Review

From gut-liver axis hijacking to intratumoral microbiota establishment: Mechanisms and therapeutic opportunities in liver cancer

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Received: 28 May 2026 | Approved: 11 June 2026 | Online: 11 June 2026

Abstract

Liver cancer, primarily hepatocellular carcinoma (HCC), remains a leading cause of global cancer mortality. Recent evidence indicates that intratumoral bacteria reside within HCC tumors, largely originating from the gut. Disruption of the intestinal barrier, coupled with impaired hepatic immune clearance, enables gut-derived microbes to translocate to the liver via the portal vein. Once established within the tumor microenvironment, these intratumoral bacteria are metabolically active: they directly engage host receptors to activate oncogenic signaling pathways, reshape local immune

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homeostasis, and induce epigenetic modifications. Notably, distinct bacterial signatures correlate consistently with tumor stage, prognosis, and therapeutic response. In this review, we provide an updated overview of intratumoral bacteria in HCC, summarize their mechanistic contributions to tumor pathogenesis, and discuss the potential of microbiome-based approaches to unveil new diagnostic and therapeutic opportunities.

Keywords: Liver cancer, gut-liver axis, intratumoral microbiota, tumor microenvironment, cancer therapeutics

INTRODUCTION

Liver cancer remains a significant threat to global health, with persistently high incidence and mortality rates. Hepatocellular carcinoma (HCC), which accounts for 90% of liver cancer cases, is the fifth most frequently diagnosed cancer and the third leading cause of cancer death worldwide[1,2]. Although chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are established major risk factors for HCC, metabolic dysfunction-associated steatotic liver disease (MASLD) and diabetes mellitus are becoming the fastest-growing aetiology of HCC incidence[1,3,4]. Most patients are diagnosed with intermediate or advanced stages, where treatment options are limited—mainly including ablation therapy, transarterial chemoembolization (TACE), targeted therapy, and immunotherapy[5]. The overall prognosis for advanced HCC patients remains poor, with a 5-year survival rate of less than 10%[6,7]. The clinical management of HCC is hampered by persistent challenges, such as high tumor recurrence and metastasis rates, significant intratumoral heterogeneity, and primary/secondary resistance to immunotherapy[8]. Thus, there is an urgent need to deeply explore novel mechanisms driving HCC development and to identify new prognostic biomarkers and effective therapeutic targets.

The tumor microenvironment (TME) plays a decisive role in HCC progression and treatment response. It comprises tumor cells, cancer-associated fibroblasts, immune

cells, extracellular matrix, and various signaling molecules[9,10]. In 2020, Nejman and colleagues first demonstrated the presence of bacteria within tumors across multiple cancer types, revealing the tumor-resident microbiota (TRM) as a previously unrecognized TME component[11]. Subsequent studies confirmed that HCC tissues harbor abundant and metabolically active intratumoral bacteria using high-throughput sequencing, fluorescence in situ hybridization, and tissue culture techniques[12-15]. These microbes are thought to colonize liver tumors primarily through the disrupted gut-liver axis, which involves intestinal barrier breakdown, impaired hepatic immune clearance, and microbial translocation via the portal vein, biliary tract, or hematogenous routes.

Evidence from large-scale cohort studies has demonstrated that HCC tissues possess a unique intratumoral bacterial profile closely associated with clinicopathological features such as tumor grade, stage, and patient survival[12,14,16,17]. Importantly, recent functional studies have begun to establish causal links between specific intratumoral microbes and HCC initiation and progression[13,15,16]. This review provides a systematic overview of the latest advances in this rapidly evolving field, including the routes of microbial translocation to liver tumors, the compositional landscape of the intratumoral microbiota, its pro-tumorigenic mechanisms in HCC, and emerging therapeutics that target the gut–liver axis and intratumoral microbiota.

GUT-LIVER AXIS HIJACKING: THE GATEWAY FOR INTRATUMORAL MICROBIOTA ESTABLISHMENT

The gut-liver axis refers to a bidirectional communication network established between the intestine and the liver via the biliary tract, portal vein, and systemic circulation. It is functionally responsible for metabolic regulation, immune surveillance, and the coordination of systemic inflammatory responses[18-20]. The establishment of intratumoral microbiota in HCC is driven by a sequential process: pathological breakdown of the gut-liver axis defense, impairment of hepatic immune surveillance, translocation of gut microbes, and active colonization within the tumor

microenvironment (TME).

Initiation of intestinal barrier disruption

Gut-liver axis hijacking begins with damage to the intestinal epithelial mucosal barrier. Metabolic disorders, alcohol, viral infection, and high-fat diets downregulate tight junction proteins (Occludin, Claudin, ZO-1) and thin the mucus layer, producing a "leaky gut" with increased permeability[20-24]. This enables gut microbial products such as lipopolysaccharide (LPS) to enter the portal circulation[21]. Simultaneously, the gut vascular barrier (GVB), a semipermeable endothelial layer, becomes disrupted, allowing entire bacteria to bypass portal filtration and directly access the bloodstream[25,26].

Compromised hepatic immune clearance

In the healthy liver, resident Kupffer cells and innate lymphoid cells constitute a highly efficient surveillance system that rapidly eliminates gut-derived microbes arriving via the portal circulation. However, during chronic liver disease and hepatocarcinogenesis, this clearance machinery is progressively crippled. In a tumor-permissive state, chronic liver inflammation induces M2-type polarization and immunosuppression of Kupffer cells, compromising their ability to clear translocated microbes[27,28]. Huang *et al*. found that HBV-related HCC remodels the hepatic immune microenvironment through gut microbiota crosstalk, attenuating immune responses responsible for clearing translocated microbiota and facilitating persistent microbial invasion into the liver[29].

Three pathways of microbial translocation into the liver

The translocation of gut microbiota and their metabolites into the liver represents a core event in gut-liver axis hijacking. This process primarily occurs through three routes: First, the portal vein route, Bacteria and metabolites (LPS, short-chain fatty acids) pass through the damaged intestinal barrier directly into the portal circulation and reach the liver. LPS-positive bacterial vesicles have been visualized in portal blood, and fecal microbiota transplantation from HCC patients introduces live bacteria into the liver

through this pathway[15,30]. Second, hematogenous dissemination occurs when GVB damage releases bacteria into the systemic circulation, where they exploit erythrocytes as carriers for immune evasion and trafficking to hepatic tissues[31-33]. Third, the retrograde biliary route enables duodenal bacteria to ascend through a dysfunctional sphincter of Oddi, particularly contributing to intrahepatic cholangiocarcinoma and mirroring the microbial similarity between HCC tumors and the upper gastrointestinal tract[34-36].

From microbial translocation to intratumoral colonization

Once in the liver, translocated microbes actively colonize the tumor microenvironment. Early intrahepatic colonization of translocated microbiota is driven by the TME. Chemokines, extracellular matrix (ECM) components, and metabolic precursors secreted by HCC cells selectively recruit and retain specific microbial communities[37]. Li *et al*. defined the intrahepatic metagenomic characteristics of the microbiota in patients with liver cancer and found that the levels of *Rhodobacter*, *Megasphaera*, and *Lactobacillus* were significantly enriched in tumor tissues compared with adjacent non-tumor tissues[37]. Ren *et al*. mechanistically demonstrated that *Enterocloster bolteae* directly binds to surface receptors on liver cancer cells, promoting firm bacterial adhesion to tumor cells and stable intratumoral colonization[38].

Once seeded, the incipient intratumoral microbiota must evade the residual immune surveillance that persists even within the compromised liver. Translocated microbiota and their metabolites can suppress antitumor immunity and induce an immunotolerant TME, thereby protecting colonizing intratumoral microbes from clearance[39]. Yoshimoto *et al*. provided evidence that gut microbiota-derived deoxycholic acid (DCA) induces a senescence-associated secretory phenotype (SASP) in liver cells, creating an immune-privileged niche for stable colonization of intratumoral microbiota[40]. Loo *et al*. showed that gut microbiota mediate PGE2-dependent antitumor immune suppression, thereby promoting intratumoral microbiota colonization[39].

Long-term persistence ultimately hinges on the establishment of a metabolic symbiosis between tumor cells and the intratumoral microbiota. Hepatoma cells provide a continuous supply of nutrients, including amino acids and bile acids, which are metabolized by the microbial community. In return, bacterial metabolites—particularly short-chain fatty acids—actively modulate metabolic–immune crosstalk to drive HCC progression while simultaneously stabilizing the microbial niche[41,42]. Che *et al*. confirmed that bile acid metabolism reshapes the metabolic homeostasis of liver cancer and facilitates long-term survival of the intratumoral microbiota[43]. Pan *et al*. reported that SCFAs regulate liver cancer progression through metabolic-immune crosstalk, establishing a state of metabolic symbiosis that supports both tumor growth and stable intratumoral microbiota persistence[41]. Collectively, through a sequential process of selective recruitment, immune evasion, and metabolic mutualism, gut-derived microbes transition from transient invaders to stable, tumor-resident microbiota for hepatocarcinogenesis.

THE COMPOSITION AND CHARACTERISTICS OF INTRATUMORAL MICROBIOTA IN LIVER CANCER

The intratumoral microbiota of liver cancer is characterized by distinct taxonomic profiles that differ markedly from those of normal liver and adjacent non-tumor tissues, both in overall abundance and in the enrichment of specific microbial lineages. Multiple independent profiling studies have converged on a core signature: at the phylum level, the hepatocellular carcinoma (HCC) microenvironment is dominated by *Proteobacteria*, *Firmicutes*, *Actinobacteriota*, and *Bacteroidetes*, with *Proteobacteria* consistently exhibiting the highest relative abundance in tumor tissues[12,14,29,44]. Huang *et al*. reported that *Streptococcaceae* and *Lactococcus* are specifically enriched in cirrhosis- associated HCC, while *Patescibacteria* constitutes a dominant phylum in both tumor and adjacent tissues[12]. At the genus level, *Klebsiella*, *Acinetobacter*, *Corynebacterium*, and *Pseudomonas* are overrepresented in HCC[14]. Notably,

Stenotrophomonas was shown to be specifically enriched in HCC tumors and virtually absent from normal controls, whereas taxa with known anti-tumor properties, such as *Pseudomonas*, are frequently depleted[13,14]. In addition, members of the *Gammaproteobacteria*, *Enterobacteriaceae*, and *Fusobacterium* are significantly enriched; many of these possess pro-inflammatory or genotoxic capabilities that may promote hepatocarcinogenesis[14,44].

Beyond bacteria, the fungal component of the intratumoral microbiota has recently gained attention. Shen *et al*. demonstrated that *Malassezia spp.* are significantly enriched in HCC tissues compared with adjacent non-tumor tissues and that their abundance correlates closely with stromal and immune features of the tumor microenvironment[45]. The intratumoral microbiota is not confined to HCC; distinct microbial signatures have also been identified in intrahepatic cholangiocarcinoma (ICC) and colorectal cancer liver metastases (CRLM)[46-48]. For instance, *Staphylococcus*, *Burkholderiales*, *Pseudomonadales*, *Xanthomonadales*, *Bacillales*, and *Clostridiales* are markedly enriched in ICC, suggesting that different histological subtypes shape unique intratumoral microbial niches[46]. Collectively, these studies reveal a consistent, multi-kingdom compositional shift that underscores the biological relevance of the intratumoral microbiota in liver cancer.

FUNCTIONAL MECHANISMS OF INTRATUMORAL MICROBIOTA IN PROMOTING LIVER CANCER

After stable colonization within the TME of liver cancer, the intratumoral microbiota functions as a non-tumor-derived oncogenic driver, mediating HCC initiation, progression, invasion, and metastasis through three major functional pathways: modulating host oncogenic pathways, reshaping tumor immune microenvironment (TIME), and affecting host epigenetic regulation.

Direct binding and secreted metabolites modulate host oncogenic pathways

Tumor development is closely associated with the widespread activation of oncogenic signaling pathways, which drive the transformation of normal cells into malignant cells and support tumor progression[56]. Accumulating evidence indicates that the intratumoral microbiota and its metabolites, as key components of the TME, specifically interact with host cells and trigger critical pro-oncogenic signaling pathways, thereby playing pivotal roles in the initiation and progression of liver cancer[57,58] [Figure 1]. Mechanistically, this pro-tumorigenic interplay operates through two primary modes: direct binding of microbial surface proteins to host receptors, and secretion of bioactive metabolites that activate intracellular signaling. Wang *et al*., using metagenomic analysis and bacterial culture of HCC tissues, found increased abundance of *Klebsiella pneumoniae* (*K. pneumoniae*) in both HCC patients and mice transplanted with microbiota from these patients[15]. The *K. pneumoniae* surface protein PBP1B was shown to bind directly to Toll-like receptor 4 (TLR4) on HCC cells, thereby promoting tumor cell proliferation and activating downstream oncogenic pathways[15] [Figure 1A]. Similarly, Ren *et al*.[38] *Enterocloster bolteae* adheres to HCC cells through the surface adhesion protein PbpT, which attenuates the tumor-suppressive function of desmoglein-1 (DSG1), accelerating HCC progression. Extending the mechanistic spectrum, Zhang *et al*. observed elevated levels of *Catenibacterium* in both tumor tissues and fecal samples of HCC patients compared with healthy individuals[59]. *Catenibacterium mitsuokai* (*C. mitsuokai*) can disrupt the intestinal barrier and migrate to the liver as live bacteria. Its surface proteins Gtr1/RagA interact with γ-catenin receptors on HCC cells, facilitating its colonization within HCC tissues. Furthermore, *C. mitsuokai* secretes the metabolite quinolinic acid, which promotes HCC progression by binding to TIE2 and activating the downstream PI3K/AKT pathway[59] [Figure 1B]. Collectively, the intratumoral microbiota drives hepatocarcinogenesis through two complementary mechanisms: direct receptor binding and paracrine metabolite signaling.

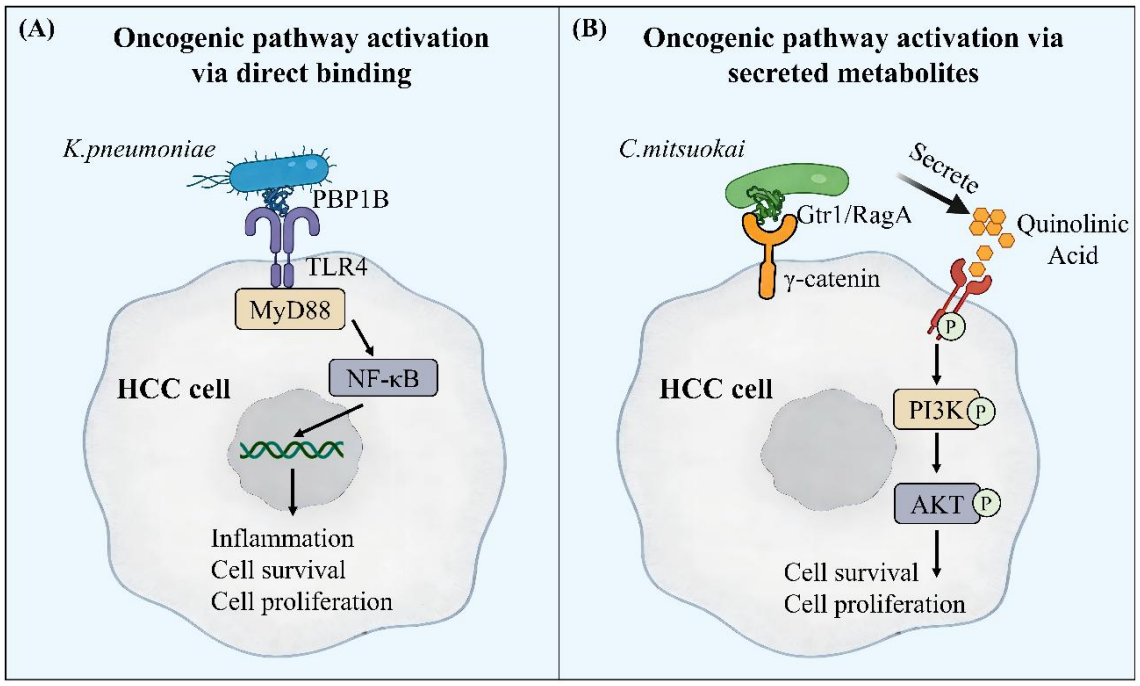


Figure 1. Mechanisms by which two tumor-resident microbes promote HCC progression via modulating host oncogenic pathways. (A) Direct binding-mediated pathway activation. *K. pneumoniae* binds to HCC cells via PBP1B and activates TLR4/NF-κB signaling pathway, leading to inflammation, cell survival and proliferation, resulting in tumorigenesis; (B) Secreted metabolite-mediated pathway activation. *C. mitsuokai* surface protein Gtr1/RagA binds to the γ-catenin receptor on HCC cells, leading to tumor colonization. It secretes Quinolinic Acid to activate PI3K/AKT signaling pathway by binding to TIE2, influencing cell survival and proliferation. Abbreviations: HCC, hepatocellular carcinoma; PBP1B, penicillin-binding protein 1B; TLR4, toll-like receptor 4; MyD88, myeloid differentiation primary response protein 88; NF-κB, nuclear factor kappa-B; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B.

Dual immunomodulatory roles of the intratumoral microbiota

Accumulating evidence demonstrates that the intratumoral microbiota, residing within both tumor cells and immune cells, actively remodels the tumor immune microenvironment (TIME) through activation, inhibition, and bystander effects[60-64] [Figure 2]. In the context of immune suppression, *Stenotrophomonas maltophilia* is

markedly enriched in cirrhosis-associated HCC and accelerates tumor progression by triggering NLRP3 inflammasome assembly[13]. Ma *et al*. reported that dysregulation of the gut-liver axis microbiota alters bile acid metabolism, which in turn suppresses natural killer T (NKT) cell activity within the TIME, thus promoting HCC development[65]. Reduced intratumoral microbiota diversity is closely associated with an immunosuppressive phenotype[49]. Fecal microbiota transplantation from HCC patients into germ-free mice induces colonic inflammation and increases hepatic infiltration of Th1, Th2, and Th17 cells, creating a proinflammatory microenvironment that promotes tumor development[15]. Moreover, bacteria enriched in metastatic HCC, such as *Enterococcus faecalis* and *Streptococcus anginosus*, directly recruit and activate myeloid-derived suppressor cells, enhancing their immunosuppressive function while impairing $CD8^+$ T cell proliferation and cytotoxicity, thus driving an immune imbalance characterized by diminished antitumor immunity[16] [Figure 2A].

Conversely, certain intratumoral microbiota constituents can suppress tumor progression by activating antitumor immune responses [Figure 2B]. *Akkermansia muciniphila* enhances the efficacy of PD-1 inhibitors in MAFLD-associated HCC by promoting $CD8^+$ T cell activation and reducing regulatory T cell infiltration[66]. *Brevibacillus parabrevis* augments antitumor immunity by inhibiting NK cell ferroptosis[67]. intratumoral microbiota-derived metabolites also contribute to immune activation: SCFAs produced by *Lactobacillus* species modulate immune cell function[68]. *Faecalibacterium prausnitzii*-derived fpPRPS enzyme depletes ATP in tumor cells, leading to Rab11a degradation and disruption of PD-L1 membrane trafficking, thereby enhancing $CD8^+$ T cell-mediated anti-tumor responses[69]. Similarly, rapamycin-induced xenophagy facilitates MHC class II-restricted presentation of *Bifidobacterium longum*-derived neoantigens, eliciting robust $CD4^+$ T cell activation and tumor-specific cytotoxicity[70]. Together, these studies demonstrate that the intratumoral microbiota can activate diverse antitumor immune pathways through direct cellular interactions, metabolite secretion, and neoantigen presentation, offering multiple therapeutic

opportunities.

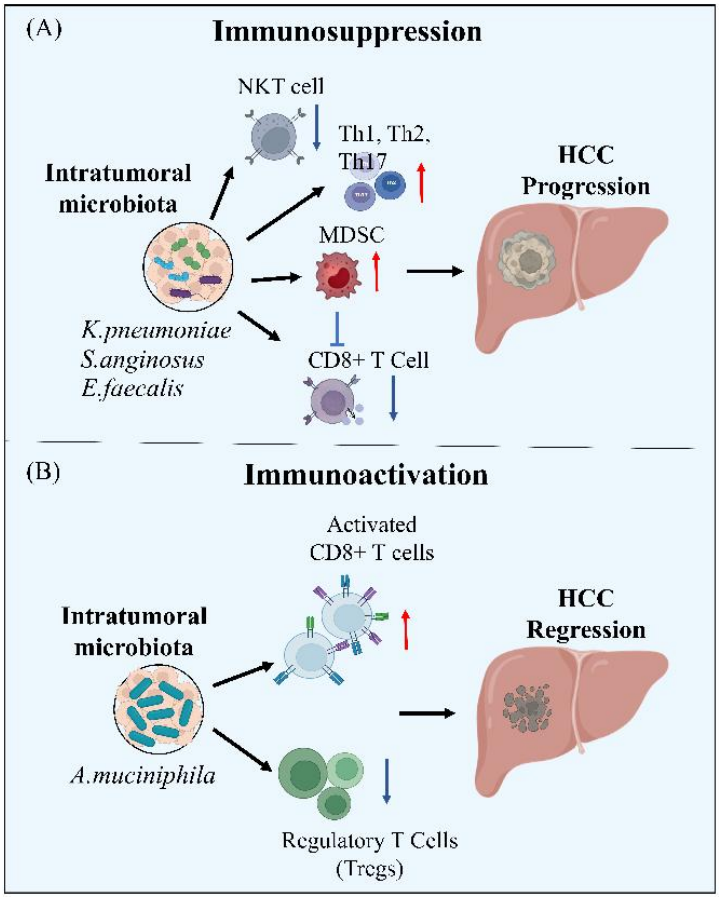


Figure 2. Dual function of intratumoral microbiota in modulating immune microenvironment in HCC. Intratumoral microbiota exerts opposing effects on the TIME. (A) Immunosuppression: Intratumoral microbiota such as *K. pneumoniae*, *S. anginosus*, and *E. faecalis* promotes an immunosuppressive microenvironment by modulating immune cell functions, including inhibiting the activity of NKT cells, increasing the infiltration of Th1, Th2, and Th17 cells, recruiting MDSCs, and impairing the proliferation of $CD8^+$T cells, leading to HCC progression; (B) Immunoactivation: Intratumoral microbiota such as *A. muciniphila* activates anti-tumor immunity by stimulating $CD8^+$T cells and reducing the infiltration of Tregs, leading to HCC regression. Abbreviations: HCC, hepatocellular carcinoma; TIME, tumor immune microenvironment; NKT, natural killer T cell; Th, T helper cell; MDSC, myeloid-derived suppressor cell; Treg, regulatory T cell.

Modulation of host epigenetics by the intratumoral microbiota

Epigenetic alterations, including DNA methylation and histone modifications, govern diverse cellular processes such as proliferation, apoptosis, invasion, and senescence, and their dysregulation is a hallmark of cancer[71]. Emerging evidence indicates that the intratumoral microbiota and its metabolites can modulate the expression of relevant genes by influencing host epigenetic modifications, such as DNA methylation and histone modifications, thereby affecting liver cancer progression [Figure 3]. A pioneering study by Li *et al*. established the first direct association between intratumoral microbiota composition and host DNA methylation profiles in HBV-related HCC, demonstrating that specific microbial taxa correlate with aberrant methylation of genes implicated in hepatocarcinogenesis[49]. Building on this, Chen *et al*.[72] integrated analyses of intratumoral microbial features and DNA methylation-based gene expression levels in HCC, further revealing that the abundances of specific intratumoral bacteria (e.g., *Pseudomonas*, *Stenotrophomonas*) are positively correlated with the expression levels of DNA methyltransferases (DNMT1, DNMT3A) and are associated with hypermethylation of tumor suppressor gene promoters.

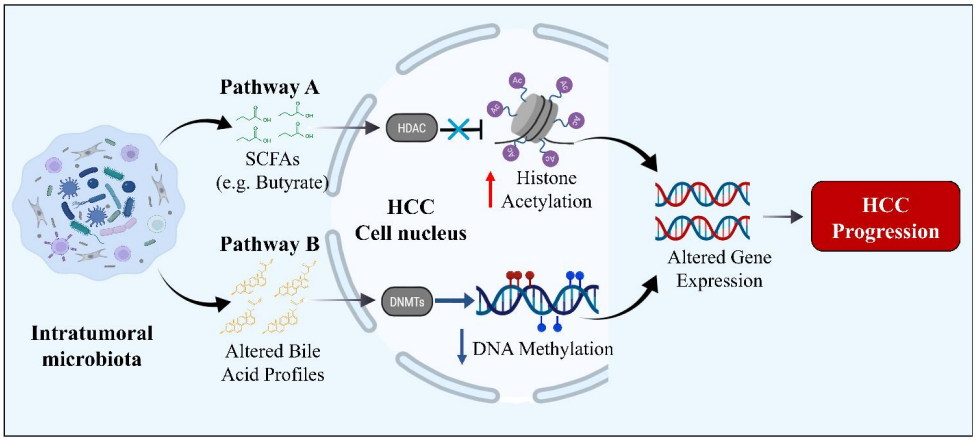


Figure 3. Mechanisms of intratumoral microbiota promoting HCC via affecting host epigenetic regulation. Intratumoral microbiota affects host epigenetic regulation mainly in two pathways. Pathway A: Intratumoral microbiota secretes SCFAs, (e.g., Butyrate) which inhibit HDAC and increase histone acetylation, leading to altered gene expression in the HCC cell nucleus, resulting in tumorigenesis; Pathway B: Intratumoral

microbial activity alters bile acid metabolism, which modulates DNMT function and leads to hypermethylation or hypomethylation of DNA, further altering gene expression, resulting in tumorigenesis. Abbreviations: HCC, hepatocellular carcinoma; SCFAs, short-chain fatty acids; HDAC, histone deacetylase; DNMT, DNA methyltransferase.

Beyond DNA methylation, intratumoral microbiota-derived metabolites, particularly short-chain fatty acids such as butyrate, can function as histone deacetylase inhibitors, modulating histone acetylation in HCC cells and consequently affecting the transcription of oncogenes and tumor suppressor genes[68]. Notably, the nature of microbiota-driven epigenetic alterations may vary with HCC etiology: in HBV-related HCC, microbes may cooperate with viral factors to silence antiviral and tumor-suppressive genes via epigenetic modifications, whereas in NAFLD-related HCC, microbial metabolites tend to target metabolism-related genes[49,68]. Despite these correlative insights, the field currently lacks direct mechanistic validation of how specific intratumoral microbiota components regulate host epigenetics. Future investigations should focus on elucidating the causal molecular mechanisms, ideally within the context of HCC etiology-specific microenvironments.

Clinical correlation between intratumoral microbiota and liver cancer

The composition and burden of the intratumoral microbiota are intimately associated with the clinicopathological features and prognosis of liver cancer patients, supporting its potential utility as both a biomarker and a therapeutic target. Regarding tumor progression, Jo *et al*. demonstrated that the intratumoral microbiota composition differs significantly between early- stage and advanced- stage HCC, with *Sphingomonadaceae* and *Skermanella* more abundant in advanced tumors[73]. Liu *et al*. further showed that intratumoral microbiota load positively correlates with tumor size, Edmondson grade, and microvascular invasion[74]. With respect to prognosis, Sun *et al*. constructed a genus-level scoring system based on intratumoral microbiota relative abundance, revealing that patients in the high-score group had significantly shorter overall

survival[44]. Jiang *et al*. reported that intratumoral microbiota α-diversity is inversely associated with overall survival, with greater diversity linked to poorer outcomes, possibly reflecting more complex immune-modulatory effects[17]. The intratumoral microbiota also shapes the tumor immune microenvironment in a species-specific manner. Enrichment of *Lachnoclostridium* correlates positively with tertiary lymphoid structure formation, a marker of antitumor immune activation[75]. Finally, emerging evidence suggests that the intratumoral microbiota may predict response to immune checkpoint inhibitors. Tumor-associated *Bifidobacterium* and *Akkermansia* have been associated with improved responses to anti-PD-1 therapy, while *Fusobacterium* is linked to resistance; although these findings largely originate from other cancer types, similar associations are plausible in liver cancer[76-78]. These multi-dimensional clinical correlations highlight the intratumoral microbiota as a functionally relevant and potentially actionable component of the liver cancer ecosystem.

THERAPEUTIC OPPORTUNITIES: TARGETING THE GUT-LIVER AND INTRATUMORAL MICROBIOTA

Insights into gut-liver axis hijacking and the tumor-promoting functions of the intratumoral microbiota have opened new avenues for liver cancer prevention and treatment. Current therapeutic strategies can be divided into two categories: preventing microbial translocation by preserving gut-liver axis integrity, and precisely eliminating established intratumoral microbes.

Modulating the gut-liver axis to prevent microbial hijacking

Interventions that block microbial translocation from the gut to the liver represent a primary preventive strategy. The core objectives are to repair the intestinal barrier, restore gut microbial homeostasis, and reduce pro-carcinogenic metabolites.

Probiotics

Probiotics exert anti-HCC effects through competitive exclusion, barrier reinforcement,

and immunomodulation[79-81]. *Lactobacillus acidophilus* produces valeric acid to disrupt tumor energy metabolism in NAFLD-HCC[82], while *Bifidobacterium pseudolongum*-derived acetate blocks MASLD-HCC by inhibiting inflammatory and oncogenic pathways[83]. *Klebsiella oxytoca* competitively inhibits oncogenic *K. pneumoniae*, preserving barrier integrity and preventing hepatic translocation[15]. *Lactobacillus rhamnosus GG* induces a cGAS/STING-dependent type I interferon response, and its combination with *Bifidobacterium* enhances anti-PD-1 efficacy in HCC models[76,84]. Probiotics thus serve both as guardians of the gut-liver axis and as immunotherapy adjuvants.

Fecal microbiota transplantation (FMT)

FMT restores intestinal homeostasis by functionally remodeling the gut microbiota. Encapsulated FMT improved clinical outcomes in cirrhosis[85], and FMT from female donors restored intestinal permeability and reduced hepatic inflammation in alcoholic liver disease models[86]. Although direct evidence in HCC is limited, the ongoing FLORA trial (NCT05690048) is evaluating FMT to overcome resistance to atezolizumab/bevacizumab in advanced HCC[87].

Dietary and pharmacological interventions

Directly reinforcing the intestinal barrier is another prophylactic approach. Drugs targeting tight junction proteins (e.g., Occludin, Claudin) reduce LPS translocation[21]. High-fiber, low-fat diets enrich butyrate-producing bacteria and suppress pro-carcinogenic metabolites[88], while natural products such as polyphenols, flavonoids, and saponins preserve gut-liver axis integrity and exert anti-HCC effects[24,89].

Precise therapy targeting intratumoral microbiota

Once the intratumoral microbiota is established, direct antimicrobial strategies become necessary. These include conventional antibiotics, engineered antimicrobial polymers, and highly specific phage therapy.

Antibiotics

Selective elimination of pro-tumorigenic bacteria can suppress HCC. Broad-spectrum antibiotics partially reverse *Enterococcus faecalis* and *Streptococcus anginosus* -driven tumor progression[16]. Antibiotics also enhance immunotherapy: a phase II trial of nivolumab, tadalafil, and oral vancomycin reshaped the gut microbiota and TIME in advanced HCC[90]. Mechanistically, antibiotics counteract dysbiosis-induced expansion of myeloid-derived suppressor cells (MDSCs) and restore T cell function[91], and vancomycin reduces serum secondary bile acids, thereby attenuating HCC promotion in mice[92]. Future efforts should focus on precision antibiotic regimens tailored to individual microbial profiles.

Antibacterial polymer therapy

Antimicrobial polymers and peptides are engineered macromolecules that selectively kill detrimental bacteria while minimizing off-target effects. Tellurium-containing polycarbonate carriers reversed chemoresistance in colorectal cancer by eradicating intratumoral microbiota[93], and colistin-crosslinked gemcitabine micelles eliminated resistance-conferring bacteria[94]. In liver cancer, nanoparticle-encapsulated antimicrobial peptides achieved intratumoral microbiota clearance and TME remodeling[95], and phage-derived peptides exhibited activity against HCC cells and multidrug-resistant *Acinetobacter baumannii*[96]. These advances support the design of liver-targeted antimicrobial polymer systems for HCC.

Phage therapy

Bacteriophages offer highly specific bacterial lysis with a low propensity for resistance[97,98]. In preclinical models, phage VA7 specifically lysed Bacteroides fragilis, restoring chemosensitivity in colorectal cancer[99]. Engineered bacteriophages can also instruct bacteria to produce tumor-specific antibodies within the TME, combining antimicrobial and immunotherapeutic effects[82]. Although phage therapy remains

largely unexplored in HCC, its precision and synergy with other treatments warrant further investigation.

DISCUSSION

This review consolidates current knowledge on the intratumoral microbiota in hepatocellular carcinoma, tracing its establishment from gut-liver axis disruption to stable colonization within the tumor microenvironment. We have summarized how intestinal barrier damage, impaired hepatic immune clearance, and microbial translocation via the portal vein, hematogenous, and biliary routes collectively enable gut-derived microbes to seed liver tumors. Once established, the intratumoral microbiota promotes HCC through three interconnected mechanisms: direct activation of oncogenic pathways such as TLR4 and PI3K/AKT via surface proteins or secreted metabolites, remodeling of the immune microenvironment toward immunosuppression or immune activation depending on the bacterial species, and modulation of host DNA methylation and histone acetylation. The distinct taxonomic profiles of the intratumoral microbiota, with consistent enrichment of *Proteobacteria* and specific genera like *Klebsiella* and *Stenotrophomonas*, and their correlation with clinicopathological features[13,14], support the potential of the intratumoral microbiota as a source of prognostic biomarkers and therapeutic targets.

The field has advanced from descriptive characterization to functional and causal investigations. Studies using fecal microbiota transplantation, bacterial monocolonization, and live-bacteria tracking have provided direct evidence that specific microbes such as *Klebsiella pneumoniae* and *Catenibacterium mitsuokai* can drive HCC progression[5,15]. Innovative therapeutic strategies, including probiotics that competitively exclude pathogenic bacteria, precision antibiotics, antibacterial polymers, and phage therapy, have shown promise in preclinical models. However, important knowledge gaps persist. The exact molecular mechanisms by which microbial metabolites interact with host receptors remain poorly defined. Causal evidence is

currently limited to a few bacterial species, and the substantial heterogeneity in intratumoral microbiota composition across studies—driven by differences in HCC etiology, geography, and detection methods—complicates the identification of universal microbial targets.

Future research should elucidate the molecular pathways through which specific intratumoral microbiota members contribute to oncogenic signaling, immune evasion, and metabolic reprogramming in HCC. Integrating multi-omics approaches with spatial profiling will be critical for mapping microbial localization and activity within the tumor microenvironment. From a translational perspective, several priorities emerge. Liver-targeted delivery systems should be designed to carry antimicrobial agents directly to tumors. Tumor-colonizing probiotics or bacteriophages can be engineered to target defined oncogenic bacteria. HCC is highly heterogeneous in its etiology and microbial composition. Personalized microbiome analysis could therefore be used to design tailored treatment combinations. These strategies would target both cancer cells and the harmful bacteria that support them, offering a way to overcome drug resistance and improve patient outcomes.

CONCLUSION

The intratumoral microbiota in HCC is established through gut-liver axis disruption and functions as an active component of the tumor microenvironment. It promotes cancer progression by directly activating oncogenic pathways, reshaping the immune microenvironment, and altering host epigenetic marks. Specific microbial profiles correlate with clinical features, highlighting their potential as biomarkers. Therapeutic strategies that restore the gut-liver barrier or precisely eliminate oncogenic bacteria, such as probiotics, phage therapy, and antimicrobial polymers, offer promising new directions. Given the high heterogeneity of HCC, personalized microbiome-based interventions may ultimately improve treatment responses and patient outcomes.

DECLARATIONS

Authors' contributions

Conceptualized and designed: WK.C;

Drafted, and revised the manuscript: WK.C, XX.L;

Wrote the paper: SL.X, W.L.

Availability of data and materials

Not applicable.

Financial support and sponsorship

This study was supported by the National Natural Science Foundation of China (82504174, 82372596).

Conflict of interest

No potential conflicts of interest are disclosed.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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