection, as the disease progresses

Table 1. Common features and etiology-specific patterns of gut microbial dysbiosis in liver diseases

Disease stage/ etiology	Key characteristics & diversity changes	Enriched taxa (pathogens/risk factors)	Depleted taxa (beneficial/protective)	Pathophysiological impact
Common features[4,5,7,21–27]	Reduced α-diversity and shifted β-diversity (simplification and disorder of ecosystem)	Proteobacteria: Enterobacteriaceae (e.g., *Escherichia-Shigella*, *Klebsiella*), Streptococcaceae	SCFA-producers: Lachnospiraceae, Ruminococcaceae (e.g., *Faecalibacterium prausnitzii*, *Roseburia*)	Gut barrier disruption, increased endotoxin (LPS) translocation, activation of hepatic TLR4/NF-κB pathway
MASLD / NAFLD[28–41]	High Firmicutes/ Bacteroidetes (F/B) ratio linked to energy absorption	*Blautia*, *Ruminococcus*, *Dorea*, *Collinsella*. Fungi: *Candida*, *Mucor* (in NASH)	*Akkermansia muciniphila*, *Bacteroides*	Associated with hepatic steatosis severity, insulin resistance, and inflammation
Alcoholic liver disease (ALD)[42–46]	Drastic changes driven by alcohol metabolism; profound metabolic profile shifts	Proteobacteria (Enterobacteriaceae), Fusobacteria (in hepatitis/ cirrhosis). Virulent *E. coli*	SCFA and Indole-3-propionic acid producers	Exacerbated gut barrier damage, endotoxemia, and evasion of hepatic immune clearance
Viral hepatitis (HBV/HCV)[47,48]	Progressive decline in diversity from immune tolerance to active phases	*Streptococcus*, *Veillonella*, *Enterococcus*. Oral Lactobacillales (HCV)	Bacteroidetes, Clostridiales	Dysbiosis parallels disease progression and fibrosis severity; associated with bile acid dysmetabolism
Cirrhosis[49–54]	Extreme ecological dysregulation; "Oralization" of gut flora	Oral-origin bacteria: *Streptococcus*, *Veillonella*. Pathogens: Enterobacteriaceae, *Klebsiella*	Lachnospiraceae, Ruminococcaceae, *Faecalibacterium*, *Bacteroides*	Collapse of gut barrier, translocation of ammonia/bacteria driving complications like hepatic encephalopathy
Hepatocellular carcinoma (HCC)[55–62]	Specific patterns related to tumor environment and treatment response	LPS-producing bacteria. *Bacteroides*, *Ruminococcus gnavus* (non-viral HCC). *Prevotella* (linked to Rx resistance)	SCFA-producing bacteria (*Faecalibacterium*, *Agathobacter*, *Coprococcus*)	Dysbiosis promotes immunosuppressive microenvironment; intratumoral microbes can predict prognosis

F/B, Firmicutes/Bacteroidetes ratio; HBV, hepatitis B virus; HCV, hepatitis C virus; LPS, lipopolysaccharide; MASLD, metabolic dysfunction-associated steatotic liver disease; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NF-κB, nuclear factor kappa B; Rx, treatment; SCFA, short-chain fatty acid; TLR4, Toll-like receptor 4.

from the immune tolerance phase to the active phase and cirrhosis phase, gut flora diversity continues to decline; beneficial bacteria such as Bacteroidetes decrease, while potential pathogens like *Streptococcus*, *Veillonella*, and *Enterococcus* gradually become enriched.[5,47,48] Cirrhosis, especially decompensated cirrhosis, represents an extreme state of intestinal ecological dysregulation. At this time, gut flora richness drops to a minimum, and resident symbiotic bacteria with protective functions (such as Lachnospiraceae and Ruminococcaceae) are largely replaced by bacteria of oral origin (such as *Streptococcus* and *Veillonella*) and typical intestinal pathogens (such as Enterobacteriaceae), a phenomenon known as "oralization".[23,49] This severe dysbiosis leads to the collapse of gut barrier function, allowing bacteria and their products (such as LPS and ammonia) to translocate to the portal vein and systemic circulation, directly driving the occurrence of fatal complications such as HE and spontaneous bacterial peritonitis (SBP).[25,50,51] Therefore, the gut microbial characteristics of cirrhosis patients can serve as powerful biomarkers for predicting complication risk and prognosis. For instance, the peripheral blood microbiome profile of cirrhosis patients is significantly different from healthy controls, and the enrichment of specific genera is associated with severe portal hypertension.[52] In patients with chronic hepatitis B-related cirrhosis, disease progression and antiviral treatment are two major factors leading to changes in gut flora and metabolite composition, and gut flora dysbiosis and metabolomics play important roles in disease progression.[53] Furthermore, gut flora analysis shows that the diversity of gut flora in HBV-related cirrhosis patients is significantly reduced, and changes in specific genera and metabolites are closely related to disease severity and inflammatory status.[54]

Microbial characteristics of HCC

Gut microbial dysbiosis in HCC integrates the characteristics of its underlying liver disease (such as viral hepatitis, cirrhosis, and MASLD) and further develops specific patterns related to the tumor immune microenvironment and treatment response. HCC patients exhibit significantly reduced gut flora diversity and altered composition.[55,56] Studies have found that, regardless of etiology, HCC patients are often accompanied by a reduction in SCFA-producing bacteria (such as *Faecalibacterium* and *Agathobacter*) and an increase in LPS-producing bacteria.[21,56] However, microbial characteristics also possess etiology specificity: virus-related HCC is enriched in *Faecalibacterium* and *Coprococcus*, while non-virus-related HCC (such as MASLD-HCC) is enriched in *Bacteroides* and the *Ruminococcus gnavus group*, with the depletion of SCFA producers being more pronounced in the latter.[55] More importantly, specific gut microbial profiles are closely related to HCC progression and therapeutic efficacy. For example, flora features rich in *Lachnoclostridium* and *Veillonella* are associated with better objective response and survival in immune checkpoint inhibitor (ICI) treatment, whereas flora rich in *Prevotella 9* are associated with treatment resistance.[57,58] In addition, the intratumoral microbiome itself exhibits heterogeneity; the enrichment of specific bacteria

(such as *Stenotrophomonas maltophilia*) can promote liver cancer progression by modulating hepatic stellate cell phenotypes, and intratumoral microbial features can also serve as independent predictors for HCC prognosis.[59–61] Genera such as *Dialister*, *Veillonella*, *Eubacterium coprostanoligenes group*, and *Lactobacillus* in the gut microbiota, as well as species like *Streptococcus pneumoniae* and *Bifidobacterium faecale*, are associated with early recurrence of HBV-related HCC.[40] Liver tissue microbial analysis shows a key link between liver microbial composition/function and HCC tumor staging, suggesting it may play a critical role in HCC development.[62] Furthermore, gut microbes are significantly associated with various gastrointestinal diseases, eight of which are related to HCC, indicating they may serve as novel biomarkers for the prevention and treatment of these diseases.[64]

Microbial metabolite axes: Intrahepatic signal decoding from bile acids, SCFAs to tryptophan derivatives

Bile acid metabolism remodeling and intrahepatic signal regulation

Gut microbes, through key enzymes they encode, such as BSH and 7α-dehydroxylase, deconjugate and dehydroxylate host primary bile acids to generate secondary bile acids, thereby profoundly remodeling the composition and signaling function of the bile acid pool. In NAFLD, gut flora dysbiosis often leads to reduced BSH activity, manifested as the accumulation of conjugated bile acids (such as taurocholic acid and taurochenodeoxycholic acid) in feces and serum, while unconjugated and secondary bile acids (such as deoxycholic acid (DCA) and lithocholic acid) decrease.[10,11] This compositional change affects host metabolism via the gut–liver axis: conjugated bile acids act as antagonists of FXR in the intestine, inhibiting the intestinal FXR-FGF15/19 signaling pathway, leading to upregulation of hepatic cholesterol 7α-hydroxylase expression and accelerating the conversion of cholesterol to bile acids, but may also promote hepatic lipogenesis.[65,66] Conversely, secondary bile acids like DCA and lithocholic acid are potent agonists of hepatic FXR and TGR5 receptors. Studies have found that serum levels of conjugated DCA (such as glycodeoxycholic acid) are significantly reduced in HCC patients, and glycodeoxycholic acid can directly inhibit the growth and migration of HCC cells *in vitro*, revealing the direct role of specific bile acid profile changes in liver cancer tumorigenesis.[11] Furthermore, novel bile acids produced by microbial metabolism, such as tauro-β-muricholic acid, have been found to indirectly regulate hepatic lipid metabolism and inflammation by antagonizing intestinal FXR, providing new targets for interventions based on the microbe-bile acid axis.[67] In MAFLD, n-3 polyunsaturated fatty acid supplementation upregulates the CYP7B1-mediated alternative bile acid synthesis pathway by activating hepatic PPARα signaling, increasing the synthesis of the secondary bile acid hyodeoxycholic acid. As an intestinal FXR antagonist, hyodeoxycholic acid can reduce ceramide accumulation in the gut and liver, thereby improving the MAFLD phenotype.[68] Additionally, large-leaf yellow tea polysaccharides remodel the gut microbiota by reducing BSH-producing genera and increasing taurine-metabolizing genera, thereby altering colonic bile acid composition, increasing levels of conjugated bile acids and non-12OH bile acids, inhibiting ileal FXR receptors and hepatic bile acid reabsorption, promoting bile acid synthesis and fecal excretion, and subsequently inhibiting NAFLD progression.[69] In patients with chronic hepatitis C, even in the early stages of the disease, their bile acid profile differs from that of healthy populations, characterized by significantly reduced fecal deoxycholic acid and dominance of lithocholic acid or ursodeoxycholic acid. This change is associated with reduced commensal Clostridiales and increased oral Lactobacillales, and the transcription level of CYP8B1, a key enzyme in bile acid synthesis, is reduced, indicating that HCV infection alters bile acid metabolism through the gut-microbiota-liver axis.[70]

Intrahepatic metabolic regulation and immune homeostasis by SCFAs

SCFAs produced by gut microbial fermentation of dietary fiber, mainly including acetate, propionate, and butyrate, are key metabolic messengers connecting gut flora and liver health. These SCFAs enter the liver via the portal vein and exert protective effects through multiple mechanisms. Butyrate and propionate are ligands for G-protein-coupled receptors (such as GPR41 and GPR43), and their activation can inhibit hepatic de novo lipogenesis. For example, acetate produced by *Bifidobacterium longum* inhibits the carcinogenic IL-6/JAK1/STAT3 signaling pathway by activating hepatocyte GPR43, thereby preventing the progression of NAFLD-related liver cancer (NAFLD-HCC).[71] SCFAs, especially butyrate, are also effective inhibitors of HDACs. In a portal hypertension model, FMT enriched butyrate-producing bacteria, and the resulting butyrate activated the PI3K/Akt/eNOS signaling pathway by inhibiting HDAC3 activity in liver sinusoidal endothelial cells, increasing nitric oxide production and thereby reducing intrahepatic vascular resistance.[12] Moreover, SCFAs indirectly mitigate liver inflammation by maintaining gut barrier integrity and reducing LPS translocation. For example, kudzu resistant starch improves the gut barrier, inhibits the LPS/Toll-like receptor 4 (TLR4)/NF-κB inflammatory pathway, and alleviates hepatic steatosis by increasing the abundance of butyrate-producing bacteria (such as *Coprococcus* and *Bifidobacterium*) and elevating plasma butyrate levels.[72] In chronic hepatitis B patients, those achieving functional cure have a higher abundance of butyrate-producing bacteria in their gut, and *in vitro* experiments confirmed that butyrate can directly inhibit HBsAg production in HBV-infected cells, revealing the potential role of SCFAs in antiviral immunity.[73] Genistein improves liver function, blood lipids, and inflammation in MAFLD rats by increasing gut microbiota-derived butyrate production, which subsequently activates the SIRT1 signaling pathway.[74] In patients with MASLD and chronic kidney disease, fecal Butyryl-CoA:acetate CoA-transferase (BCoAT) gene expression levels are positively correlated with estimated glomerular filtration rate, and compared with MASLD patients, chronic kidney disease patients have lower BCoAT and higher plasma intestinal fatty acid-binding protein levels, revealing shared and unique gut microbiota dysbiosis and related biomarkers in both diseases.[75] Additionally, fructooligosaccharides and galactooligosaccharides alleviate MASLD by increasing the abundance of acetate-producing bacteria (such as *Bacteroides acidifaciens* and *Bacteroides dorei*) and inducing POMC/GPR43-positive neurons in the hypothalamic arcuate nucleus, indicating the existence of gut microbiota-brain axis signal regulation.[76]

Tryptophan metabolites and the AhR-mediated intrahepatic signaling network

Gut microbes metabolize dietary tryptophan into a series of bioactive molecules, including indole, indole-propionic acid, indole-3-carboxaldehyde (ICA), and indole-3-acetic acid (I3A). These metabolites regulate hepatic immunity and metabolic homeostasis primarily by activating AhR within host cells. AhR activation has

dual roles in liver diseases, with effects highly dependent on the ligand and cellular environment. In autoimmune hepatitis and T-cell-mediated hepatitis models, gut microbiota-derived ICA induces the expression of PI3K-interacting protein 1 by activating AhR in $CD8^+$ T cells, thereby inhibiting the PI3K/Akt/mTOR pathway, limiting excessive activation of effector T cells, and attenuating liver injury.[13,77] Supplementation with *Lactobacillus reuteri*, a bacterium capable of producing ICA, increases circulating ICA levels and exerts hepatoprotective effects.[13] However, in the context of hepatocarcinogenesis, gut flora dysbiosis may shift tryptophan metabolism in a harmful direction. Studies have found that depletion of gut flora impairs tryptophan metabolism and reduces the production of AhR agonists, thereby relieving AhR's post-translational suppression of sterol regulatory element binding protein 2, promoting cholesterol synthesis and liver cancer initiation.[78] Furthermore, the tryptophan metabolite IPA is often reduced in patients with ALD and NAFLD. IPA exerts anti-inflammatory effects in macrophages by activating AhR and can promote intestinal IL-22 production, which mitigates oxidative stress and ferroptosis in drug-induced liver injury via STAT3 signaling.[79] Therefore, targeting the microbial tryptophan metabolism-AhR axis by supplementing specific probiotics (such as IPA-producing bacteria) or their beneficial metabolites is a potential strategy for regulating hepatic inflammation and metabolic disorders. Pseudopunicic acid B improves high-fat diet-induced MAFLD by significantly downregulating gut flora positively correlated with liver injury and enriching tryptophan metabolic pathways, elevating the level of its microbial metabolite cinnamic acid. Cinnamic acid can stably bind and activate AhR, subsequently downregulating hepatic lipogenesis genes through the AhR-mediated IL-22/JAK1/STAT3 signaling pathway.[80] In a gossypol-induced Nile tilapia fatty liver model, *Lactobacillus plantarum* YC17 reduced hepatic free fatty acid content and alleviated liver injury by restoring the abundance of *Lactobacillus*, *Clostridium*, and *Cetobacterium* in the gut and significantly increasing serum concentrations of microbial tryptophan metabolites IPA and I3A. This strain activates the AhR, promotes P53 protein ubiquitination and degradation to inhibit the P53 signaling pathway, and upregulates the expression of free fatty acid esterification genes.[81] Additionally, CB2R knockout mice exhibit gut flora dysbiosis similar to that of NAFLD patients and model mice. Microbial functional analysis and metabolomics showed that tryptophan metabolism is clearly disturbed in NAFLD patients, model mice, and CB2R knockout mice, where increased tryptophan metabolites like indole lactate are correlated with NAFLD severity indicators. *In vitro* and *in vivo* validation experiments confirmed that indole lactate aggravates the NAFLD phenotype, indicating that CB2R participates in the NAFLD process by regulating gut microbiota-mediated tryptophan metabolism.[82]

Intrahepatic mechanisms of other key microbial metabolites

Beyond the three major classes mentioned above, gut microbes produce a series of other metabolites that precisely regulate hepatic pathophysiology. Microbial-derived D-lactate is elevated in obesity and can be metabolized in the liver into pyruvate, tricarboxylic acid cycle cycle intermediates, lipids, and glucose, thereby directly participating in host glucose and lipid metabolism. Oral administration of a biocompatible polymer that captures intestinal D-lactate and promotes its fecal excretion can significantly reduce blood glucose, insulin resistance, liver inflammation, and fibrosis in mice with obesity and MAFLD.[83] Trimethylamine N-oxide (TMAO) is a product of choline and carnitine metabolism by gut microbes. High levels of TMAO are associated with the severity of fatty liver, and the mechanism may involve activation of the AMPK signaling pathway and interaction with oxidative phosphorylation pathways, thereby promoting hepatic lipid accumulation.[84,85] In liver fibrosis, the microbial metabolite 2-oleoylglycerol (2-OG) has been identified as a key mediator. It is produced by the gut bacterium *Blautia producta* and drives macrophage priming and hepatic stellate cell activation by activating the GPR119/TAK1/NF-κB/TGF-β1 signaling pathway, thereby promoting inflammation and fibrosis.[86] These findings reveal the precise and complex regulatory roles of microbial metabolites as direct signaling molecules or through affecting the epigenetic and metabolic states of host cells in liver disease progression. In high-fat diet-induced obese mice, the abundance of *Blautia producta* in the gut flora increases, leading to elevated 2-OG levels. This metabolite enhances hepatic de novo lipogenesis by activating ChREBP and SREBP-1 pathways and induces mitochondrial dysfunction, thereby promoting hepatic steatosis. In human MASLD patients, serum 2-OG levels in grade II and III hepatic steatosis patients are significantly higher than those in healthy subjects, suggesting that circulating 2-OG acts as a potential predictive biomarker for hepatic steatosis.[87] Furthermore, zinc supplementation increases *Blautia producta* abundance and promotes p-coumaric acid production by altering the gut microbiota. P-coumaric acid is negatively correlated with liver injury parameters in patients with cholestatic liver disease, directly binds NADPH oxidase 2, and inhibits reactive oxygen species production in hepatocytes, thereby preventing hepatocyte death and liver injury. This reveals a new mechanism by which zinc supplementation stimulates host–microbiota interactions to alleviate cholestatic liver injury.[88] In NAFLD patients, plasma histidine levels are strongly negatively correlated with steatosis and are associated with hepatic transcriptomic signatures involving insulin signaling, inflammation, and trace amine-associated receptor 1. Circulating histidine is negatively correlated with Proteobacteria and positively correlated with bacteria lacking the histidine utilization system. Histidine supplementation improves NAFLD and reduces de novo lipogenesis in different animal models. FMT from low-histidine donors and mono-colonization of germ-free fruit flies with *Enterobacter cloacae* increase triglyceride accumulation and decrease histidine content, revealing interactions between microbiota, histidine catabolism, and NAFLD.[89]

Integration and interactive regulation of multi-metabolite networks

In the progression of liver disease, different microbial metabolite axes do not operate in isolation but form a dynamic, interactive network that collectively shapes the liver microenvironment. For example, bile acids and SCFAs can synergistically regulate the same signaling pathway. Butyrate, as an HDAC inhibitor, can enhance FXR expression and activity, thus synergizing with bile acid signaling to jointly inhibit hepatic lipogenesis.[12] Cross-talk also exists between tryptophan metabolism and bile acid metabolism: tryptophan can modulate gut microbiota–bile acid crosstalk by altering BSH-enriched microbes and intestinal FXR signaling, thereby influencing hepatic bile acid synthesis.[90] The imbalance of this multi-metabolite network is central to liver disease deterioration. In patients progressing from NASH to liver fibrosis, an increase in secondary bile acid (e.g., DCA) generation is observed alongside a decrease in anti-inflammatory tryptophan metabolites (e.g., IPA) and an increase in pro-fibrotic metabolites (e.g., 2-OG); this multi-axis dysregulation jointly drives the disease phenotype.[86,91] Therefore, future therapeutic strategies should not be limited to single

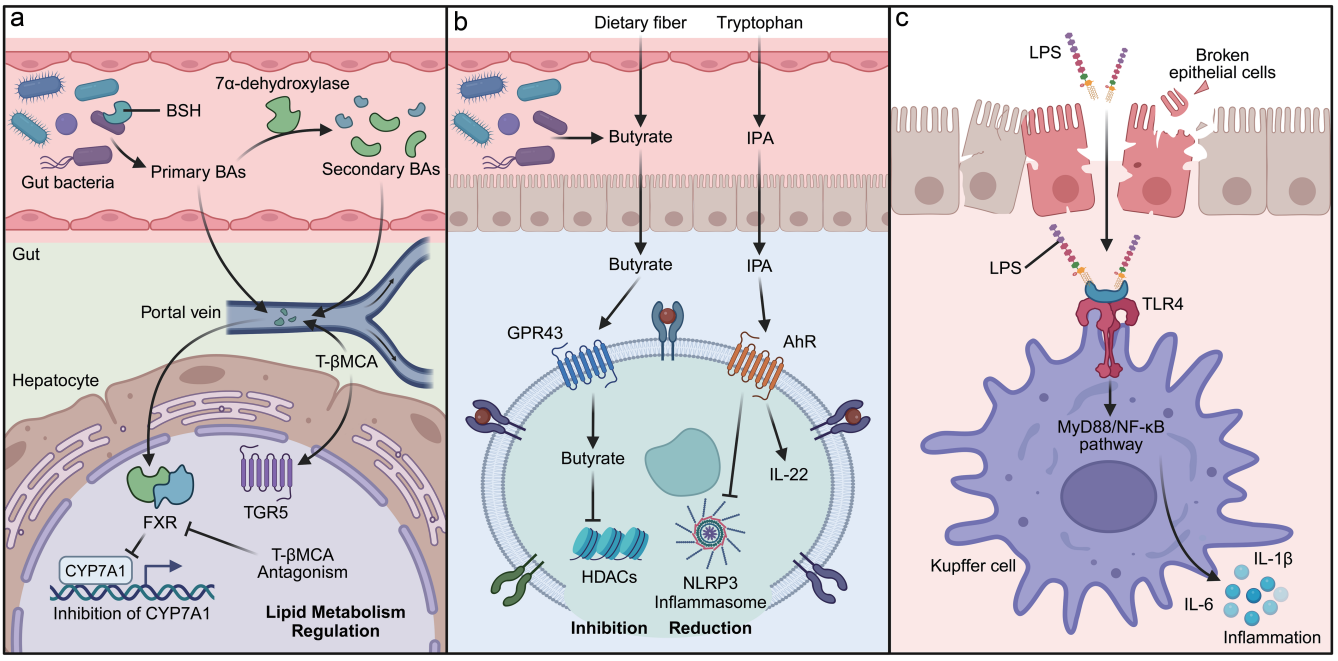

Fig. 2. Deciphering intrahepatic signaling: Metabolites, immunity, and barrier integrity. This figure details the core mechanisms by which gut microbial signals regulate hepatic pathophysiology. Panel A highlights the bile acid axis, where bacterial enzymes like bile salt hydrolase (BSH) and 7α-dehydroxylase remodel the bile acid pool (converting primary to secondary bile acids), influencing hepatic FXR and TGR5 signaling to regulate lipid metabolism and CYP7A1 expression. Panel B illustrates the SCFA and Tryptophan Axes, showing how fiber-derived butyrate inhibits histone deacetylases (HDACs) and activates GPR43, while tryptophan metabolites like IPA activate AhR to modulate immunity. Panel C depicts the Immune-Barrier Axis, where disrupted barrier integrity leads to LPS translocation, triggering the TLR4–MyD88–NF-κB pathway in Kupffer cells and the release of pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6. This figure was created with BioRender (https://biorender.com/). AhR, aryl hydrocarbon receptor; BAs, bile acids; BSH, bile salt hydrolase; FXR, farnesoid X receptor; GPR43, G protein-coupled receptor 43; HDACs, histone deacetylases; IL-1β, interleukin-1 beta; IL-22, interleukin-22; IL-6, interleukin-6; IPA, indole-3-propionic acid; LPS, lipopolysaccharide; MyD88, myeloid differentiation primary response 88; NF-κB, nuclear factor kappa B; NLRP3, NLR family pyrin domain containing 3; SCFA, short-chain fatty acid; TGR5, Takeda G protein-coupled receptor 5; TLR4, Toll-like receptor 4; T-βMCA, tauro-β-muricholic acid.

metabolites or pathways but should focus on rebuilding healthy microbial metabolite networks. By comprehensively correcting disorders across multiple metabolite axes through dietary interventions (such as supplementing specific prebiotics and fibers), probiotic/postbiotic therapies, or small-molecule inhibitors (such as targeting microbial enzymes CutC/D to inhibit TMAO generation), it is expected that more fundamental and effective management of liver diseases can be achieved. In NAFLD patients, two heterogeneous subgroups based on gut microbial composition were identified: PHC-like patients and P-patients. PHC-like patients have significant enrichment of Enterobacteriaceae in feces, and metabolic pathway analysis suggests enrichment of dicarboxylic acid sugar degradation products; the glyceric acid produced may reduce IL-6 levels and fat accumulation through the PPAR-α pathway. P-patients have significant colonization of *Prevotella* in feces, accompanied by enrichment of heme b biosynthesis and sulfate reduction metabolic pathways; the protoporphyrin IX/heme produced may participate in liver injury, and endogenous hydrogen sulfide may elevate serum IL-6 levels. These findings offer possibilities for personalized treatment of NAFLD.[92] Furthermore, in an NAFLD mouse model, gut flora imbalance—specifically the increase of pathogenic *Blautia* and *Helicobacter* and the decrease of beneficial *Allobaculum*—is an important cause of intestinal metabolic disorder. This disorder reduces serum unsaturated fatty acid content, especially eicosapentaenoic acid and docosahexaenoic acid, while branched-chain fatty acids accumulate, subsequently leading to significantly elevated liver injury indicators. This may exacerbate the progression of NAFLD and obesity (Fig. 2).[93]

Gut–liver immune crosstalk: microbiota shaping of hepatic innate and adaptive immunity

Microbiota Regulation of hepatic innate immune cells

The gut microbiota and its products continuously shape the function of liver-resident innate immune cells through the portal circulation, among which Kupffer cells, as the major macrophage population in the liver, are key sentinels sensing gut-derived signals. Microbial-associated molecular patterns, such as LPS, translocate to the liver through the damaged gut barrier, are recognized by TLR4 on the surface of Kupffer cells, activate the downstream MyD88/NF-κB signaling pathway, drive the massive release of pro-inflammatory cytokines (such as TNF-α, IL-1β, IL-6), and thereby initiate and maintain the inflammatory state of the liver, which is crucial in the pathogenesis of ALD and NASH.[8,9] Besides direct activation, the gut microbiota also indirectly regulates innate immunity through its metabolic products. For example, the reduction of SCFAs (such as butyrate) caused by gut microbiota dysbiosis weakens their inhibitory effect on HDACs, thereby enhancing the pro-inflammatory phenotype of Kupffer cells.[12] In HCC models, cyclic di-AMP from gut microbiota was found to act as an agonist for STING receptors, activating intrahepatic in-

nate immunity and enhancing antitumor immune responses, while microbiota dysbiosis inhibits this pathway, leading to radiotherapy resistance.[94] Additionally, gut microbiota affects the function of hepatic natural killer (NK) cells and natural killer T cells. Studies have found that supplementing specific probiotics or regulating microbiota can increase the infiltration and activation of hepatic NK cells and natural killer T cells, thereby enhancing the clearance capability against tumors or virus-infected cells.[95] In MASLD mouse models, early antibiotic exposure accelerates the progression of MASLD-HCC by continuously disrupting hepatocyte function, immune balance, and metabolic homeostasis, manifested as disorders of various immune cells such as T cells, B cells, NK cells, and macrophages in the liver.[96] Moreover, in cystic fibrosis transmembrane conductance regulator gene knockout mice, gut microbiota dysbiosis leads to increased neutrophils, macrophages, and T cells in the periportal region of the liver and activates pro-inflammatory and pathogen-mediated immune pathways. Treatment with non-absorbable antibiotics improves intestinal permeability and liver inflammation.[97]

Microbiota shaping of hepatic adaptive immunity

The gut microbiota profoundly influences hepatic adaptive immune responses by regulating antigen presentation and T cell differentiation. In HCC, gut microbiota dysbiosis inhibits the cGAS-STING-IFN-I pathway, impairing the antigen presentation function of dendritic cells and weakening the activation and function of effector $CD8^+$ T cells, leading to primary resistance to radiotherapy or ICI.[94] Conversely, specific beneficial microbiota can promote antitumor immunity. For example, in HCC mouse models, stigmasterol remodels gut microbiota, increases *Lactobacillus* abundance, leads to a decrease in the proportion of regulatory T cells (Tregs) in the tumor microenvironment, and simultaneously increases the proportion of IFN-γ^+ $CD8^+$ T cells with killing function, thereby enhancing antitumor immunity.[98] In autoimmune hepatitis, gut microbiota dysbiosis plays a driving role. Berberine regulates gut microbiota, increases beneficial bacteria, decreases harmful bacteria, and enhances the gut barrier, thereby reducing LPS translocation and its mediated TLR4/NF-κB pathway activation to inhibit liver inflammation. Meanwhile, it can also regulate the T cell balance in the spleen and liver, reducing the proportion of pro-inflammatory Th17 cells and increasing anti-inflammatory Tregs and IL-10 levels, thereby alleviating autoimmune liver injury.[99] This evidence indicates that gut microbiota is a key regulator of local and systemic adaptive immune responses in the liver. In MAFLD, washed microbiota transplantation (WMT) promotes the migration of group 3 innate lymphoid cells (ILC3s) to the liver via the CXCL16/CXCR6 axis by upregulating CXCR6 expression on ILC3s, thereby mitigating hepatic steatosis through IL-22 release, suggesting that targeting liver-homing ILC3s is a potential therapeutic strategy.[100] Additionally, in an autoimmune hepatitis mouse model, *Bifidobacterium* triple viable capsules alleviated liver injury by downregulating IL-33 production and inhibiting TLR2/4 signaling pathways, restoring the Treg/Th17 balance.[101]

Microbial translocation and establishment of the hepatic immune microenvironment

In advanced liver diseases like cirrhosis, gut barrier function is severely impaired, leading to massive translocation of live bacteria and their products (such as LPS) to the liver, directly participating in shaping the local immune microenvironment. This translocation not only activates Kupffer cells but also leads to the detection of bacterial DNA in the liver. Studies have found distinct bacterial communities in tumor tissues and non-tumor tissues of HCC patients, where bacteria enriched in metastatic nodules, such as *Enterococcus* and *Streptococcus anginosus*, can induce an immunosuppressive microenvironment and promote tumor progression through epithelial-mesenchymal transition.[102] Similarly, in patients with MASLD, universal translocation of obesity-induced gut bacteria to the liver and adipose tissue is observed. The abundance of *Enterococcus* and *Granulicatella* is positively correlated with liver immune cell counts and inflammatory gene expression levels, and they are significantly enriched in steatohepatitis (MASH) patients, suggesting that these translocated bacteria may directly drive disease severity.[103] Furthermore, translocated microbes or their components can act as antigens, continuously stimulating the hepatic immune system and breaking immune tolerance, which may play an important role in the pathogenesis of autoimmune liver diseases such as primary biliary cholangitis.[104] In a liver fibrosis mouse model, dihydromyricetin alleviates liver fibrosis by remodeling gut microbiota and host metabolism to improve inflammatory responses.[105] In an ALD rat model, gut microbiota dysbiosis induced by bismuth quadruple therapy led to damaged gut barrier, elevated serum LPS levels, activation of the hepatic NLRP3 inflammasome pathway, increased IL-18 and IL-1β, and exacerbated liver injury.[106] Moreover, in an autoimmune hepatitis mouse model, dextran sulfate sodium-induced gut microbiota dysbiosis may aggravate liver inflammation and injury by disrupting the gut barrier and leading to microbiota translocation to the liver.[107] Furthermore, this microbial crosstalk is pivotal in liver transplantation. Perioperative ischemia-reperfusion injury severely compromises the intestinal barrier, facilitating the translocation of gut-derived signals that exacerbate graft damage. Notably, specific commensals like Lachnospiraceae have been identified to alleviate hepatic ischemia-reperfusion injury (HIRI), particularly in steatotic donor livers, by inhibiting ferroptosis.[108] Post-transplantation, the resulting dysbiosis actively modulates the recipient's hepatic immune microenvironment, potentially dictating the critical balance between immune tolerance and acute cellular rejection.[109,110]

Crucially, across all these diverse hepatic pathologies and clinical interventions, the paradigms of microbial translocation are actively evolving. Beyond direct bacterial infiltration and the passive diffusion of free microbial products, bacterial extracellular vesicles have recently emerged as a pivotal, independent communication modality along the gut–liver axis.[111] Unlike whole bacteria, these nanosized vesicles can efficiently traverse both intact and compromised intestinal barriers, entering the portal circulation without requiring severe mucosal damage.[112] Upon reaching the liver, bacterial extracellular vesicles function as highly targeted delivery vehicles, independently unloading concentrated packages of virulence factors, microbial small RNAs, and active metabolites directly into hepatic non-parenchymal cells. This vesicle-mediated transport mechanism allows the gut microbiota to profoundly shape the hepatic immune microenvironment and drive localized inflammatory cascades, even in the complete absence of viable bacteremia.[113]

Microbial metabolites as immune regulatory signaling molecules

Gut flora-derived metabolites are core chemical messengers remotely regulating hepatic immunity. SCFAs like butyrate, besides serving as energy substrates, are important immune modulators. Butyrate, by inhibiting HDACs and activating G-protein-coupled receptors (such as GPR109A), can promote the differentiation of macrophages and dendritic cells toward anti-inflammatory pheno-

types (M2, tolerogenic dendritic cells) and enhance the function of Tregs, thereby alleviating liver inflammation in ALD and non-alcoholic fatty liver models.[12,114] Tryptophan metabolites, such as I3A and IPA, play key roles in immune regulation by activating AhR. AhR activation can inhibit inflammasome (such as NLRP3) activation, reduce the production of pro-inflammatory factors like IL-1β, and promote IL-22 secretion, which has a protective effect on hepatocytes and can reduce oxidative stress and steatosis.[79,115] In an autoimmune hepatitis model, Yinchenhao Tang alleviated liver injury by regulating gut microbiota, increasing the release of SCFAs like butyrate, and subsequently restoring the Th1/Treg balance in the spleen and hepatic hilar lymph nodes through G-protein-coupled receptor-mediated mechanisms.[116] These metabolites constitute the molecular language of the fine dialogue between gut flora and the hepatic immune system. In a NASH mouse model, Paeonol inhibited NOD-like receptor protein 3 inflammasome production and inflammation by regulating gut microbiota, reducing the abundance of certain Gram-negative tryptophan-metabolizing bacteria, and significantly increasing the level of the metabolite indole acetic acid, which enhanced the expression of AhR-related pathway proteins.[117] Additionally, in an ALD mouse model, Galangin effectively alleviated alcohol-induced liver disease by regulating gut microbiota dysbiosis and increasing SCFA levels, improving intestinal microecological imbalance, and thus inhibiting the inflammatory cascade through the gut–liver axis mediated by gut microbiota.[118]

To fully decode how these microbial metabolite signals orchestrate the hepatic immune system, it is crucial to move beyond traditional bulk tissue analysis.[119] Recent breakthroughs utilizing single-cell RNA sequencing and spatial multi-omics (such as spatial transcriptomics and proteogenomics) have revolutionized our understanding of hepatic niches.[120] These advanced technologies have mapped the precise spatial zonation of immune responses, revealing how distinct subpopulations of hepatic non-parenchymal cells, such as specific lipid-associated macrophages localized at fibrotic zones or bile ducts, uniquely respond to gut-derived metabolic signals.[121] Incorporating this high-resolution spatial dimension is indispensable for deciphering exactly where and how these specific molecules trigger inflammatory or fibrotic remodeling within the liver lobule.[122]

Therapeutic prospects of targeting the microbe-immune axis

Based on the deep understanding of gut–liver immune dialogue mechanisms, targeting the microbiota to regulate hepatic immunity has become a highly promising therapeutic strategy. By holistically remodeling the gut ecosystem, FMT has been proven to improve survival rates in patients with severe alcoholic hepatitis (SAH) and cirrhosis, with mechanisms closely related to increasing beneficial flora, reducing pathogenic bacteria, and thereby alleviating systemic and hepatic inflammation.[123,124] The application of probiotics and synbiotics is more precise. For example, combined probiotic and prebiotic treatment for autoimmune hepatitis can act by remodeling gut microbiota, maintaining the gut barrier, blocking LPS/TLR4/NF-κB pathway activation, and restoring immune imbalance, with effects superior to probiotics or prebiotics alone.[125] Furthermore, small molecule drugs targeting specific microbial enzymes or metabolic pathways are under development. For instance, inhibiting microbial TMA lyase (CutC/D) to reduce TMAO generation, or using D-lactate scavengers, have shown potential in preclinical models to improve metabolic liver disease and inflammation.[83] In the future, combining microbiome sequencing and immune profiling is expected to enable personalized microbial interventions, such as transplanting "beneficial" flora to sensitize HCC patients ineffective to ICI therapy, or customizing probiotic formulas regulating immune balance for autoimmune liver disease patients, truly realizing the immune therapy paradigm shift from "targeting the liver" to "targeting the intestinal niche." In HCC patients, the treatment regimen of nivolumab combined with oral vancomycin and tadalafil led to changes in the gut microbiome, reduced secondary bile acids, and significant changes in peripheral blood monocyte subsets; although the expected clinical efficacy was not observed, it provided an exploratory direction for immunotherapy combined with microbial regulation.[126] In an ALD mouse model, combined *Lactobacillus rhamnosus* GG and metformin treatment corrected immune response dysregulation by enhancing the gut microbiome, restoring mucosal barrier integrity, regulating immune function, and reducing liver injury, thereby improving ALD.[127] Additionally, in cirrhosis patients, a 12-month multifactorial intervention (home exercise, branched-chain amino acids, and multi-strain probiotics) improved the Liver Frailty Index, while a decrease in *Akkermansia muciniphila* abundance and an increase in multiple *Bifidobacterium* species abundance were observed, indicating that the improvement in frailty status occurs synchronously with changes in gut flora composition.[128]

Disruption of gut barrier integrity and microbial translocation: The accelerator of liver disease progression

Pathophysiological changes in gut barrier structure and function

As a key physical and immunological defense line separating intestinal lumen contents from the host's internal environment, the integrity of the gut barrier suffers systemic destruction during the progression of liver diseases. Pathophysiological changes involve multiple levels: at the cellular level, the expression of tight junction proteins (such as ZO-1, occludin, and the claudin family) is significantly downregulated, leading to the loss of the "sealing" function between intestinal epithelial cells and increased intestinal permeability.[129–131] At the chemical barrier level, mucins (such as MUC2) secreted by goblet cells decrease, thinning the mucus layer covering the intestinal epithelium and failing to effectively block direct contact between bacteria and the epithelium.[132] Simultaneously, the expression of antimicrobial peptides (such as lysozyme and defensins) secreted by Paneth cells decreases, weakening the innate immune defense capability against commensal and pathogenic bacteria.[133] This multi-level barrier dysfunction is not an isolated event but forms a vicious cycle with gut flora dysbiosis. For example, in ALD models, ethanol and its metabolites directly induce necroptosis and endoplasmic reticulum stress in intestinal epithelial cells, while altering the bile acid profile to further impair barrier protein expression.[134,135] In MASLD, high-fat diet-induced oxidative stress and the release of inflammatory cytokines (such as TNF-α) directly downregulate the transcription and translation of tight junction proteins by activating signaling pathways like NF-κB.[131,132] These structural and functional changes collectively constitute the pathological basis of gut barrier "leakiness," opening the gateway for subsequent translocation of microbes and their products. In high-severity patients after liver transplantation, gut barrier function is more persistently and severely impaired, with a higher proportion of pathogens like *Escherichia coli* and *Shigella flexneri* in their feces, while butyrate producers like *Roseburia intestinalis* are positively correlated with albumin levels, suggesting an interconnection between dysbiosis and barrier damage.[136] Chronic apical periodontitis damages gut barrier integrity by altering gut flora and their

metabolites, disrupting intestinal tight junction protein and mucin expression, thereby promoting liver fibrosis progression in NAFLD.[137] Arsenic exposure significantly reduces the expression of gut barrier proteins occludin, ZO-1, and MUC2 in mice, elevates serum FITC levels indicating increased intestinal permeability, and FMT experiments confirm that arsenic-induced dysbiosis and barrier dysfunction play a key role in liver injury.[138] In patients with compensated cirrhosis, duodenal epithelial permeability is increased, and the mucosal microbial community structure is related to barrier function, where beneficial bacteria like *Lactobacillus* and *Bifidobacterium* have a protective effect on duodenal permeability.[139] Splenectomy improves cirrhosis by restoring gut barrier function and maintaining gut microbiota balance. *Veillonella* is a key genus whose conditioned medium promotes hepatic stellate cell activation and induces hepatocyte pyroptosis.[140] Nanoplastic exposure alters gut flora composition in mice, disrupts the gut barrier, leads to increased circulating LPS, and promotes liver cell pyroptosis and inflammation. Recipient mice receiving fecal transplants from nanoplastic-treated mice also develop similar gut barrier damage and liver inflammation.[141] Methamphetamine administration leads to impaired gut barrier, increased circulating LPS, and promotes liver dysfunction and inflammation by disturbing the cecal microbiota and impairing bile acid homeostasis.[142] In a bile duct ligation-induced liver fibrosis rat model, intervention with cinnamaldehyde nanoemulsion formulated with vitamin A exerts therapeutic effects by restoring gut flora, increasing SCFA concentration, and improving gut integrity.[143] A hyperammonemia mouse model shows decreased gut microbial load, diversity, and aerobic/facultative anaerobic bacteria ratio, and gut flora diversity decreases in a time-dependent manner; data suggest that ammonia-induced motor coordination deficits may develop through direct and indirect pathways acting on the gut-brain axis, indicating impaired barrier function.[144] IL-17 deficiency leads to gut flora dysbiosis, inhibiting probiotic growth while pathogenic bacteria overproliferate, triggering higher endotoxemia and more severe gut barrier defects; transplanting flora from IL-17-deficient mice to germ-free mice exacerbates gut barrier damage and promotes the development of NASH.[145] *Helicobacter pylori*-infected high-fat diet mice exhibit more severe hepatic steatosis; infection triggers gastric flora dysbiosis, leading to significant enrichment of the *Helicobacter* genus. Gastric tissue energy metabolomics analysis shows elevated glycolytic pathway activity after infection, and the disturbance of the gastric flora–metabolic axis is significantly positively correlated with the severity of hepatic steatosis and inflammation.[146] Oral exposure to high concentrations of microplastics for six weeks, even without inducing leaky gut syndrome, leads to elevated serum lipid levels and exacerbated fatty liver function in mice. Exposure does not affect gut innate lymphoid cell numbers or SCFAs but increases NK cell numbers, alters gut flora, induces gut inflammation, and regulates the expression of genes related to nutrient transport in the gut.[147] In an intrahepatic cholestasis of pregnancy rat model, 17α-ethinylestradiol treatment leads to reduced gut flora α-diversity and significantly altered structure; resveratrol intervention partially rescues gut flora dysbiosis and improves biochemical abnormalities.[148] Cognitive impairment caused by HIRI exhibits circadian oscillation; FMT from ZT12-HIRI mice can induce cognitive impairment behavior in recipient mice, and gut flora composition and metabolite analysis show significant enrichment of differential fecal metabolites in lipid metabolism pathways.[149] In specific pathogen-free mice, a low-iron diet reduces serum triglycerides and induces MAFLD, while germ-free mice on a low-iron diet show elevated serum triglycerides and do not develop hepatic steatosis; significant changes in hepatic lipid metabolism and increased insulin resistance depend on the presence of gut flora.[150] Chronic fructose intake leads to gut flora dysbiosis, tight junction protein downregulation, secretory cell depletion, and elevated pro-inflammatory cytokines, thereby disrupting the gut barrier and triggering endotoxemia-mediated liver inflammation and fibrosis. Calcitriol intervention significantly restores vitamin D receptor expression, enhances autophagy flux, stimulates mucin/antimicrobial peptide production, and inhibits NF-κB-mediated inflammatory responses.[151] Multi-donor FMT significantly improves liver fat accumulation in high-fat diet-fed mice, increases relative protein levels of gut barrier proteins (claudin-1, occludin, and E-cadherin), and reduces serum LPS levels.[152] Fecal microbiomes of cirrhosis patients treated with oral L-ornithine L-aspartate show higher abundances of *Flavonifractor* and *Oscillospira*, but there are no differences in intestinal permeability or inflammatory markers.[153] Patchoulene epoxide significantly reduces the disease activity index and alleviates colon atrophy in ulcerative colitis mice, improving pathological changes in the colon and liver by protecting tight junctions and mucus connections and inhibiting pro-inflammatory cytokine and LPS generation. These beneficial effects are attributed to patchoulene epoxide's ability to regulate colonic microbiota and metabolic processes.[154] Long-term high-energy diet reduces anti-infective, immune, and antioxidant functions, increases cell death, and leads to liver inflammation and activation of cytokine/chemokine signaling pathways by altering rumen and jejunum microbiomes; meanwhile, indoxyl sulfate and p-cresol sulfate increase while triterpenoids decrease in the liver.[155] In an ALD mouse model, NLRP6 deficiency has no effect on hepatic steatosis and injury but slightly interferes with intestinal homeostasis by affecting intestinal epithelial function and gut flora, and unexpectedly significantly reduces hepatic immune cell infiltration.[156] Hepatic ischemia/reperfusion injury mice induce a depression-like phenotype via the subdiaphragmatic vagus nerve-mediated gut–microbiota–liver–brain axis, manifested as splenomegaly, systemic inflammation, reduced synaptic protein expression in the prefrontal cortex, abnormal gut flora composition, and altered blood metabolites and lipids; subdiaphragmatic vagotomy significantly blocks these changes.[157] An NAFLD mouse model induced by a high-fat, high-sugar diet for 6 months exhibits hypercholesterolemia, glucose intolerance, and hyperinsulinemia, accompanied by severe hepatic macro- and microvesicular steatosis and human-like pericellular fibrosis, along with hepatic stellate cell activation, $CD68^+$ macrophage infiltration, and elevated hepatic pro-inflammatory factors p65-NF-κB, IL-6, and TNF-α protein levels. Gut flora analysis shows reduced bacterial diversity, enriched Firmicutes and Proteobacteria, and reduced Bacteroidetes and Fusobacteria.[158] Oral exposure to cylindrospermopsin leads to reduced gut bacterial phylum diversity, accompanied by increased *Clostridioides difficile* abundance and reduced beneficial flora like *Roseburia*, *Akkermansia*, and *Bacteroides thetaiotaomicron* (*B. theta*). This feature is closely related to gut and liver pathology, and gut flora dysbiosis is also associated with increased intestinal Claudin2 protein, a marker of leaky gut and endotoxemia.[159] In a nonalcoholic fatty liver mouse model, the β-diversity of cecal microbiota changes significantly, where *Blautia*, *Unidentified-Lachnospiraceae*, *Romboutsia*, *Faecalibaculum*, and *Ileibacterium* abundance increase significantly, while *Allobaculum* and *Enterorhabdus* decrease significantly. Metabolomics analysis identifies 167 differential metabolites involving amino acids, lipids, bile acids, and nucleotides.[160] Combined triptolide and triptonide treatment causes intestinal bleeding and microbial dysbiosis, subsequently elevating plasma LPS levels and exacerbating

triptolide-induced liver injury. Metabolomics and flora analysis confirm that the toxic metabolite p-cresol sulfate is significantly associated with gut barrier damage, and p-cresol sulfate supplementation *in vivo* verifies its ability to promote combined medication hepatotoxicity.[161] In gut microbiota analysis of early-stage liver fibrosis (F0–F2), 50% of disease-associated taxa are Enterobacteriaceae, Pseudomonadaceae, Flavobacteriaceae, and Burkholderiaceae, among which Flavobacteriaceae and Xanthomonadaceae can distinguish F0 from F1 stages. Predictive metagenomics analysis finds that preQ0 biosynthesis and potential pathways involving glucopyranose and glycogen degradation are negatively correlated with F1–F2 fibrosis.[162] Copper exposure significantly elevates duck liver AST and ALT levels and induces liver inflammation by upregulating pro-inflammatory cytokines and activating the LPS/TLR4/NF-κB signaling pathway. Meanwhile, copper exposure alters gut flora composition, significantly reduces the expression of gut barrier-related proteins (occludin, claudin-1, ZO-1), and promotes the secretion of intestinal pro-inflammatory cytokines. FMT experiments further confirm that transplanting fecal samples from copper-exposed ducks to microbiota-depleted ducks disrupts intestinal function, leading to impaired liver function and activation of liver inflammation.[163] In the high liver fat group (>5%), fecal abundances of Prevotellaceae NK3B31 group and *Bacteroides* are lower, while lysine and histidine degradation product levels are higher. Elevated plasma caffeine and its metabolite levels indicate reduced hepatic CYP1A2 activity, and fecal 6β-hydroxytestosterone (metabolized by CYP3A4) levels are lower.[164] Oxaliplatin-induced drug-induced fatty liver disease in a tree shrew model manifests as early severe hepatocyte steatosis and ballooning, late mild steatosis with sinusoidal dilation, and persistent hepatic oxidative stress. Hepatic transcriptome analysis identifies 1,503 differentially expressed genes, 601 of which differ in both early and late disease stages, involving significant dysregulation of oxidative stress and lipid metabolic pathways. Gut microbial analysis shows increased relative abundance of potentially harmful bacteria (such as *Parabacteroides*, *Rikenella*, *Alistipes*, and *Faecalitalea*) and decreased abundance of antioxidant bacteria (such as *Lactococcus* and *Flavobacterium*).[165] Oral nano-silica for 12 weeks leads to gut flora dysbiosis, metabolite imbalance, and gut barrier damage in mice, causing liver-specific silicon accumulation, which subsequently triggers hepatic lipid deposition, senescence, and fibrosis via the microbe–gut–liver axis. 16S rRNA sequencing shows that nano-silica reduces the abundance of beneficial bacteria *Muribaculum* and *Ligilactobacillus* and increases pathogenic *Helicobacter*.[166] In overweight and obese Iranian children and adolescents, the only significant gut flora change associated with MASLD is reduced *Coprococcus* abundance. After adjusting for age, gender, and body mass index, *Coprococcus* count is negatively correlated with MASLD prevalence odds and ALT levels; conversely, *Prevotella* is significantly positively correlated with ALT and AST levels.[167] Long-term skin exposure to UVB not only triggers liver inflammation and oxidative stress but also leads to abnormal hepatic lipid metabolism, specifically significant changes in glyceride, sphingolipid, and glycerophospholipid metabolism. Meanwhile, UVB exposure disrupts gut flora structure and function. Co-culturing fecal supernatant from UVB-exposed mice with HepG2 cells induces increased inflammatory factor IL-8 secretion, MDA accumulation, reduced SOD activity, and reduced hepatocyte lipid content.[168] Cadmium exposure leads to gut flora dysbiosis, reduced fecal BSH activity, and elevated intestinal tauro-β-muricholic acid levels in mice, subsequently inhibiting the intestinal FXR/FGF-15 signaling pathway, promoting hepatic bile acid synthesis, and ultimately triggering bile duct proliferation, inflammation, and injury. Mice receiving fecal microbiota transplants from cadmium-treated mice recapitulate signal inhibition, increased bile acid synthesis, and liver injury, while antibiotic clearance of flora blocks these effects.[169] The synergistic action of fructose and potassium sorbate significantly induces liver pathological changes of MASLD, including steatosis, inflammation, and fibrosis, accompanied by elevated liver function markers and altered lipid profiles. These changes are associated with significant alterations in gut bacterial and fungal communities, gut barrier function disruption, and enhanced pro-inflammatory responses in mesenteric lymph nodes.[170] Gentiopicroside significantly attenuates weight loss and disease activity index scores in dextran sulfate sodium-induced colitis mice, restores intestinal tight junction protein expression, and improves colonic permeability. Simultaneously, it regulates gut flora, significantly increasing the abundance of beneficial bacteria like *Bacteroides* and *Clostridium* cluster IV. Mechanistically, it inhibits colonic and hepatic inflammatory responses by suppressing TLR4/MyD88/NF-κB and JAK2/STAT3 signaling pathways.[171] In NAFLD patients, no significant association is observed between dietary n-6/n-3 fatty acid ratio and gut flora composition or disease severity. However, the abundance of specific bacteria like *Catenibacterium* and *Lactobacillus ruminis* is positively correlated with dietary n-6 fatty acid intake, while *Clostridium* abundance is negatively correlated.[172] *Bacillus subtilis* C10 intervention improves hepatic lipid metabolism and oxidative stress in an alcoholic liver injury mouse model by regulating gut flora balance, reducing harmful bacteria numbers, and increasing beneficial bacteria. Specific mechanisms include regulating key hepatic lipid metabolism factors and interfering with the Nrf-2/HO-1 signaling pathway, while reducing harmful metabolites and increasing beneficial metabolites by regulating multiple hepatic metabolic pathways such as glutathione metabolism, purine metabolism, pantothenate and CoA biosynthesis, ABC transporters, and the HIF-1 signaling pathway.[173]

Mechanisms and consequences of microbial and product translocation

The direct consequence of gut barrier integrity disruption is the translocation of microbes and their metabolic products from the intestinal lumen to the portal circulation and systemic circulation, a process that is a core accelerator driving liver disease deterioration. Translocated substances mainly include live bacteria, bacterial fragments (such as LPS and peptidoglycans), and microbial metabolic products (such as D-lactate and TMAO). LPS, as a cell wall component of Gram-negative bacteria, is the most representative translocated product. In patients and animal models of cirrhosis, ALD, and NASH, serum LPS levels are significantly elevated and positively correlated with disease severity.[130,131,174] Translocated LPS reaches the liver via the portal vein, is recognized by TLR4 on the surface of liver sinusoidal endothelial cells and Kupffer cells, activates the downstream MyD88/NF-κB signaling pathway, triggers a strong pro-inflammatory response, releases large amounts of cytokines such as TNF-α, IL-1β, and IL-6, and exacerbates liver inflammation and cell injury.[8,9,174] Besides LPS, translocation of live bacteria is equally harmful. Studies confirm that gut-derived bacteria (such as *Klebsiella pneumoniae* and *Escherichia coli*) can be detected in the liver tissues of HCC patients and animal models; colonization by these bacteria can directly activate carcinogenic signaling pathways (such as TLR4) within hepatocytes, promoting tumor occurrence and progression.[175] Microbial translocation also leads to "metabolic endotoxemia," an abnormal elevation of microbial-derived metabolite levels in circulation. For example,

elevated serum levels of D-lactate, a bacterial fermentation product, act as a sensitive marker for increased intestinal permeability, while TMAO is associated with the degree of hepatic steatosis and inflammation, possibly promoting disease by affecting cholesterol metabolism and macrophage foam cell formation.[83,84] These translocated microbial components act together to transform local intestinal disturbances into systemic and sustained hepatic inflammatory attacks. In HCC patients, the microbiome differs between tumor and peritumoral tissues; tumor tissues are enriched in Lactobacillales, Veillonellaceae, *Rhodobacter*, and *Megasphaera*, while peritumoral tissues are enriched in *Pseudochrobactrum*. Patients with capsular invasion exhibit higher α-diversity at the genus level in liver tissues.[176] In operable HBV-related HCC patients, there is a significant difference in gut flora β-diversity between the microvascular invasion (MVI) group and the non-MVI group. A random forest model based on nine optimal microbial markers achieved areas under the curve of 79.76% and 79.80% for predicting MVI risk in training and independent validation sets, respectively.[177] Significant heterogeneity exists between multifocal tumor nodules in HCC.

The microbiome as non-invasive biomarkers for liver disease diagnosis and prognosis: From association to application

Liver disease diagnosis models based on gut microbial features

Gut microbiome features have moved beyond simple association studies to develop into high-precision non-invasive diagnostic tools for liver disease. In the field of MASLD, machine learning models constructed based on fecal 16S rRNA or metagenomic sequencing data demonstrate superior diagnostic performance. For instance, a study using a classifier containing ten core microbial genera achieved an area under the curve (AUC) as high as 0.93 for predicting fatty liver disease in insulin-resistant individuals, with accuracy comparable to or better than traditional fatty liver indices.[17] Another study focusing on pediatric MASLD also confirmed that diagnostic models based on gut flora features possess high discriminatory power.[178] In Chinese children with NAFLD, a microbial model based on fecal flora also showed a high AUC, capable of distinguishing NAFLD patients from healthy individuals.[179] For HCC, the construction of diagnostic models is even more refined. Research integrating oral and gut microbial markers developed a consensus classifier that achieved an AUC of 0.9405 in distinguishing HCC from controls; when combined with serum α-fetoprotein, the AUC further improved to 0.9811, significantly surpassing the diagnostic capability of single biomarkers.[18] Furthermore, a diagnostic model constructed based on the urine microbiome achieved an AUC of 0.94 and an accuracy of 88.4% in an independent validation cohort, providing a brand-new avenue for non-invasive HCC detection.[180] These models not only distinguish disease from health but can also identify different liver disease types. For example, a classification model based on eight gut bacterial genera can distinguish HCC, cholangiocarcinoma, and healthy controls with high precision, with AUCs reaching 0.967, 0.920, and 0.989 for the three groups in the validation cohort.[181] Similarly, specific gut fungal signatures (such as *Scopulariopsis* and *Kluyveromyces*) achieved an AUC of 0.93 in distinguishing ALD from NAFLD and an AUC of 0.99 in distinguishing advanced fibrosis.[182] In elderly HCC patients, a random forest model constructed based on specific genera like *Eggerthella*, *Anaerostipes*, and the *Lachnospiraceae_ND3007_group* also showed good predictive ability (AUCs of 0.791, 0.766, and 0.730, respectively).[183] Machine learning models based on gut microbes also performed well in predicting HBV-related HCC risk, with AUC values of seven models reaching 0.821–0.898 and 0.813–0.885 in training and validation sets, respectively.[184] In viral hepatitis patients, prediction models constructed based on gut flora α-diversity and key microbial markers such as *Butyricimonas* and *Escherichia-Shigella* also had AUC values exceeding 0.7.[185]

Microbial biomarkers predicting disease progression and liver fibrosis

The gut microbiome shows immense prognostic value in predicting liver disease progression, particularly the severity of liver fibrosis. In patients with chronic hepatitis B-related liver disease, changes in the abundance of specific genera are tightly linked to fibrosis stages. For example, the relative abundance of *Dorea* decreases significantly with increasing liver fibrosis severity, serving as a potential microbial marker for identifying fibrosis occurrence and progression.[186] In MASLD patients, the gut flora characteristics of the moderate-to-severe fibrosis (F2–F4) group manifest as enrichment of *Fusobacterium* and *Escherichia-Shigella* and reduction of *Lachnospira*; a random forest classifier constructed based on three bacterial genera could distinguish fibrosis degree with high precision (AUC of 0.93).[187] In NAFLD patients, severe fibrosis (F3–F4) patients show reduced abundance of anti-inflammatory species (such as *Eubacterium ventriosum* and *Alistipes finegoldii*) and increased abundance of genera like *Enterobacter* and *Klebsiella* in feces.[188,189] Additionally, microbial markers can predict the progression of liver disease to end-stage events. In cirrhosis patients, specific patterns of gut flora dysbiosis are associated with adverse clinical outcomes. Studies found that as the disease progresses from compensated to decompensated cirrhosis and liver cancer, gut flora diversity progressively declines, *Bacteroides*, *Prevotella*, and *Faecalibacterium* gradually decrease, while *Klebsiella*, *Haemophilus*, and *Streptococcus* increase. A predictive nomogram constructed based on these features achieved AUC values of 0.865 and 0.848 in training and external validation cohorts, respectively.[190] More specifically, in cirrhosis patients, a denser, more uniform bacterial–archaeal–viral network centered on Ruminococcaceae and Christensenellaceae at baseline is associated with the risk of future decompensation events.[191] In cirrhosis patients, gut flora dysbiosis is significantly associated with 90-day mortality and hospitalization rates; Firmicutes/Bacteroidetes and Firmicutes/Proteobacteria ratios progressively decrease and are significantly correlated with 90-day mortality.[192] These findings indicate that gut microbiome features can dynamically reflect the accumulation of hepatic pathological injury and are powerful tools for non-invasive assessment of disease stage and prognosis prediction.

Microbiome predicting treatment response and efficacy

Gut microbiome profiles are becoming novel biomarkers for predicting patient response to specific treatments, especially in the fields of immunotherapy and antiviral therapy for HCC. In HCC patients, those achieving durable clinical benefit prior to ICI treatment have significantly higher overall gut bacterial and fungal diversity compared to non-durable benefit patients. A study established a prediction model containing 18 bacterial species to predict whether immunotherapy would yield sustained benefits, achieving an AUC of 75.63%.[193] Another study also found that patients with higher baseline gut flora α-diversity respond better to immunotherapy, and a machine learning classifier based on serum metabolites performed better (AUC 0.793) than a classifier based on gut flora in

predicting potential beneficiaries of immunotherapy.[194] In chronic hepatitis B treatment, gut flora features are closely related to antiviral efficacy. Research found that a gut flora cluster dominated by *Bacteroides* is associated with a higher probability of undetectable plasma HBV-DNA (OR 3.49), and patients in this cluster have higher plasma ursodeoxycholic acid levels and secondary bile acid biotransformation activity; whereas a cluster dominated by *Blautia* is associated with increased risk of advanced liver fibrosis (OR 2.74).[195] Additionally, in *Fasciola hepatica*-infected patients, gut microbiome characteristics differ significantly between responders and non-responders to triclabendazole treatment both before and after therapy. Responders have higher abundance of Firmicutes A and *Bacteroides* species and phospholipid synthesis pathways in their microbiome, suggesting that gut flora may play a role in modulating drug efficacy.[196] In nonalcoholic fatty liver and prediabetic patients, personalized gut flora networks at baseline can predict individual hepatic fat response to exercise intervention.[197] These evidences promote the potential application of pre-treatment microbiome testing in clinical decision-making.

Application of microbial biomarkers in warning of liver disease complications

Gut microbiome features have significant value for predicting common and fatal complications of cirrhosis, providing a window for early intervention. Regarding the prediction of HE, microbial markers show high specificity. Studies found that the gut flora of HE patients is dominated by *Escherichia/Shigella*, Burkholderiales, and Lactobacillales, while non-HE patients are characterized by *Veillonella* and *Bacteroides*. A rapid fecal test model based on 20 microbes can serve as an effective tool to rule out HE and avoid misdiagnosis.[198] Deeper mechanistic studies discovered that urease-positive *Streptococcus salivarius* producing ammonia is significantly enriched in the gut of HE patients, while urease-negative *R. gnavus* enriched in rifaximin non-responders can enhance the ammonia-producing activity of surrounding urease-positive bacteria; the sensitivity of these two bacteria to rifaximin depends on conjugated secondary bile acid levels, providing targets for personalized treatment.[199] Regarding the prediction of HE after transjugular intrahepatic portosystemic shunt, increased abundance of *Phocaeicola vulgatus* in the gut pre-surgery is significantly associated with elevated postoperative blood ammonia levels and HE occurrence; multiple machine learning models indicate *P. vulgatus* can serve as an important microbial marker for predicting postoperative complications.[200] In HBV-related cirrhosis patients, the occurrence of postoperative HE in patients receiving transjugular intrahepatic portosystemic shunt treatment is associated with an increase in non-probiotic bacteria and the appearance of *Morganella* in the gut flora.[201] For SBP, gut flora features can also provide early warning. SBP patients have significantly reduced gut flora richness and increased diversity, dominated by pathogens like *Klebsiella pneumoniae* and *Serratia marcescens*, whereas non-SBP decompensated cirrhosis patients are dominated by beneficial bacteria like *Faecalibacterium prausnitzii* and *Lactobacillus reuteri*. A model based on five optimal microbial markers discriminated SBP from decompensated cirrhosis with an AUC of 0.8383.[202] Additionally, serum metabolites and gut flora features at admission are associated with the occurrence of nosocomial infections in cirrhosis patients; combining metabolites with clinical variables improved the AUC for predicting nosocomial infection from 0.74 to 0.77.[203] In cirrhosis patients, during colonization by toxigenic *Clostridioides difficile* (pre-CDI), gut microbial richness and diversity significantly decreased, relative abundance of opportunistic pathogen *Enterococcus* increased, while beneficial commensals like *Faecalibacterium* decreased; a model based on three biomarkers distinguished pre-CDI from non-colonized controls with an AUC as high as 0.81.[204]

Challenges and future directions toward clinical translation

Although the gut microbiome shows immense potential as biomarkers for liver disease, its move toward large-scale clinical application still faces multiple challenges such as standardization, causality, and personalization. Current research is mostly based on observational associations, urgently requiring prospective large-cohort studies to validate the robustness of markers. For example, although many diagnostic models perform excellently in discovery cohorts, validation in independent populations, different regions, and races still needs strengthening.[180,181] Standardization of microbial testing (including sample collection, DNA extraction, sequencing platforms, and bioinformatics pipelines) is a prerequisite for result reproducibility and comparability. Furthermore, distinguishing whether microbial changes are the cause or result of liver disease is crucial for the disease specificity of markers. Analysis tools like Mendelian randomization help infer causality; for instance, studies confirmed that Lachnospiraceae increases cirrhosis risk, while Lactobacillaceae, *Butyricicoccus*, and *Lactobacillus* have protective effects.[205] Future development directions lie in developing composite biomarker panels integrating multi-omics data. For example, combining gut microbial features with serum metabolites (such as bile acids and tryptophan metabolites), clinical indicators (such as liver function and fibrosis scores), and even imaging features is expected to build more powerful prediction models. One study combined gut flora and serum metabolites, achieving a diagnostic accuracy (AUC) of 0.93 for MAFLD and its severity.[206] Another study found that multi-kingdom markers integrating oral-gut-tumor microbiota can greatly improve early detection efficiency for HCC.[18] In MAFLD patients, the combination of phenomics and metabolomics had the highest accuracy for MAFLD diagnosis (AUC = 0.97), while the combination of phenomics and metagenomics had the highest accuracy for predicting MAFLD hepatic steatosis progression (AUC = 0.94).[207] In HCC patients, a diagnostic combination of gut flora (such as *Odoribacter splanchnicus* and *Ruminococcus bicirculans*) and serum metabolites (such as ouabain and taurochenodeoxycholic acid) had diagnostic value superior to α-fetoprotein.[208] Ultimately, locking in key microbial or genetic markers through low-cost, rapid detection technologies (such as qPCR and microarrays) and conducting interventional clinical trials to verify their value in guiding treatment decisions and improving patient outcomes is the only way for microbiome markers to move from the laboratory to the clinical consultation room.

Ecological niche remodeling strategy i: evidence and limitations of FMT, probiotics, and prebiotics

Efficacy and challenges of FMT in liver disease treatment

As the most direct “niche remodeling” strategy, FMT has shown therapeutic potential in various liver diseases by holistically importing a healthy donor’s gut microbial ecosystem, yet its efficacy coexists with challenges (Fig. 3). In patients with SAH, a study showed that the 90-day survival rate of patients receiving healthy donor FMT treatment was as high as 87.5%, significantly better than patients receiving only corticosteroid treatment (64.3%) or high-dose probiotic infusion (55%), and FMT significantly im-

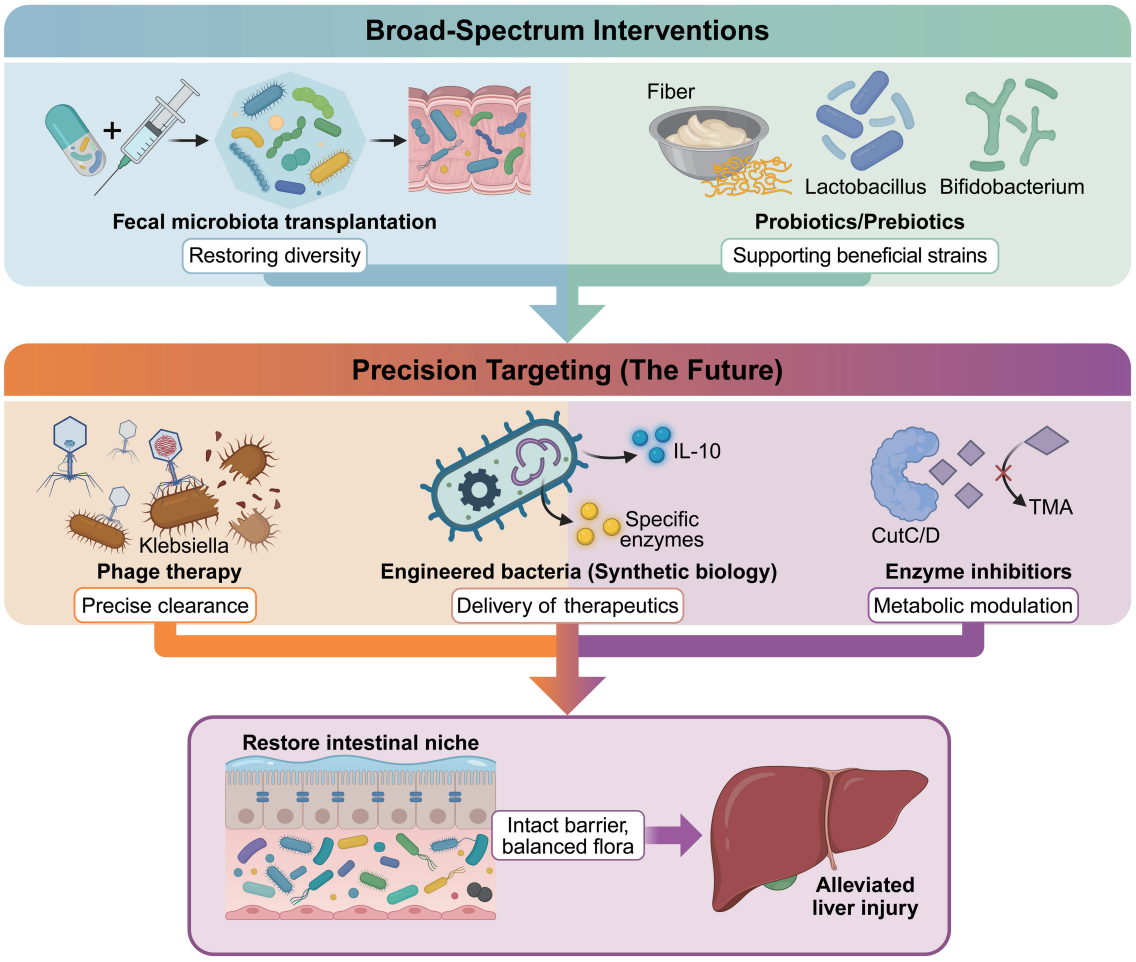

Fig. 3. Strategies for ecological niche remodeling: From broad-spectrum to precision targeting. This figure summarizes therapeutic approaches for modulating the intestinal niche. The upper section presents broad-spectrum interventions, including fecal microbiota transplantation to restore diversity and the use of probiotics and prebiotics to support beneficial strains. The middle section highlights future precision targeting strategies, such as phage therapy for the precise clearance of pathogens like Klebsiella, engineered bacteria for the synthetic delivery of therapeutic molecules (e.g., IL-10), and microbial enzyme inhibitors targeting pathways like CutC/D to reduce harmful metabolites such as TMA/TMAO. The bottom section depicts the therapeutic goal: a restored intestinal niche with an intact barrier and balanced flora, leading to alleviated liver injury. This figure was created with BioRender (https://biorender.com/). IL-10, interleukin-10; TMA, trimethylamine; TMAO, trimethylamine N-oxide.

proved gut flora dysbiosis, increased beneficial flora, and reduced pathogenic bacteria.[19] In cirrhosis patients, FMT also demonstrates potential for improving the gut barrier and clinical outcomes. For example, a study using vegan donor FMT for cirrhosis patients found it induced significant changes in gut flora (such as *Eubacterium siraeum* and *Blautia wexlerae*) and plasma metabolites (such as phenylacetylcarnitine) and affected hepatic DNA methylation profiles, suggesting FMT may act through multi-omics-level meta-organism pathways.[209] In an acute liver failure mouse model, FMT significantly improved liver injury and inflammation by regulating gut flora composition and hepatic metabolites.[210] However, the efficacy of FMT is not universally consistent and faces significant challenges. A 12-week randomized controlled trial in patients with MASLD found that, compared to autologous FMT, allogenic FMT did not significantly reduce liver fat fraction or improve glucose tolerance; although patient fecal microbiota composition diverged, no microbial signatures clearly associated with treatment response were found, and colonization of donor flora presented donor specificity rather than efficacy specificity.[14] In an ALD rat model, oral FMT effectively reversed alcohol-induced liver injury by improving gut flora disorders and metabolic patterns.[211] In a cirrhosis portal hypertension model, FMT improved visceral circulation and vascular reactivity, indicating microbial intervention may affect portal hypertension by regulating visceral circulation.[212] In SAH patients, compared to corticosteroid treatment, FMT treatment altered the abundance of specific gut bacteria associated with alcohol relapse, such as *Pedobacter* genus and *Streptophyta* species, and non-relapsers had elevated levels of SCFA-producing bacterial taxa.[213] In cirrhosis patients, FMT improved intestinal mucosal mitochondrial oxidative phosphorylation function, thereby influencing the gut barrier.[214] In Budd-Chiari syndrome patients, mice transplanted with patient flora developed liver injury and gut flora dysbiosis, indicating that flora dysbiosis may lead to the disease through immune dysregulation.[215] In MAFLD patients, WMT improved hepatic fat deposition by regulating tongue coating microbial structure.[216] In an intrahepatic cholestasis of pregnancy mouse model, microbiota transplantation from patients induced the intrahepatic cholestasis of pregnancy phenotype, while Yinchenhao

Tang intervention partially restored flora balance.[217] In liver fibrosis macaques, significant differences existed in gut flora α- and β-diversity compared to normal macaques, with beneficial bacteria like *Lactobacillus* significantly reduced.[218] In Wilson's disease mice, healthy microbiota transplantation increased *Lactobacillus* abundance, reduced hepatic copper concentration, and alleviated liver injury.[219] In HCC mouse models, FMT from healthy donors alleviated intrahepatic metastasis promoted by dysbiotic flora.[220] In an NAFLD mouse model, FMT from FGF21-treated mice produced improvement effects similar to FGF21 treatment.[221] In an NAFLD mouse model, FMT from silymarin-treated mice confirmed that changes in gut flora and their metabolites are the cause of NAFLD improvement.[222] In a MAFLD mouse model, FMT from patients supplemented with hydroxytyrosol improved the Western diet-induced MAFLD phenotype.[223] In an ALD mouse model, FMT from urolithin A-treated mice achieved protective effects comparable to direct treatment.[224] In drug-induced liver injury mice, FMT from *Codonopsis pilosula* polysaccharide-intervened mice alleviated liver injury.[225] In APAP-induced liver injury mice, reconstruction of gut flora structure from *Broussonetia papyrifera* polysaccharide-treated mice effectively alleviated liver injury symptoms.[226] In pseudo-germ-free MAFLD rats, the efficacy of receiving fecal microbiota from rats treated with Shenling Jianpiwei Granule was drastically reduced, indicating that the anti-MAFLD effect of this formula is largely gut microbiota-dependent.[227] In antibiotic-induced pseudo-germ-free MAFLD rats, the efficacy of hawthorn ethanol extract was affected, revealing its action mediated by the gut microbiota.[228] In CCl_4-induced liver fibrosis mice, FMT from metformin-treated mice alleviated liver fibrosis in recipient mice.[229] In an NAFLD mouse model, FMT from mice treated with Ginsenoside Rg5 also demonstrated similar NAFLD improvement effects.[230] In an NAFLD mouse model, FMT from mice treated with Tangshen formula confirmed the key role of gut flora in its efficacy.[231] In an NAFLD mouse model, FMT from mice treated with Qushi Huayu decoction confirmed that its induced gut flora remodeling partially mediated the efficacy.[232] In mice with antibiotic-cleared gut flora, vine tea extract lost its hepatoprotective effect, indicating its efficacy depends on the gut microbiota.[233] However, in drug-induced liver injury mice, transplantation of fecal microbiota suspension from Sangyu Granule-treated mice did not produce a therapeutic effect.[234] This highlights the core bottlenecks currently facing FMT: strong donor dependence, lack of standardization in preparation processes, complex and obscure mechanisms of action, and significant individual differences in efficacy. Compounding these clinical challenges is a significant translational barrier: current mechanistic studies rely heavily on commercialized cell lines and rodent models. The inherent discrepancies in immune-metabolic baselines, gastrointestinal anatomy, and foundational gut microbiota composition between these preclinical models and humans partially explain the inconsistent efficacies frequently observed in clinical trials.[235,236]

Therefore, although the concept of FMT is highly attractive, its large-scale clinical application still needs to resolve key issues such as donor screening, preparation standardization, elucidation of mechanisms, and long-term safety assessment (Table 2).[209–225,227,229–232,237–288] In direct response to the specific bottlenecks regarding preparation and safety, WMT has recently emerged as a standardized clinical evolution of traditional FMT. By employing automated purification systems and rigorous consensus-based protocols, WMT explicitly addresses the demands for preparation standardization and enhanced safety. This methodology effectively eliminates pro-inflammatory mediators and undigested particles present in crude feces, thereby significantly reducing adverse events and improving clinical reproducibility. Consequently, WMT paves a promising pathway toward the large-scale, safe clinical application of microbiome interventions.[289,290]

Evidence and strain specificity of probiotics in improving liver disease phenotypes

Probiotics regulate gut microecology by supplementing specific live beneficial bacteria and have accumulated extensive preclinical and partial clinical evidence in liver disease management, but their efficacy is highly dependent on strain specificity. In the field of NAFLD, multiple studies have confirmed the benefits of specific probiotic strains. For example, supplementation with *Bifidobacterium breve* CM02-09T can alleviate liver injury and fat accumulation in high-fat diet mice by reducing the Firmicutes/Bacteroidetes ratio, increasing beneficial bacteria abundance, and enhancing lipid metabolism function.[239] *Lactobacillus plantarum* ZGHY combined with entecavir treatment for 24 weeks in chronic hepatitis B liver fibrosis patients effectively increased gut flora diversity, reduced potential pathogens (such as *Klebsiella* and *Enterococcus*), and simultaneously increased beneficial bacteria like *Bacteroides*, showing a positive role in assisting flora regulation.[240] In ALD, the novel exopolysaccharide BVP1 from *Lactobacillus plantarum* CGMCC 24752 significantly improved hepatic steatosis and inflammation in mouse models by remodeling gut flora and fecal metabolite profiles and upregulating hepatocyte lipid degradation gene expression.[241] *Lactobacillus paracasei* N1115 supplementation for 12 weeks significantly increased gut microbial diversity in hepatitis B cirrhosis patients, improved liver function, and reduced inflammatory factor levels.[242] In a T2DM+HCC mouse model, *Lactobacillus brevis* intervention improved blood glucose and insulin resistance and delayed disease progression.[243] In an NAFLD rat model, ZW3 probiotic improved liver injury and inflammation by regulating gut flora and inhibiting the TLR4-MyD88/JNK pathway.[244] In a MAFLD mouse model, EcNI and EcNA intervention improved the recovery process, reducing liver fat and plasma cholesterol.[245] In an NAFLD mouse model, T3L probiotic improved obesity-induced NAFLD by regulating gut–liver axis pathways.[246] In an ALD rat model, fermented milk containing *Bifidobacterium animalis* subsp. *lactis* Probio-M8 effectively maintained gut flora stability and alleviated liver injury.[247] In NAFLD children, probiotic intervention regulated gut flora and maintained gut barrier integrity, providing a potential strategy for treatment.[248] In a MAFLD rat model, *Bifidobacterium* combined with rosuvastatin treatment regulated gut flora, promoted gastrointestinal emptying, and improved liver pathology and function better than monotherapy.[249] In NAFLD patients, *Clostridium butyricum* capsules combined with rosuvastatin treatment improved efficacy and ameliorated gut flora imbalance.[250] In an ALD mouse model, pretreatment with various lactic acid bacteria improved liver injury and gut flora dysbiosis, with JN-8 showing superior effects in improving hepatic antioxidant capacity.[251] Screened from 498 lactic acid bacteria strains, *Lactobacillus brevis* SR52-2 and *Lactobacillus delbrueckii* subsp. *bulgaricus* Q80 inhibited HBeAg and HBsAg expression *in vitro* and improved the gut microenvironment in a liver cancer group.[252] *Lacticaseibacillus paracasei* HP-B1337 showed good probiotic properties and was confirmed to effectively alleviate fatty liver disease in a mouse model.[253] In an obese mouse model, *Lactobacillus plantarum* 1-2-3 alleviated obesity, glycolipid metabolism abnormalities, and liver injury by regulating the gut–liver axis.[254] In an obese mouse model, *Lactobacillus plantarum* NCUH001046 and *Lactobacillus fermentum* alleviated obesity development by regulating the hepatic AMPK signaling pathway and

Table 2. Ecological niche remodeling strategies: Mechanisms, evidence, and limitations

Therapeutic strategy	Core mechanism	Key evidence & efficacy	Current limitations & challenges
Fecal microbiota transplantation (FMT)[209–225,227,229–232,237,238]	Holistically imports a healthy donor ecosystem to restore diversity and barrier function	High 90-day survival (87.5%) in severe alcoholic hepatitis. Improves portal hypertension and cognition in cirrhosis	Strong donor dependence; efficacy is not universally consistent (e.g., in MASLD); risk of pathogen transmission; lack of standardization
Probiotics[239–258]	Supplementing specific live beneficial bacteria to regulate microecology and immune response	*B. breve* reduces fat in NAFLD mice. *L. plantarum* combined with antivirals improves fibrosis	Efficacy is strain-specific. Some strains (e.g., *E. faecalis*) or high doses in severe disease may be harmful or ineffective
Prebiotics & synbiotics[259–276]	Dietary fibers act as substrates for beneficial bacteria to produce SCFAs; Synbiotics combine this with probiotics	Resistant starch reduces liver triglycerides by ~9% in NAFLD. Synbiotics reduce hepatic steatosis and inflammation	Effects depend on the patient's baseline flora (responders vs. non-responders); without weight loss, prebiotic efficacy may be limited
Phage therapy[277–279]	Specifically lyses target pathogenic bacteria without disrupting the broader community	Effectively targets alcohol-producing *Klebsiella pneumoniae* to alleviate steatohepatitis in mice	Narrow host range; potential for bacterial resistance; challenges in delivery to target sites
Microbial enzyme inhibitors[280–283]	Blocks production of harmful metabolites without killing bacteria	CutC/D inhibitors reduce TMAO generation. BSH regulation alters bile acid pools to improve NAFLD	Requires high specificity to avoid affecting host enzymes; ensuring effective intestinal concentration
Engineered bacteria[284–286]	Synthetic biology modification to deliver therapeutic molecules (e.g., IL-10, metabolites)	*Sporosalibacterium* pathways identified for insulin-sensitizing metabolites. Potential for tumor microenvironment modulation	Biosafety concerns (gene transfer, stability); ethical and regulatory hurdles regarding "live drugs"
Integrated/Combined therapy[287,288]	Synergizes microbiota modulation with standard care (drugs, surgery)	Improves antiviral efficacy (HBV). Sensitizes HCC to immunotherapy (overcoming resistance)	Requires precision stratification (multi-omics) to identify optimal combinations; lack of large-scale RCTs

BSH, bile salt hydrolase; FMT, fecal microbiota transplantation; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; IL-10, interleukin-10; MASLD, metabolic dysfunction-associated steatotic liver disease; NAFLD, nonalcoholic fatty liver disease; RCTs, randomized controlled trials; SCFAs, short-chain fatty acids; TMAO, trimethylamine N-oxide.

gut flora via the microbe-fat-liver axis.[255] In an NAFLD mouse model, supplementation with Prohep probiotic mixture alleviated hepatic steatosis and prevented the progression from MAFLD to MASH.[256] In an NAFLD mouse model, *Faecalibacterium prausnitzii* strains LC49 and LB8 had significant anti-NAFLD and flora-regulating effects.[257] However, the efficacy of probiotics is not always positive. In SAH patients, high-dose probiotic infusion (containing four *Lactobacillus* and four *Bifidobacterium* species) had a 90-day survival rate (55%) even lower than corticosteroids and failed to significantly improve bacterial α-diversity, instead leading to an increase in pathogenic bacteria (such as *Bilophila* and *Roseburia*) and harmful expansion of fungal communities.[19] Supplementation with commensal *Bacteroides fragilis* exacerbated NAFLD progression in high-fat diet mice, increasing hepatic lipid accumulation.[20] In children with obesity and NAFLD, isolated *Enterococcus faecalis* B6 and its metabolite tyramine significantly exacerbated NAFLD symptoms in mice.[258] This warns us that probiotic interventions may produce vastly different or even harmful results depending on the disease background, strain combination, dosage, and route of administration. Therefore, future probiotic therapies must be based on a deep understanding of specific strain functions, host-microbe interactions, and the disease microenvironment, moving toward "strain-level" precision application.

Prebiotics and synbiotics modulating the gut–liver axis via dietary fibers

Prebiotics (mainly non-digestible dietary fibers) and synbiotics (combinations of probiotics and prebiotics) indirectly remodel gut flora by providing selective fermentation substrates for beneficial host bacteria, representing a more sustainable and safer niche modulation strategy. Resistant starch, as a classic prebiotic, absolutely reduced intrahepatic triglyceride content by 9.08% after 12 weeks of intervention in NAFLD patients; its mechanism involves regulating gut flora (such as *Bacteroides stercoris*) and serum branched-chain amino acids, and causality was confirmed via mouse FMT.[259] Synbiotic intervention also shows promise. A study on metabolically healthy men found that 12-week synbiotic intervention significantly reduced serum alanine aminotransferase levels, with a 20.70% reduction in the subgroup with elevated body fat percentage, and significant changes in gut microbiome composition occurred in this subgroup, suggesting synbiotics may exert hepatoprotective effects on specific populations by regulating gut flora.[260] Another randomized controlled trial in MASLD patients showed that 12-week synbiotic intervention significantly reduced hepatic steatosis and enriched beneficial bacteria such as *Lactobacillus*, *Bifidobacterium*, and *Faecalibacterium* in the gut, while reducing *Ruminococcus* and *Enterobacter*.[261] In an obese mouse model, synbiotic treatment containing *Lactobacillus acidophilus*, *Bifidobacterium infantis*, and konjac glucomannan oligosaccharides improved obesity, fatty liver, and gut flora dysbiosis.[262] Fructooligosaccharide treatment alleviated metabolic changes and hepatic steatosis in an NAFLD mouse model and remodeled gut flora structure.[263] Flaxseed meal intervention for 12 weeks improved hepatic lipid deposition, body composition, and lipid metabolism

in NAFLD patients, and increased beneficial bacteria while reducing harmful bacteria by regulating gut flora.[264] In long-term alcohol drinkers, a 60-day intervention regulated flora imbalance, increased beneficial bacteria abundance, and reduced opportunistic pathogens.[265] In NAFLD patients, sulforaphane intervention increased GLP-1 levels, revealing a new pathway for alleviating insulin resistance through the gut flora-SCFA-GPR41/43-GLP1 axis.[266] In MAFLD patients, butyrate supplementation had potential benefits for specific patient subgroups.[267] In NAFLD patients, curcumin intervention reduced liver fat content, an effect associated with regulating gut flora-dependent bile acid metabolism and activating the TGR5 pathway.[268] In type 2 diabetes patients with nonalcoholic fatty liver, exenatide combined with metformin treatment regulated gut flora while improving metabolism.[269] In NAFLD patients, a Mediterranean diet combined with aerobic exercise intervention had a synergistic effect on gut microbiota composition.[270] In NAFLD patients, the Dietary Index for Gut Microbiota was negatively correlated with NAFLD prevalence.[271] In MAFLD patients, daily consumption of 400 g "Navelina" oranges for 28 days identified specific flora and volatile organic compound combinations associated with MAFLD.[272] In NAFLD patients, a freshwater fish diet significantly reduced hepatic steatosis more than a diet alternating freshwater fish with red meat, and increased the enrichment of fecal SCFAs and unconjugated bile acids.[273] In cirrhosis patients, intermittently replacing meat with vegetarian meals may help reduce ammonia production.[274] However, the efficacy of prebiotics/synbiotics also has limitations and controversies. A study using inulin-type fructans to treat NAFLD patients for 12 weeks found that, although it increased fecal *Bifidobacterium* content, it failed to significantly reduce liver fat content or improve metabolic and inflammatory mediators, indicating that without weight loss, prebiotic intervention alone may be insufficient to improve NAFLD.[275] In MAFLD patients, the beneficial effects of fish oil combined with vitamin D3 supplementation on nonalcoholic fatty liver may be partially attributed to its regulation of gut microbiota and fecal metabolites.[276] In NAFLD patients, no significant association was observed between dietary n-6/n-3 fatty acid ratio and gut flora composition or disease severity.[172] Additionally, the effect of prebiotics is highly dependent on the individual's original gut flora structure, and the quantity and type of fermentation products (such as SCFAs) generated vary from person to person, which may lead to significant individual differences in efficacy. Therefore, developing personalized prebiotic/synbiotic formulas based on individual microbiome characteristics is a key direction for improving their efficacy and reliability.

Prebiotic-like components in traditional herbs and natural products

Many traditional herbs and natural food extracts are rich in polysaccharides, polyphenols, and other components. Although not prebiotics by traditional definition, these substances can exert significant "prebiotic-like" effects by regulating gut flora, providing rich resources for liver disease management. For example, hawthorn fruit polysaccharides alleviate NAFLD in mice by improving gut flora dysbiosis (affecting Lachnospiraceae and *Dubosiella*), increasing intestinal acetate levels, and subsequently correcting hepatic amino acid, lipid, and vitamin metabolic disorders; *in vitro* experiments confirmed no direct effect, highlighting the mechanism mediated by the gut–liver axis.[291] *In vitro* fermentation of kudzu starch specifically increased the abundance of *Lactobacillus*, *Bifidobacterium*, and *Turicibacter*, reduced *Desulfovibrio*, and alleviated inflammation and hepatic steatosis in an NAFLD mouse model, supporting its use as a functional prebiotic.[292] Fuzhuan brick tea intervention significantly regulated gut flora (increasing *Blautia* and *Fusicatenibacter*, inhibiting *Prevotella_9*), affected SCFA, bile acid, and LPS levels, and improved hepatic steatosis and inflammation in NAFLD mice dependent on gut flora.[293] Lingguizhugan decoction improved NAFLD by remodeling gut flora structure and metabolism, with flora-derived SCFAs and bile acids as potential mediators.[294] Qushi Huayu formula exerted therapeutic effects by regulating specific gut flora and their metabolites.[295] Honeysuckle-Cassia seed extract, after co-fermentation, had increased bioactive component content in its mixed bacterial fermentation broth and improved liver injury, oxidative stress, and gut flora dysbiosis in a mouse ALD model.[296] Shenling Jianpiwei Granule improved MAFLD by restoring gut flora dysbiosis, and most of its anti-MAFLD effect was gut flora-dependent.[227] Baoganning Decoction alleviated liver fibrosis by enriching beneficial bacteria and reducing pathogenic bacteria to remodel gut flora, while simultaneously regulating bile acid homeostasis.[297] Saikosaponin a improved fatty liver in laying hens by regulating the gut flora-bile acid-intestinal FXR axis pathway.[298] Berberine improved fatty liver hemorrhagic syndrome in laying hens by remodeling gut flora.[299] *Swertia* alleviated liver inflammation and injury by regulating oxidative stress and restoring gut flora.[300] Jianggan Jiangzhi pill had good effects on treating NAFLD, and its mechanism may be closely related to improving gut flora dysbiosis.[301] Glycyrrhizic acid's effect in improving NAFLD may be related to improving gut flora dysbiosis.[302] Ganfule capsule exerted anti-liver cancer effects via the microbe-metabolic axis.[303] THSWD exerted anti-liver cancer effects via the gut flora-metabolite-lysosomal autophagy axis.[304] Zhizi Chi Decoction alleviated liver inflammation and injury by regulating the microbe-gut–liver axis via pleiotropic mechanisms.[305] These natural products usually contain diverse active ingredients, which may regulate microbe-host interactions through multi-target and multi-pathway synergistic effects. However, their complex composition, difficult quality control, and unclear mechanisms of action are bottlenecks restricting their standardization and widespread application. Future research needs to combine metabolomics, metagenomics, and culturomics technologies to elucidate their key active ingredients, specific microbial targets of action, and downstream host signaling pathways, thereby elevating them from empirical application to the level of precision intervention.

Ecological niche remodeling strategy ii: precision targeting—from specific strains, phages to microbial enzyme inhibitors

Isolation and application of specific beneficial strains

Going beyond broad-spectrum probiotics, isolating and applying specific bacterial strains with distinct hepatoprotective functions represents the frontier of precision niche remodeling. Multiple studies have successfully identified single strains with therapeutic potential. For example, a *Bacteroides eggerthii* strain isolated from healthy human feces significantly attenuated hepatic lipid peroxidation and lobular inflammation in a MASLD mouse model by improving gut flora disorders; although its improvement of hyperlipidemia and steatosis was limited, it suggests its potential as a biotherapeutic candidate.[306] In an ALD model, a *Bacteroides acidifaciens* strain isolated from the gut of gentamicin-treated mice was confirmed to reduce CD95/CD95L-mediated hepatocyte apoptosis by inhibiting hepatocyte surface CD95 expression, thereby exerting protective effects against both Concanavalin A-

and alcohol-induced liver injury.[307] In the field of NAFLD, the abundance of *B. theta* is positively correlated with the remission of metabolic syndrome; administering *B. theta* to high-fat diet mice regulated gut flora composition, increased gut–liver folate levels and hepatic polyunsaturated fatty acid ratio, thereby preventing hepatic steatohepatitis and liver injury.[308] Furthermore, *Prevotella plebeius* isolated from healthy donor feces is significantly reduced in abundance in cirrhosis patients; supplementing this strain significantly improved phenotypes and biochemical indicators in flora-depleted cirrhosis models, exerting multifunctional biotherapeutic effects by downregulating the expression of genes related to liver inflammation, fibrosis, and hepatotoxicity.[309] These studies provide a solid experimental basis for developing "live biotherapeutics" based on specific, culturable beneficial strains. Notably, in NAFLD patients, the abundance of *Adlercreutzia equolifaciens* decreases with disease progression and disappears in the end stage; its anti-inflammatory properties suggest that supplementing this bacterium may be a promising live biotherapeutic strategy.[310] Similarly, in MASLD patients, the relative abundance of *Bacteroides dorei* is negatively correlated with disease severity; its cell-free supernatant improved hepatic lipid accumulation and inflammation in animal models by increasing β-oxidation gene expression and inhibiting inflammatory responses, indicating it holds promise as a candidate for novel microbiome-based therapeutic strategies.[311]

Precision clearance of specific pathogens by phage therapy

Phage therapy, by specifically lysing target bacteria, offers a highly promising tool for precise deletion of pathogenic bacteria in the gut, avoiding the overall destruction of flora caused by broad-spectrum antibiotics. In NAFLD, high alcohol-producing *Klebsiella pneumoniae* was identified as a key pathogen. Phage therapy targeting this bacterium effectively alleviated steatohepatitis, improved liver function, and reduced the expression of inflammatory cytokines and lipogenic genes in mouse models, without causing significant pathological changes in liver/kidney function or gut flora composition, proving its efficacy and safety.[277] In sensitizing HCC to immunotherapy, phage therapy also shows potential. Oncolytic virus VSVδ51 treatment causes gut flora dysbiosis, reducing commensal *Lactobacillus*, thereby weakening efficacy; supplementing *Lactobacillus acidophilus* restored tumor sensitivity to VSVδ51 by restoring the disrupted gut barrier and flora homeostasis, suggesting that targeting specific microbes (such as through phage modulation) may improve the efficacy of oncolytic virus therapies.[278] Additionally, in MASLD patients, gut virome perturbations coexist with bacterial dysbiosis; the expansion of phages targeting typical oral bacteria corresponds to the expansion of their bacterial hosts in the gut, implying the possibility of using phages to regulate cross-kingdom microbial networks.[16] Despite broad prospects, phage therapy still faces challenges, including narrow phage host ranges, potential rapid development of bacterial resistance, and how to safely and effectively deliver phages to target sites in the gut. Future development needs to combine metagenomics to identify key pathogens and develop targeted phage cocktail therapies to achieve precise clearance of specific harmful members in complex flora. For example, in MAFLD and steatohepatitis patients, *Mushu* phage was identified as a key hub species in disease pathogenesis, suggesting it may become a target for precision intervention.[279]

Building upon the concept of precision niche remodeling, CRISPR-armed bacteriophages represent a transformative frontier in microbiome engineering. Unlike conventional lytic phages that obligately kill their bacterial targets and may inadvertently perturb community dynamics, this advanced technology utilizes engineered phages as highly specific delivery vectors for CRISPR-Cas machinery or base editors.[312] This enables in situ targeted silencing or excision of specific virulence factors and detrimental metabolic pathways without killing the host bacterium.[313] By selectively disarming pathogenic functions while preserving the host cell, CRISPR-phage therapy facilitates highly precise therapeutic modulation along the gut–liver axis while strictly maintaining overall microbiome stability and colonization resistance.

Intervention in harmful metabolic pathways by microbial enzyme inhibitors

Developing small molecule inhibitors against specific harmful metabolic enzymes encoded by gut microbes is a strategy for precision intervention at the functional level, aiming to block the production of pathogenic metabolites without directly affecting bacterial survival. TMA lyase (such as CutC/D) is a well-studied target, which converts dietary choline into TMA; TMA is then oxidized in the host liver to TMAO, which is associated with increased risks of fatty liver and cardiovascular disease. Developing CutC/D inhibitors to reduce TMAO generation at the source has shown potential to improve metabolic liver disease in preclinical models.[314] Another key target is microbial BSH. Excessive BSH activity leads to premature deconjugation of conjugated bile acids, affecting bile acid signaling. Studies found that Ginsenoside Re altered bile acid synthesis pathways by regulating microbial genera associated with BSH, thereby improving NAFLD; while antibiotic co-administration counteracted its effect, confirming the microbial dependence of its action.[280] Similarly, nobiletin slowed the progression of MAFLD by increasing the abundance of BSH-producing bacteria, promoting bile acid excretion, and downregulating hepatic FXR signaling.[281] Furthermore, microbial D-lactate generation is also an intervention target. Oral administration of a biocompatible polymer that captures intestinal D-lactate and promotes its fecal excretion significantly improved metabolic phenotypes in obese and MASLD mice.[83] The advantage of these enzyme inhibitor strategies lies in their clear mechanism of action and potential to avoid drastic perturbations to flora structure. However, the challenge lies in ensuring inhibitor specificity (targeting only microbial enzymes without affecting host homologs), achieving effective concentration in the gut, and ensuring long-term safety. For example, in an NAFLD mouse model, the efficacy of obeticholic acid depends on the gut microbiota; its intervention significantly increased the abundance of beneficial bacteria like *Akkermansia muciniphila* and regulated the host bile acid pool, indicating that specific gut microbes mediated the alleviation effect of obeticholic acid by regulating host bile acid metabolism.[282] Similarly, in an NAFLD mouse model, the protective effect of fenofibrate on NAFLD depended on the TFEB-autophagy axis and significantly regulated gut flora composition.[283]

Engineered bacteria and metabolite delivery systems

Utilizing synthetic biology techniques to modify engineered bacteria so they can colonize the gut and continuously produce therapeutic molecules is a revolutionary strategy for precision-targeted therapy. For example, research revealed the pathway by which the common gut commensal *Sporosalibacterium* produces the metabolite 3-phenylpropionic acid, which possesses insulin-sensitizing and antisteatotic activities.[284] This provides a blueprint for engineering this bacterium or other safe strains to stably and efficiently produce 3-phenylpropionic acid or other beneficial metabolites (such as IPA and butyrate). In HCC treatment, the ap-

plication of engineered bacteria also shows promise. Some studies plan to evaluate advanced HCC patients ineffective to immunotherapy receiving FMT from responders or healthy donors via colonoscopy to alter the tumor microenvironment and overcome drug resistance.[285] Although this is not strictly engineered bacteria, it embodies the concept of utilizing microbes as therapeutic vectors or regulatory factors. A further strategy is to design "smart" engineered bacteria capable of sensing disease states (such as specific metabolites or pH changes) and responsively releasing therapeutic proteins (such as anti-inflammatory cytokines and enzyme inhibitors). For example, engineered bacteria can be designed to locally deliver IL-10 or TGF-β in the intestinal inflammatory environment to regulate hepatic immunity. However, engineered bacterial therapy faces severe biosafety, ethical, and regulatory challenges, including the stability of engineered bacteria *in vivo*, risks of horizontal gene transfer, immunogenicity, and controllable clearance from the body. Nevertheless, with advances in synthetic biology and microbiomics, engineered bacteria as "live drugs" have immeasurable potential in precisely regulating the gut–liver axis. For instance, the gut microbe *Rikenella microfusus* promotes intestinal absorption of the isoflavone biochanin A through its β-galactosidase activity, thereby alleviating acute liver injury caused by acetaminophen overdose, revealing a new mechanism by which microbiome composition affects the severity of acute liver injury by regulating isoflavone absorption.[286]

Future prospects of multi-target precision combination strategies

Future precision niche remodeling will tend toward multi-target, personalized combination strategies to address complex microbial disturbances in liver diseases. This includes the organic integration of the different strategies mentioned above. For example, first using a phage cocktail to precisely clear identified key pathogens (such as ethanol-producing *Klebsiella pneumoniae*), followed by supplementing combinations of screened probiotic strains capable of producing specific beneficial metabolites (such as butyrate and indole-propionic acid) to fill the ecological niche and restore function. Concurrently, small molecule inhibitors targeting remaining harmful metabolic pathways (such as CutC/D inhibitors) can be administered. This combination of "subtraction" (clearing harmful bacteria) + "addition" (supplementing beneficial bacteria/functions) + "regulation" (inhibiting harmful functions) is expected to rebuild a healthy gut ecological niche more comprehensively and durably. Realizing this vision depends on advances in precision diagnostic technologies. It is necessary to integrate multi-omics data such as gut metagenomics, metatranscriptomics, and metabolomics, combined with machine learning, to map unique "microbe-metabolic dysfunction landscapes" for each patient, identifying key pathogens, defective beneficial bacteria, and dysregulated core metabolic pathways. On this basis, true individualized precision intervention plans can be formulated. For instance, for a MASLD patient characterized by enrichment of a specific pathogen and lack of SCFAs, the treatment plan might include phages targeting that pathogen, supplementation with specific butyrate-producing strains, and dietary guidance rich in fermentable fibers. This paradigm shift from "broad-spectrum" to "precision," and from "flora composition" to "functional output," will elevate ecological niche management of liver diseases to a completely new height, laying the foundation for achieving efficient and safe "targeted gut microbial niche" therapy. For example, in HCC patients, gut microbe-associated feature scores showed cancer-type-specific genomic alterations and immune microenvironment feature associations, and can serve as potential clinical biomarkers for immunotherapy responsiveness and recurrence in multiple malignancies, providing a comprehensive framework for quantifying microbe-driven transcriptional activity and its clinical significance in cancer.[287] Additionally, in a NASH mouse model, combined AFO-202 and N-163 treatment significantly increased gut microbial diversity, maximized Bacteroidetes abundance, and reduced Firmicutes abundance, exhibiting anticancer activity, suggesting the potential of combined intervention.[288]

Integrated intervention: Synergizing microbiota modulation with existing therapies

Synergistic potentiation of microbiota modulation and antiviral therapy

The synergistic effect of gut microbiota modulation and antiviral therapy for HBV has been preliminarily validated, with mechanisms involving improved immune response and restoration of metabolic homeostasis (Fig. 4). Research found that a gut flora profile dominated by *Bacteroides* is associated with a higher probability of undetectable plasma HBV-DNA, and patients in this flora cluster have higher plasma ursodeoxycholic acid levels and secondary bile acid biotransformation activity, suggesting specific flora structures may enhance antiviral efficacy through metabolite axes.[195] In terms of clinical intervention, Jianpi Shugan formula combined with lifestyle intervention for 12 weeks in NAFLD patients significantly improved liver function, liver stiffness, and glucolipid metabolism compared to lifestyle intervention alone; its efficacy was associated with upregulating beneficial genera like *Coprococcus*, *Lachnospiraceae_NK4A136 group*, and *Ruminococcus*, revealing the potential of traditional Chinese medicine to treat NAFLD by regulating flora.[315] Notably, although tenofovir disoproxil fumarate treatment can significantly alter the gut flora of HBV-infected individuals, it failed to fully restore it to a healthy state, and serum inflammatory cytokine concentrations did not improve significantly, suggesting that treatment duration may affect flora recovery and inflammation remission.[316] In the field of HCV infection, after achieving viral clearance with direct-acting antivirals, some studies observed an increasing trend in gut flora α-diversity and a decreasing trend in potential pathogens (such as Enterobacteriaceae); this microbial improvement was more pronounced in patients without cirrhosis, indicating that viral eradication and partial recovery of gut microbiota may promote each other.[317] However, some studies also pointed out that chronic hepatitis C patients did not show significant gut flora dysbiosis, and curing HCV infection via direct-acting antivirals was not associated with significant changes in the gut microbiome.[318] In patients achieving sustained virologic response for HCV, the β-diversity of mucosa-associated microbiota, especially in the ascending colon, was associated with liver fibrosis progression, and multiple SCFA-producing genera were reduced in the ascending colon of cirrhosis patients.[319] These evidences collectively support the sequential or combined application of microbial modulation strategies such as probiotics, prebiotics, or traditional Chinese medicine with antiviral drugs to optimize viral clearance, alleviate liver inflammation, and improve long-term prognosis.

Microbiota modulation sensitizing HCC immunotherapy

The gut microbiota is a key regulator determining the response of HCC patients to ICI therapy, and flora-based intervention strategies are becoming new avenues to overcome immunotherapy resistance. Clinical observations found that HCC patients with

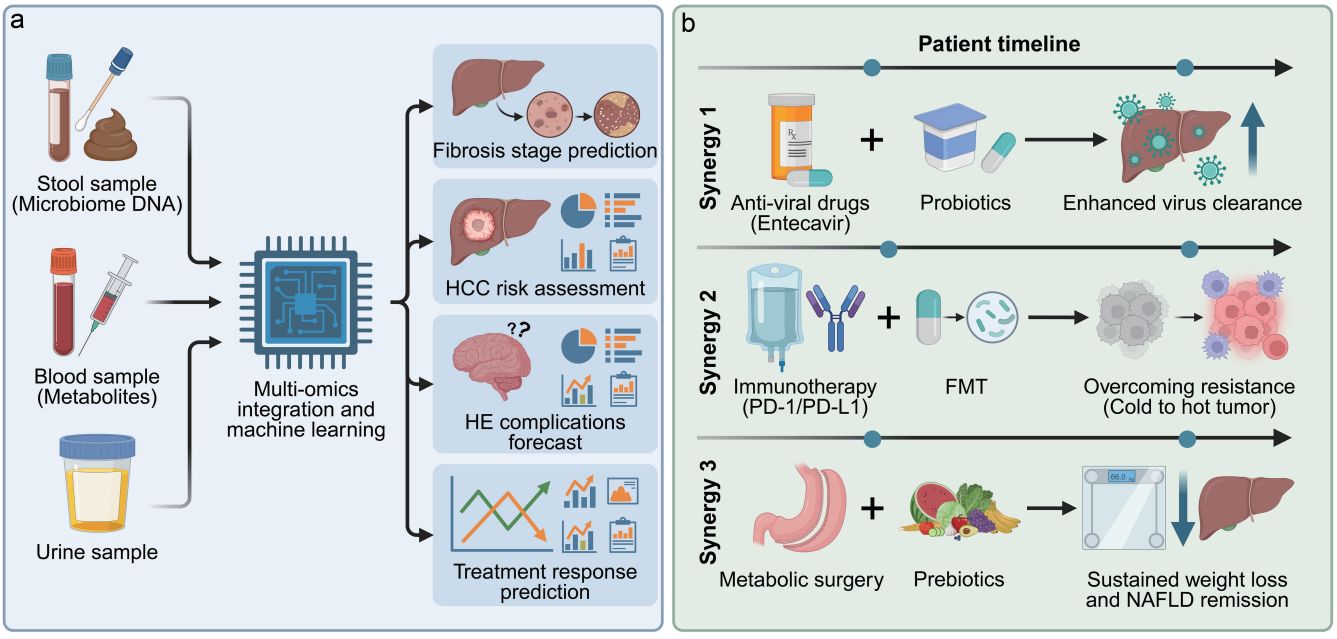

Fig. 4. Clinical translation: Microbiome as biomarkers and integrated therapy. This figure outlines the translational potential of the microbiome in liver disease management. Panel a demonstrates the use of non-invasive biomarkers derived from stool (microbiome DNA), blood (metabolites), and urine, integrated via multi-omics and machine learning to predict fibrosis stages, assess HCC risk, forecast complications like HE, and predict treatment responses. Panel b illustrates integrated intervention strategies that synergize microbiota modulation with standard therapies, including combining antivirals with probiotics to enhance viral clearance, using FMT to sensitize tumors to immunotherapy by overcoming resistance, and pairing metabolic surgery with prebiotics to sustain weight loss and NAFLD remission. This figure was created with BioRender (https://biorender.com/). FMT, fecal microbiota transplantation; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; NAFLD, nonalcoholic fatty liver disease; PD-1, programmed cell death 1; PD-L1, programmed death-ligand 1.

higher baseline gut flora α-diversity respond better to ICI therapy, and classifiers based on serum metabolites perform excellently in predicting potential beneficiaries of immunotherapy, providing a basis for patient stratification via microbial features before treatment.[194] Mechanistically, specific beneficial flora can shape a favorable tumor immune microenvironment. For example, in HCC mouse models, stigmasterol remodels gut flora, increases *Lactobacillus* abundance, leads to a decrease in the proportion of Tregs in the tumor microenvironment, and simultaneously increases the proportion of IFN-γ^+ $CD8^+$ T cells with killing function, thereby enhancing antitumor immunity.[98] Clinical translational studies are underway; for instance, trials plan to evaluate advanced HCC patients ineffective to ICI receiving FMT from treatment responders or healthy donors via colonoscopy, aiming to alter the tumor microenvironment and overcome resistance.[285] Additionally, traditional Chinese medicine also shows potential in sensitizing immunotherapy via flora modulation. Jiedu Granule treatment in advanced HCC patients significantly prolonged median overall survival and caused dose-dependent changes in gut flora, such as reducing Peptostreptococcaceae associated with liver carcinogenesis and maintaining *Akkermansia muciniphila* abundance associated with immunotherapy efficacy, revealing the potential microbial mechanism of its efficacy.[320] Notably, significant differences exist in microbial communities in HCC tumor tissues, where the abundance of bacteria with antitumor effects like Pseudomonadaceae is reduced, and their reduction is linearly correlated with patient prognosis.[321] Meanwhile, significant microbial heterogeneity exists between multifocal tumor nodules in HCC, with specific bacterial communities enriched in metastatic clones, driving epithelial-mesenchymal transition and immune suppression.[322] These findings strongly support the combined or sequential treatment of FMT, specific probiotics/synbiotics, or flora-regulating traditional Chinese medicines with ICIs to expand the beneficiary population of immunotherapy and enhance efficacy.

Synergistic action of microbiota modulation and metabolic surgery

The significant improvement of NAFLD by metabolic surgery (such as sleeve gastrectomy) is partly attributed to its remodeling of the gut microbiota, providing a theoretical basis for combined microbial intervention in the perioperative period. Studies found that six months after sleeve gastrectomy, clinical parameters of NAFLD patients improved significantly, while gut flora changed, including increases in beneficial bacteria like *Lactobacillus crispatus* and *Lactobacillus iners*, and decreases in harmful bacteria like Erysipelotrichia.[323] Key mechanistic studies indicate that changes in gut flora of postoperative patients reduced glucose-dependent insulinotropic polypeptide (GIP) signaling; transplanting postoperative patient feces to antibiotic-treated mice effectively resisted diet-induced obesity and NAFLD, and this resistance was associated with reduced GIP levels in mice.[324] Furthermore, the gut microbiome characteristics of patients with NAFLD remission after bariatric surgery manifested as higher abundance of *Bacteroides*, *Akkermansia*, and multiple genera of SCFA-producing Clostridia (such as *Blautia*, *Faecalibacterium*); these specific gut microbes and accompanying bile acid changes may jointly promote liver disease remission.[325] Notably, patients after pancreaticoduodenectomy exhibit gut flora dysbiosis; at 6 months post-surgery, their β-diversity still differs significantly from healthy volunteers, and the abundance of *Lactobacillus gasseri* in patients developing fatty liver post-surgery is significantly lower than in healthy volunteers,

indicating that the occurrence of postoperative fatty liver may be related to significant differences in gut flora composition.[326] These evidences suggest that actively applying prebiotics, probiotics, or synbiotics before and after metabolic surgery to further optimize and consolidate surgically induced favorable flora changes may produce synergistic effects, accelerating NAFLD reversal and preventing recurrence. For example, postoperative supplementation with polyphenol-rich prebiotics (such as Camu Camu) or specific probiotic strains may further increase beneficial bacterial colonization and promote SCFA production, thereby more effectively improving hepatic steatosis and metabolic disorders.[327]

Microbiota modulation assisting standard treatment for liver fibrosis and cirrhosis

In the management of liver fibrosis and cirrhosis, microbiota modulation can serve as an effective adjunct to antifibrotic drugs and complication prevention medications, improving disease progression through multi-target actions. Studies show that Biejiajian Pill combined with entecavir treatment for 48 weeks in hepatitis B cirrhosis/fibrosis patients resulted in a significantly higher liver fibrosis improvement rate than the control group using entecavir alone; its mechanism is closely related to regulating gut flora, increasing beneficial bacteria (*Bifidobacterium*, *Lactobacillus*, *Faecalibacterium*) and reducing potential pathogens (*Escherichia*, *Bacteroides*, *Ruminococcus*).[328] For cirrhosis complications, microbial modulation strategies demonstrate unique value. In the prevention and treatment of HE, probiotics, prebiotics, antibiotics, and FMT can all improve hyperammonemia and endotoxemia by regulating the gut microbiome.[329] For instance, a randomized controlled trial showed that combined probiotic and prebiotic treatment for autoimmune hepatitis had effects comparable to prednisone with no adverse effects; its mechanism involved regulating flora composition, enhancing the gut barrier, and inhibiting TLR4/NF-κB and NLRP3/Caspase-1 inflammatory pathways.[330] Regarding infection prevention in cirrhosis patients, research found that diets rich in grains and yogurt are associated with higher microbial diversity, beneficial flora abundance, and lower 90-day hospitalization risk, suggesting dietary flora modulation as an adjunct strategy for infection prevention.[331] Notably, 12 months after splenectomy plus pericardial devascularization in chronic hepatitis B cirrhosis patients, gut flora composition restored to near healthy control levels, and liver function, intestinal permeability, and inflammation levels improved compared to pre-surgery, indicating that the improvement in liver function and intestinal permeability after splenectomy plus pericardial devascularization may be related to gut flora recovery.[332] For portal hypertension, the non-absorbable antibiotic rifaximin is a standard treatment, with partial efficacy derived from gut flora regulation. Studies found that although fructooligosaccharides did not affect portal pressure, they reduced hepatic vascular resistance in cirrhotic rats by improving gut flora dysbiosis and oxidative stress, offering new ideas for dietary intervention assisting blood pressure reduction.[333] Therefore, integrating microbiota management (including dietary guidance, probiotics/prebiotics, selective intestinal decontamination) into the full-course treatment of liver fibrosis/cirrhosis is expected to synergize with existing therapies from multiple dimensions such as reducing pathogenic signal output, enhancing the gut barrier, and regulating immunity, delaying disease progression and improving patient quality of life.

Construction and future challenges of individualized integrated intervention strategies

Achieving optimal integration of microbiota modulation and existing liver disease therapies ultimately depends on developing individualized, dynamic intervention strategies, but this faces multiple challenges such as mechanistic complexity, efficacy prediction, and clinical translation. The core lies in establishing a precision stratification system based on multi-omics. By integrating patients' gut metagenomic, metabolomic, immunomic, and clinical data, specific "microbe-host" interaction patterns can be identified, thereby predicting their likely response to different interventions (such as specific probiotic strains, FMT donor types, dietary fiber types). For example, microbial network features centered on Ruminococcaceae and Christensenellaceae at baseline may be associated with future risk of decompensation events; such patients might initiate intensive flora intervention early.[191] The timing of intervention is also crucial. For HCC patients planning to receive immunotherapy, flora "pre-conditioning" (such as using specific synbiotics) can be performed before treatment to shape a microenvironment conducive to immune response; for patients receiving antiviral therapy, simultaneous flora modulation can be conducted to alleviate liver inflammation and improve metabolism. However, most current evidence still comes from observational studies or small-scale clinical trials; large-scale, prospective, randomized controlled trials are urgently needed to verify the impact of integrated intervention strategies on hard clinical endpoints (such as liver cancer occurrence, cirrhosis decompensation, overall survival). For example, a randomized double-blind placebo-controlled trial targeting MASH patients aims to evaluate the efficacy of lyophilized fecal microbiota capsules combined with next-generation beneficial bacteria and oligofructose; its results will provide high-level evidence.[334] Standardization issues are also prominent, including FMT donor screening and preparation standards, probiotic/prebiotic strain and dosage specifications, and intervention efficacy evaluation systems all need unification. In the future, with deeper understanding of gut–liver axis mechanisms and the popularization of microbiome testing technologies, liver disease treatment will truly enter a new era of "liver-gut combined therapy." Clinicians are expected to formulate integrated prescriptions containing "traditional liver-targeted drugs" and "personalized intestinal niche management plans" for each patient, thereby maximizing therapeutic benefits and achieving a fundamental shift from disease treatment to healthy ecological niche maintenance.

Limitations

Despite the significant advancements described in this review, several critical limitations in the current field of gut–liver axis research must be acknowledged. First, a vast majority of existing evidence is derived from cross-sectional clinical observations and animal models, which establish strong correlations but often fail to provide definitive proof of causality. Human microbiome studies are highly susceptible to confounding factors such as diet, genetics, and concomitant medications; thus, the complex relationship between microbiome shifts and liver pathology remains a fundamental challenge.[236] Furthermore, the heavy reliance on commercialized cell lines and rodent models creates a significant translational barrier. The inherent discrepancies in immune-metabolic baselines, gastrointestinal anatomy, and foundational gut microbiota composition—exacerbated by behaviors like murine coprophagia—mean that preclinical mechanistic findings frequently fail to translate into consistent clinical efficacies.[235]

Second, the lack of universal standardization severely hinders the reproducibility and comparability of results. Variations at every methodological step, including sample collection, DNA extrac-

tion kits, sequencing platforms, and bioinformatic pipelines, can introduce substantial technical bias. Additionally, the current research focus remains predominantly on the bacteriome, frequently neglecting the critical roles of the mycobiome, virome, and their cross-kingdom interactions, which are essential for a holistic understanding of the intestinal ecosystem.[16] Finally, there is a profound individual heterogeneity in response to microbiome-targeted therapies. The efficacy of broad-spectrum interventions is highly dependent on the recipient's baseline mucosal colonization resistance,[335] highlighting the urgent need to transition toward personalized microbiome engineering.

Perspectives

Despite these insights, existing research is largely limited by observational associations, a lack of global standardization in microbiome analysis, and significant individual heterogeneity in response to broad-spectrum interventions like FMT. To advance the field toward "precision hepatology," future research must address several critical frontiers: Future studies should utilize Mendelian randomization, prospective longitudinal cohorts, and multi-omics integration combined with advanced spatiotemporal technologies. This will dynamically resolve the interactive evolution of the microbiome and host networks, identifying key functional modules driving disease turning points. Developing predictive machine-learning models that integrate microbial and metabolite features will be essential to guide precise patient stratification and tailor individualized therapies. Clinical focus should shift from broad interventions to targeted combinations, such as utilizing phage therapy to clear specific pathogens alongside supplementation with engineered beneficial metabolite-producing strains. Large-scale randomized controlled trials (RCTs) are urgently needed to validate these approaches. Establishing a robust, standardized system for microbial therapeutic products—covering donor screening, formulation preparation, and strict efficacy evaluation—is imperative for clinical translation. Ultimately, shifting the clinical paradigm from a singular "liver-targeted" approach to a holistic "liver–gut combined therapy" will pave the way for a new era of fundamental and effective precision management in liver diseases.

Conclusions

This review comprehensively elucidates the common features and etiology-specific patterns of gut microbiota dysbiosis across various liver diseases, ranging from MASLD and ALD to cirrhosis and HCC. The core consensus is that the gut microbiota is not merely a passive companion but a key active regulator of liver disease pathogenesis. Disruption of gut barrier integrity leads to the translocation of microbes and their products, accelerating disease progression. Concurrently, microbial metabolites critically modulate hepatic metabolism and host immunity via the gut–liver axis. Ultimately, these distinct gut microbiome signatures hold great potential as non-invasive biomarkers for diagnosis, prognosis, and therapeutic efficacy assessment, establishing intestinal niche modulation as a viable synergistic strategy with existing hepatology therapies.

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Conflict of interest

XL has been an Editorial Board Member of *Journal of Translational Gastroenterology* since 2026. The authors declare no other conflicts of interest.

Author contributions

Research design (XL, KZ, FW, JC), literature search and evidence synthesis (XL, RD, PJ, XtW, GG, XW, CX, HL), and writing of the manuscript (XL, RD). All authors contributed to the article and approved the publication of the manuscript.

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