

The microbiome in cancer

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Abstract

The human microbiome is now recognized as a central regulator of cancer biology, intricately shaping tumor development, immune dynamics, and therapeutic response. This comprehensive review delineates the multifaceted roles of bacteria, viruses, and fungi in modulating the tumor microenvironment and systemic immunity across diverse cancer types. We synthesize current evidence on how microbial dysbiosis promotes carcinogenesis via chronic inflammation, metabolic reprogramming, genotoxic stress, immune evasion, and epigenetic remodeling. This review emphasizes organ-specific microbiome signatures and highlights their potential as non-invasive biomarkers for early detection, treatment stratification, and prognosis. Furthermore, we explore the impact of intratumoral microbiota on cancer therapies, uncovering how microbial metabolites and host-microbe interactions shape therapeutic efficacy and resistance. Finally, advances in microbiome-targeted strategies, such as probiotics, fecal

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microbiota transplantation, and engineered microbes offer new avenues for adjunctive cancer therapy. This review provides a roadmap for future investigation and underscores the transformative promise of microbiome modulation in cancer prevention and treatment.

KEY WORDS

cancer, microbiome, precision oncology, treatment, tumor microenvironment

Highlights

- Microbiome dysbiosis drives carcinogenesis via multiple mechanisms.
- Microbiome-targeted strategies offer novel therapeutic avenues.
- Organ-specific microbiome signatures serve as non-invasive biomarkers.
- Intratumoral microbiota modulate therapy efficacy and resistance.
- Microbial metabolites reprogram the tumor microenvironment.

INTRODUCTION

Microorganisms comprise diverse microscopic entities, including bacteria, fungi, viruses, archaea, and protists. These microorganisms, including 10^{13} – 10^{14} bacteria colonizing human skin, intestines, and respiratory tract, establish complex symbiotic relationships with the host and are collectively referred to as the body's "second genome" [1–4]. Symbiotic microbes maintain host health through complex metabolic reciprocity [5]. In contrast, pathogenic microorganisms pose a threat to the host's health. Notably, microorganisms can have dual (beneficial and pathogenic) roles. When host immune function is compromised, commensal microbes may convert to conditionally opportunistic pathogens, potentially disrupting host health [6]. Clinical studies have confirmed that the composition of the gut microbiome can be modulated through fecal microbiota transplantation (FMT) and the administration of probiotic preparations, influencing immune cell infiltration, immune factor release, and inflammatory responses in the intestine and surrounding tumor tissues, thereby improving the immune status of the tumor microenvironment (TME) [7–9]. Consequently, the microbiome serves not only as a biomarker for disease diagnosis but also as a promising target for therapeutic intervention [10–12].

While research on gut microbes dates back to the 18th century, comprehensive investigations into the gut microbes expanded exponentially in the 21st century. A study in 1972 established that gut microbes play a critical role in drug transformation [13]. This seminal work laid

the groundwork for understanding the microbiome as a key modulator of pharmacology, a concept fundamental to modern microbiome–drug interaction studies. Since 2006, several pivotal studies have begun to emphasize the significant impact of diet on gut microbial composition and host metabolism [14–19]. In 2007, the National Institutes of Health (NIH) launched the Human Microbiome Project (HMP), the first large-scale collaborative program to study the human gut microbiome [20]. The Metagenomics of the Human Intestinal Tract (MetaHIT) project, initiated by the European Union in 2008, represents another landmark effort in the comprehensive and systematic study of gut microbiota. This initiative systematically characterized the genomic architecture of intestinal microbial communities and established foundational frameworks for investigating microbiome–disease associations, significantly advancing the development of precision medicine approaches [21]. Subsequently, Yatsunenko et al. conducted a large-scale comparative analysis demonstrating that human populations across distinct geographic regions have significantly different compositions and functional characteristics of gut microbes [22]. The American Gut Project (AGP), launched in 2012, was further expanded into a global microbiome research program to explore the composition and diversity of microbes in geographically diverse populations [23]. Notably, the study of gut microbes–host interactions has gradually extended to the field of disease treatment. A groundbreaking study in 2018 demonstrated that gut microbial signatures can predict immunotherapeutic response in patients with

melanoma, non-small cell lung cancer, and renal cell carcinoma [24]. This landmark discovery provided the first robust clinical evidence establishing a causal relationship between the gut microbiome composition and the efficacy of cutting-edge cancer immunotherapies, thereby creating a paradigm-shifting theoretical framework for understanding the microbiome's pivotal role in developing therapeutic intervention. These findings establish a crucial theoretical framework for understanding the pivotal role of tumor-associated microbes in cancer initiation, progression, and therapeutic intervention.

Investigations into intratumoral microbes began in the 19th century, but significant advances remained limited until recent decades [25]. In 2020, through a large-scale multi-omic analysis of diverse primary human malignancies, researchers established the presence of highly specific microbiome profiles and functional characteristics across different tumor types [26]. This study provides comprehensive evidence for the existence of distinct tumor-type-specific intratumoral microbiomes. In recent years, the prevalence of microbes within tumors has been further confirmed by increasing amounts of reliable evidence obtained through various advanced technological approaches [27, 28]. Studies have demonstrated that the species composition and abundance distribution of intratumoral microbes in different cancer types show marked heterogeneity [29–31]. As investigations into tumor-associated microbiota intensify, the precise origins and molecular mechanisms governing microbial colonization remain fundamental unresolved questions in the field. Recent investigations have characterized three potential routes of microbial access to tumor tissues: disruption of epithelial barrier integrity, migration from adjacent microenvironmental niches, and systemic dissemination [29, 32]. Substantial evidence indicates that intratumoral microbes are involved in the regulation of tumorigenesis, progression, and therapeutic response through multiple molecular mechanisms, including DNA damage induction, oncogenic signaling pathway activation, and alteration of epigenetic regulation [33]. Additionally, intratumoral microbes significantly affect the clinical efficacy of immunotherapy and chemotherapy by remodeling the tumor immune microenvironment (TIME). As intratumoral microbiome research advances, microbiome-targeted tumor precision diagnosis and individualized treatment strategies have emerged as an international research frontier. This recognition underscores the immense translational potential of the intratumoral microbiome and its associated metabolites, positioning them as critical targets for the next generation of diagnostics and personalized therapeutic interventions, particularly within the TME and immunomodulation approaches.

However, methodological challenges still exist, including sample acquisition, microbial detection, and functional validation [34–37]. The study of intratumoral microbiota holds profound clinical translational potential and is positioned to constitute a significant breakthrough and promising research direction in anti-tumor therapy.

The microbiome plays a critical role in multiple aspects of tumor growth, proliferation, diagnosis, treatment, and prognosis. Microorganisms and malignant cells engage in complex bidirectional interactions [38]. Microorganisms can promote tumorigenesis and development through direct genotoxic mechanisms or indirect immunomodulatory effects [39, 40]. Certain beneficial bacteria are also associated with anti-cancer effects. Probiotics maintain intestinal barrier homeostasis, regulate anti-inflammatory cytokine levels with anti-cancer properties, and enhance immune surveillance through activation of phagocytic cells. Germ-free murine models demonstrate compromised immunosurveillance and increased susceptibility to chemical carcinogenesis [41]. *Lactobacillus* and *Bifidobacterium* have also demonstrated potential to bind and degrade carcinogenic compounds [42]. Importantly, the microbial community serves as a diagnostic and prognostic biomarker [43–45]. Furthermore, the microbiome influences therapeutic effects by metabolizing drugs and dynamically modulating the immune microenvironment [46]. In immunotherapy, dysbiosis of the intestinal microbes (such as reduction of *Bifidobacteria*) exacerbates anti-CTLA-4 therapy-induced colitis, whereas probiotic supplementation both mitigates toxicity and enhances therapeutic efficacy [47]. As research exploring microbiome–tumor interactions intensifies, microbe-targeted therapies are gradually being recognized for their anti-tumor effects. For example, probiotics help maintain intestinal homeostasis and inhibit proliferation of malignant cells [48]. FMT therapy contributes to immunomodulation of the TME, resulting in a tumor-preventive effect at an early stage [8, 49]. The microbiome, as an emerging biomarker and potential therapeutic target, has broad applications in tumor diagnosis and treatment [50–53]. Consequently, microbial dysbiosis and intervention emerge as critical factors throughout carcinogenesis and disease progression. Targeted microbial therapy is emerging as a promising approach for integrative oncological strategies [54–59].

This review comprehensively synthesizes recent advances in understanding the complex interactions between the microbiome and cancer biology. Initially, we examine the intrinsic relationships between the intestinal microbiota (encompassing bacteria, viruses, fungi, and their metabolites) and the intestinal barrier in carcinogenesis, characterize microbial signatures within tumor tissues, and assess their organ-specific manifestations

and diagnostic implications across diverse anatomical sites including the oral cavity, integumentary system, urogenital tract, and respiratory tract. We subsequently focus on the diagnostic and prognostic implications of microbiome profiles, emphasizing the potential applications of site-specific and kingdom-specific microbial signatures as clinically actionable biomarkers for early cancer detection, therapeutic response prediction, and outcome assessment. Building upon the above studies, we further elucidate the synergistic effects of microbiome regulation in chemotherapy, radiotherapy, immunotherapy, targeted therapy, and surgery. Additionally, we comprehensively summarize various innovative microbiome-based therapeutic strategies, including probiotic/prebiotic interventions, FMT, engineered bacteria therapy, and targeted antimicrobial approaches. Studies have shown that the microbiome not only influences tumor initiation and progression but also offers promising new targets for tumor prevention and treatment. Looking forward, continued technological innovation in microbiome research methodologies, elucidation of molecular mechanisms underlying microbiome–host interactions, development of precision microbiome-targeted therapeutic strategies, and advancement of robust clinical translational studies will collectively deliver more personalized, effective, and safer therapeutic interventions for cancer patients.

GUT MICROBIOME AND TUMOR DEVELOPMENT

Association of bacteria with tumorigenesis

Gut microbes contribute to tumor development through a variety of complex mechanisms, predominantly promoting neoplastic progression via induction of chronic inflammatory responses, disruption of epithelial barrier integrity, and comprehensive remodeling of the TME [60–63]. The relationship between microbiota composition and carcinogenesis demonstrates pronounced species-specificity, with pro-tumorigenic effects predominantly characterized by depletion of beneficial commensal taxa, enrichment of pathogenic bacteria, and dysregulated expansion of opportunistic bacteria [64–66]. However, some investigations have reported heterogeneous findings [67, 68]. Table 1 summarizes the associations between different types of bacteria (probiotics and pathogenic bacteria) and various tumors, delineating their proposed mechanistic contributions to carcinogenesis or tumor suppression, thereby providing a comprehensive framework for understanding the diverse roles of the microbiome in cancer pathogenesis.

Probiotics and tumorigenesis

Intestinal probiotics, beneficial bacteria colonizing the human gastrointestinal tract, play a crucial role in promoting nutrient absorption and maintaining gastrointestinal health by orchestrating gut microbial balance and calibrating intestinal mucosa and systemic immune function through multiple mechanisms [69–71]. Common intestinal probiotics primarily include *Bifidobacterium*, *Lactobacillus*, and *Bacillus* [72, 73, 83, 84]. *Lactobacillus* and *Bifidobacterium* demonstrate significant anti-tumor activity, inhibiting not only digestive malignancies, such as esophageal, gastric, colon, and liver cancer, but also bladder cancer (BCa), through mechanisms including regulation of the pH of the TME, modulation of bile acid metabolism, and degradation of potential carcinogens and their metabolites [66, 85–88]. Additionally, tumor metastasis in patients with gastric cardia adenocarcinoma considerably correlates with decreased *Lactobacillus* counts in the stomach [89]. Patients with hepatocellular carcinoma (HCC) exhibit significantly altered gut microbial composition, with hepatitis B virus (HBV)-associated HCC displaying significant enrichment of *Bacteroides* and *Lachnospiraceae incertae sedis*, while non-HBV-associated HCC shows decreased abundance of *Faecalibacterium*, *Ruminococcus*, and *Ruminoclostridium* [90, 91]. Notably, patients with intrahepatic cholangiocarcinoma had a significantly higher abundance of *Lactobacillus* in fecal samples compared to healthy controls [67]. Comprehensive analyses have established significantly reduced duodenal microbial diversity in patients with pancreatic cancer (PC), with enrichment of *Bifidobacterium spp.* and *Rothia* bacteria [67]. Furthermore, multiple microorganisms, including seven *Bacteroidales* species, significantly enhanced anti-tumor immune responses mediated by CD8⁺ T cells in mice through synergistic effects [92]. Although *Bifidobacterium* and *Lactobacillus* are widely recognized as probiotics within the intestinal ecosystems, their functions in a specific TME may diverge substantially from their canonical probiotic activities. This effect is influenced by multiple factors, including tumor histology, metabolic state, and the dominant bacterial strain. Therefore, “probiotics” cannot be simplistically equated with “anti-tumor,” necessitating that future microbiome-targeted therapies carefully consider strain-specific functions within particular TME.

Pathogenic bacteria and tumorigenesis

Pathogenic bacteria are disease-causing microorganisms. These bacteria can damage host cells either directly or

TABLE 1 Associations and potential mechanisms between different bacterial types and various tumors.

Bacterial type	Representative strains	Associated cancer types	Mechanism	Specificity	References
Probiotics	<i>Lactobacillus</i>	GC CRC Liver cancer BCa	<ul style="list-style-type: none"> Regulate the TME pH and bile acid metabolism; Degrade carcinogens. 	Particular case: elevated <i>Lactobacillus</i> abundance in intrahepatic cholangiocarcinoma	[58, 67, 69–73]
<i>Bifidobacterium</i>		GC CRC Liver cancer	<ul style="list-style-type: none"> Competitively inhibit pathogen colonization; Regulate the TME pH and bile acid metabolism; Maintain intestinal barrier integrity. 	Enriched in PC	[58, 67, 73]
Pathogens	<i>Helicobacter pylori</i>	GC CRC PC HCC	<ul style="list-style-type: none"> Induce DNA damage; Disrupt DNA repair; Activate STAT3 signaling; Decrease Treg cells; Increase CD3 cells. 	Reduces Barrett's esophagus, EAC and IBD risk	[64, 68, 74–78]
	<i>Fusobacterium nucleatum</i>	CRC PC Oral cancer Gliomas	<ul style="list-style-type: none"> Activate pro-cancer pathways; Induce DNA methylation; Suppress immune cell anti-tumor function. 	Promotes tumorigenesis in PC	[40, 79–81]
	<i>Pseudomonas</i>	PC	<ul style="list-style-type: none"> <i>Pseudoxanthomonas</i>: recruits CD8⁺ T cells (anti-tumor). Highly inducible to inflammatory stimuli. 	Improve the OS of PC	[81]
	<i>Enterotoxigenic Bacteroides fragilis</i>	CRC	<ul style="list-style-type: none"> Altering the enterovirus composition. 		[82]
Microbial synergy	<i>Helicobacter pylori + phage</i>	CRC	<ul style="list-style-type: none"> Induce hepatic steatosis; Accumulate toxic metabolites (such as ammonia) 	Synergism promotes CRC progression	[75]
	<i>Ruminococcaceae + Bacteroides</i>	HCC		Alters liver metabolic microenvironment	[66]

Abbreviations: BCa, bladder cancer; CRC, colorectal cancer; EAC, esophageal adenocarcinoma; GC, gastric cancer; HCC, hepatocellular carcinoma; IBD, inflammatory bowel disease; OS, overall survival; PC, pancreatic cancer; pH, potential of hydrogen; STAT3, signal transducer and activator of transcription 3; TME, tumor microenvironment.

indirectly by releasing toxins or inducing immune responses. Intestinal pathogenic bacteria can induce acute or chronic inflammatory responses in the host, several of which directly contribute to tumor development and progression [93–98]. Common intestinal pathogenic bacteria include *Salmonella*, *Shigella*, *enterohemorrhagic E.coli*, *Staphylococcus aureus* (*S. aureus*), and *Clostridium difficile* [99–104]. Gastrointestinal tumor development closely relates to the dynamics of various intestinal microbiota, including *enterotoxigenic Bacteroides fragilis*, *Porphyromonas*, *Flavonifractor plauti* [105], *Campylobacter* spp. [106, 107], and *Fusobacterium nucleatum* (*F. nucleatum*) [66]. *Bacteroides* and *Ruminococcaceae* can contribute to HCC development through promoting inflammatory responses, facilitating toxic substances, and inducing hepatic steatosis [66]. Significant enrichment of *Actinomyces* spp. has been identified in extrahepatic cholangiocarcinoma tissues [108], while chronic *Salmonella typhi* infection significantly correlates with gallbladder cancer development [109]. PC tissues harbor significant *Elizabethkingia* enrichment [110], and *Hungatella hathewayi* can promote cancer by reprogramming host DNA methylation patterns [79]. Beyond digestive system tumors, gut microbiome dysregulation exhibits associations with malignancies in other organ systems. Breast cancer (BC) patients' fecal samples show significantly lower relative abundance of *Bacteroidetes*, *Firmicutes*, and *Faecalibacterium prausnitzii*, with higher levels of *Proteobacteria*, *Actinobacteria*, *Verrucomicrobia*, and *Firmicutes/Bacteroidetes* ratio [111, 112]. Specific *Clostridium* species and *Ruminococcaceae* family members increase BC risk by altering estrogen metabolic pathways [113, 114]. Lung cancer patients show significantly upregulated *Ruminococci* (*R. gnarus*) abundance in fecal microbiome, with squamous cell carcinoma (SCC) patients having higher *Proteobacteria*, *Gammaproteobacteria*, *Bacteroides*, and *Enterobacteriaceae* abundance, while adenocarcinoma patients' feces contain higher *Fusicatenibacter* and *Roseburia* abundance [115]. Prostate cancer (PCa) studies demonstrate a significant correlation between cancer development and relative abundance of *Alphaproteobacteria* and *Bacteroides massiliensis* [116].

Among microorganisms closely associated with gastric tumors, *Helicobacter pylori* (*H. pylori*) is the most extensively documented. *H. pylori* is the most common pathogenic bacterium in gastric tissues, promoting tumorigenesis and progression by inducing DNA damage, interfering with DNA repair mechanisms, and activating oncogenic pathways [64]. Numerous studies confirm *H. pylori*'s significant positive association with gastric, colorectal, and PC risks, leading to its classification as a class I carcinogen by the World Health

Organization [117–119]. Cross-sectional studies demonstrate that *H. pylori* infection significantly correlates with colorectal cancer (CRC) risk (OR = 1.9), surpassing the associations observed with established risk factors including body mass index (BMI), smoking, and alcohol consumption [120]. Research indicates that both *H. pylori*-infected CRC patients and mouse models exhibit activation of pro-carcinogenic signal transducer and activator of transcription 3 (STAT3) signaling, loss of intestinal epithelial goblet cells, reduction in Treg cells, and significant increases in CD3 cells (pro-inflammatory T cells) [74]. These findings suggest that *H. pylori* functions not merely as a risk indicator for CRC but also establishes a pro-carcinogenic microenvironment within the colon. Additionally, animal experiments demonstrate that *H. pylori* can increase the abundance of CRC-associated intestinal bacteriophages, thereby altering the intestinal virome composition, which is associated with CRC development [75]. Cohort studies reveal that serological responses to the *H. pylori* virulence factor VacA exhibit positive correlations with CRC risk [76]. A recent cohort study demonstrated that *H. pylori* has significant positive associations with both CRC incidence and mortality. Individuals with untreated *H. pylori* infection exhibited significantly higher incidence and mortality rates compared to those who received treatment [121]. *Helicobacter hepaticus* has been identified in hepatitis C virus (HCV)-associated HCC tissue specimens [122, 123], although subsequent research challenged its pathogenic role in HBV-associated HCC [122]. Mouse model studies have shown that *Helicobacter hepaticus* can inhibit HCC progression by suppressing intrinsic immunity's recognition and clearance functions of tumor cells [124]. The detection of *Helicobacter bilis*, *Helicobacter hepaticus*, or *H. pylori* in biliary tract cancer tissues demonstrates significant correlations with increased cancer risk [109, 125–127]. Various intestinal microorganisms, including *Bacteroidetes*, *Proteobacteria*, and *Streptococcaceae*, show synergistic effects with *H. pylori* in promoting gastrointestinal tumorigenesis [128]. Interestingly, *H. pylori* exhibits protective effects against Barrett's esophagus, esophageal adenocarcinoma (EAC), and inflammatory bowel disease (IBD) [69, 77, 78]. Multiple studies have demonstrated a negative correlation between *H. pylori* infection and EAC and Barrett's esophagus [129]. A case-control study established that *H. pylori* infection exhibits strong negative associations with both erosive esophagitis and Barrett's esophagus [68]. A previous community-based study reached the same conclusion, showing that *H. pylori* infection and CagA⁺ status are negatively associated with newly diagnosed Barrett's esophagus [130]. A subsequent meta-analysis including 10 studies revealed that among Asian populations, IBD patients had significantly

lower *H. pylori* infection rates compared to non-IBD patients [78]. The negative association between *H. pylori* infection and IBD is independent of ethnicity, age, *H. pylori* detection methods, and previous medication use, while antibiotic use influenced this association [131, 132]. Research suggests that the *H. pylori* genome contains immunomodulatory elements that may explain its protective effect against IBD through suppression of inflammatory responses via downregulation of dendritic cell (DC)-produced IL-12 and type I interferon levels [133, 134]. Case-control studies show that both gastric atrophy and *H. pylori* seropositivity are associated with reduced risk of EAC, Barrett's esophagus, and reflux esophagitis, with this negative correlation persisting in patients without gastric atrophy [135, 136]. A recent study postulates that *H. pylori* eradication may disrupt the inflammatory microenvironment, thereby inhibiting the proliferation of other bacteria and reducing EAC risk [137]. However, some cohort studies have not observed increased EAC risk following *H. pylori* eradication [138].

Conditional pathogens are bacteria that may cause disease when there is an imbalance in the host microbiota homeostasis [139, 140], and they are associated with impaired immune systems. These bacteria can elevate cancer risk and facilitate tumorigenesis and progression through direct DNA damage or by inducing microbiota dysbiosis [6, 141, 142]. *Veillonella* and *Prevotella* are commensal in the gut most of the time, but can also cause disease in the context of the dysregulated immune microenvironment. *Veillonella spp.* and specific species of *Prevotella* are associated with gastric cancer (GC) risk [143]. Elevated levels of *Bacteroides fragilis* [144–146] and *Streptococcus gallolyticus* (*S. gallolyticus*) [147, 148] were detected in tumor tissues of patients with CRC, and fecal specimens from these patients demonstrated significantly higher prevalence of *Enterococcus faecalis* [149]. Additionally, enterotoxigenic *Bacteroides fragili* (ETBF) is highly responsive to inflammatory stimuli and considered a risk factor for CRC [82]. *Enterococcus faecalis* potentially promotes chromosomal instability associated with both sporadic adenomatous polyps and CRC [150].

Hepatobiliary tumors have also been associated with various conditionally pathogenic bacteria. Enrichment of *Fusobacterium*, *Prevotella*, and *Novosphingobium* was observed in extrahepatic cholangiocarcinoma tissues [108]. *Fusobacteria* enrichment was observed in duodenal fluids from PC patients, especially those with short-term survival [151]. The presence of *Pseudoxanthomonas* in PC tissues correlated with increased density of CD8⁺ T cells and improved overall survival (OS) [152]. In contrast, animal experiments showed *B. pseudolongum* migrating from intestine to pancreas and

enriched in PC tissues, obstructing immunity mediated by T cells, and suppressing immune responses to pancreatic tumors [110]. Additionally, large amounts of *Fusobacterium* in PC tumor tissues often indicate poor prognosis [153].

F. nucleatum is a common opportunistic pathogen residing in the gastrointestinal tract and oral cavity, associated with multiple cancers, including CRC, PC, oral cancer, and gliomas [40, 80, 110, 154]. This microorganism is significantly enriched in neoplastic tissues compared to healthy mucosa across these diverse cancer types. *F. nucleatum* contributes to tumor development and progression through diverse mechanisms: it reprograms host DNA methylation patterns, potentially facilitating the initiation of PC [79]; enhances CRC metastasis by suppressing anti-tumor immunity, promoting immune evasion, and modulating the E-cadherin/β-catenin signaling pathway via FadA adhesin [81, 154–156]; recruits tumor-associated macrophages (TAMs) to the TME via CCL20 upregulation, thereby accelerating the progression of CRC [157]; promotes M2 macrophage polarization and activation [158]; and stimulates cancer cell invasion in PC through autocrine/paracrine pathways [159]. Within the TME, intratumoral *F. nucleatum* modulates immune responses by inducing T helper 17 (Th17) cell enrichment and promoting secretion of IL-17 family cytokines via the metabolite-sensing receptor FFAR2, thereby establishing pro-inflammatory microenvironmental conditions [160]. Clinically, *F. nucleatum* serves as a specific diagnostic and prognostic biomarker in CRC, GC, oral cancer, PC, and lung cancer, with its intratumoral abundance demonstrating a significant negative correlation with OS in CRC patients [40, 161–164]. Furthermore, *F. nucleatum* induces chemoresistance in CRC, particularly to oxaliplatin, by inhibiting caspase-mediated cascades via autophagy modulation and BIRC3 upregulation [165–167]. As previously described, *F. nucleatum* can regulate the expression of β-catenin [156]. Studies have shown that the β-catenin signaling pathway, which can be activated through multiple pathways, is associated with the development of resistance to lenvatinib in HCC [168–170]. Therefore, the modulation of β-catenin expression by *F. nucleatum* may influence the sensitivity of tumor cells to lenvatinib, although the precision molecular mechanisms and clinical relevance of this association require further rigorous investigation. Conversely, the development of targeted therapeutic approaches, such as employing butyrate derivatives to inhibit bacterial proliferation and adhesion, utilizing engineered bacterial outer membrane vesicles to specifically target *F. nucleatum*, or leveraging its presence to implement immunostimulatory strategies, collectively demonstrates

promising therapeutic potential, particularly when integrated with established treatment modalities [165, 171].

Association of viruses with tumorigenesis

Viruses contribute to tumor development through both direct oncogenic mechanisms and modulation of the host immune microenvironment [172–174]. The molecular mechanisms span multiple pathways, including oncogenic virus-induced genetic material damage, microbiota dysregulation, and phage-mediated metabolic network regulation [175–177]. Among these, oncogenic viruses function as primary drivers of tumorigenesis, exerting critical regulatory influences on cancer development. Table 2 summarizes the oncogenic mechanisms of major viral types in different tumors and their clinical significance, providing a systematic reference for understanding virus-mediated tumorigenesis.

Carcinogenic viruses and tumorigenesis

Oncogenic viruses represent a specialized category of viruses that infect host cells and interfere with cellular growth regulatory mechanisms, thereby inducing aberrant cell proliferation and ultimately promoting tumor formation [191–195]. These viruses can promote tumorigenesis through multiple mechanisms, including induction of DNA damage, disruption of DNA damage response (DDR) system, expression of oncogenic proteins, activating cancer-related signaling pathways, activation of cell cycle control, and dysregulation of apoptosis [196, 197]. Within the spectrum of digestive system oncogenic viruses, HBV and HCV represent the predominant pathogens responsible for HCC. These viruses could promote HCC development and progression through multiple mechanisms, including inducing epithelial–mesenchymal transition (EMT), regulating the cell cycle, and inducing chronic inflammatory responses and tissue fibrosis [175, 178, 198]. Epstein–Barr virus (EBV) demonstrates strong associations with B-cell lymphoproliferative disorders and nasopharyngeal carcinoma (NPC) [179], while additionally influencing tumor development through modulation of intestinal microbiota and their metabolites [199], as well as contributing to GC progression [180]. Human papillomavirus (HPV) may contribute to cervical cancer (CC) pathogenesis by suppressing immune surveillance and inhibiting cytotoxic responses in lymphocytes, thereby significantly influencing the TME [181]. Additionally, human immunodeficiency virus (HIV) may contribute

to the development and progression of oral and anal cancerous lesions through alteration of regional microbiota composition via mechanisms linked to carcinogenesis [182].

Phages and tumorigenesis

In recent years, the role of phages in tumor development has garnered increasing attention, with their regulatory mechanisms exhibiting distinct characteristics across different tumor types [200–206]. Several studies in CRC have revealed specific alterations in phage communities. Phages of the families *Siphoviridae* and *Myoviridae* were significantly enriched in the feces of CRC patients, while streptococcal phages and *Vibrio*-inhabiting phage populations were also abnormally increased [176, 183]. Although the biological significance of temperate phages remains controversial [176], experiments have shown that they may indirectly influence CRC progression through modulation of gut microbial composition and metabolic functions [184].

Dysbiosis in phage communities induces lysis of host bacteria and subsequent alterations in gut microbial abundance, resulting in the release of antigenic substances including proteins, lipids, and nucleic acids from bacteria. This process can induce host inflammatory responses and tissue damage, promoting CRC [185]. Notably, *Caudovirales* phages exhibit dual roles in the intestinal inflammatory environment, both enhancing survival in CRC-prone animals through inhibition of oncogenic bacterial colonization, while paradoxically exacerbating IBD pathology through their over-amplification [186]. Certain phages directly interact with cancer cells and modulate the expression levels of proteins involved in carcinogenesis and metastasis, particularly integrins [207]. These findings indicate that phages function as both potential drivers of tumorigenesis and novel bioregulatory targets, though their specific mechanisms warrant comprehensive investigation within the context of cancer-specific microbial-immune microenvironments.

Other viruses and tumorigenesis

Beyond established oncogenic viruses, diverse viral agents contribute to tumorigenesis and progression through both direct and indirect mechanisms. In patients with persistent enterovirus 71 (EV71) infection, chronic presence of EV71 viral antigen in intestinal tissue significantly correlates with advanced CRC, potentially promoting disease progression through recruitment and stimulation of Th17 cells in the TME [177]. In BC studies,

TABLE 2 Oncogenic mechanisms of different virus types in different tumors and their clinical significance.

Virus type	Representative viruses	Associated cancer types	Primary carcinogenic mechanisms	Clinical significance	References
Carcinogenic viruses	HBV HCV	HCC	<ul style="list-style-type: none"> Induce chronic inflammation and fibrosis; Regulate cell cycle; Promote EMT. 	HBV/HCV vaccination and antiviral therapy significantly reduce HCC risk.	[175, 178]
EBV	NPC GC	B-cell lymphoma	<ul style="list-style-type: none"> Encode oncoproteins (such as LMP1 and EBNA2); Modulate gut microbiota metabolites. 	EBV DNA detection for early screening of NPC.	[179, 180]
HPV	CC		<ul style="list-style-type: none"> Suppress immune surveillance; Inhibit lymphocyte cytotoxicity; Regulate TIM. 	The HPV vaccine can prevent CC and other related cancers.	[181]
HIV	Oral cancer Anal cancer		<ul style="list-style-type: none"> Alter local microbiota composition; Chronic immunosuppression promotes carcinogenesis. 	HIV-infected individuals require intensified cancer screening.	[182]
Phages	<i>Siphoviridae</i> <i>Myoviridae</i>	CRC	<ul style="list-style-type: none"> Regulate gut microbiota composition; Release bacterial antigens to induce inflammation; Indirectly promote carcinogenic bacterial proliferation. 	Phage community analysis as a potential early diagnostic marker for CRC.	[176, 183, 184]
<i>Caudovirales</i>		CRC	<p>Bidirectional role:</p> <ul style="list-style-type: none"> Inhibit carcinogen colonization (anti-cancer); Exacerbate inflammation (pro-cancer) upon overgrowth. 	Phage therapy requires precise regulation to avoid inflammatory aggravation.	[185, 186]
Other viruses	EV71	Advanced CRC	<ul style="list-style-type: none"> Recruit Th17 cells to promote TME inflammation; Persistent viral antigen stimulation drives cell proliferation. 	EV71-persistent infection requires enhanced CRC monitoring.	[177]
MMTV BLV	BC		<ul style="list-style-type: none"> Genomic integration activates host oncogenes; Evade immune clearance. 	MMTV/BLV antibody detection as a potential BC risk prediction tool.	[187]
HCMV	BC Glioma		<ul style="list-style-type: none"> Encode oncogenes; Suppress tumor suppressor proteins. 	HCMV-targeted therapy may enhance chemo/radiotherapy sensitivity.	[188, 189]
HERV-K	OC PC HCC		<ul style="list-style-type: none"> Retrotransposition induces genomic instability; Activate pro-cancer signalling pathways. 	HERV-K expression correlates with tumor prognosis.	[190]

Abbreviations: BLV, bovine leukemia virus; CC, cervical cancer; EBNA2, Epstein–Barr virus nuclear antigen-2; EBV, Epstein–Barr virus; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HIV, human immunodeficiency virus; HPV, human papilloma virus; EMT, epithelial–mesenchymal transition; EV71, enterovirus 71; HCMV, human cytomegalovirus; HERV-K, human endogenous retrovirus-K; LMP1, latent membrane protein1; MMTV, mouse mammary tumor virus; NPC, nasopharyngeal carcinoma; OC, ovarian cancer; Th17, T helper 17; TME, tumor microenvironment.

both mouse mammary tumor virus (MMTV) and Bovine leukemia virus (BLV) have been associated with BC development, with studies suggesting a likely causal relationship [187]. Additionally, human cytomegalovirus (HCMV) has been associated with various malignant tumors, including BC, possibly related to potent oncogenes in its genome [188, 189]. Human endogenous retrovirus K (HERV-K) is highly expressed in various reproductive tumors, including ovarian cancer, and has also been associated with the progression of PC and HCC [190].

Association of fungi with tumorigenesis

Fungal communities represent a key component of the human microbiome, with their homeostatic imbalances strongly associated with tumor development. Specific fungal species induce inflammatory responses and disrupt immune homeostasis, consequently promoting tumorigenesis and tumor progression [208–211]. This process manifests primarily through aberrant proliferation of commensal fungi or excessive colonization by pathogenic fungi [212, 213].

As shown in Table 3, distinct tumors exhibit characteristic fungal signatures that correlate significantly with tumorigenesis, progression, and prognosis, providing critical insights into fungal-mediated tumor pathogenesis and potential therapeutic interventions.

Symbiotic fungi and tumorigenesis

The human body harbors numerous fungi that establish symbiotic relationships with host tissues, predominantly colonizing mucosal surfaces (including the oral cavity, intestines, and vagina) and skin [223, 224]. These symbiotic fungi serve critical functions in maintaining microbial community equilibrium, regulating metabolic processes, and preserving immune system homeostasis [225]. However, ecological dysbiosis within the fungal microbiome contributes to both initiation and progression of digestive system malignancies through diverse mechanisms, including modulation of the host immune microenvironment and fungal–bacterial interactions [212]. Studies demonstrate that fungal community

TABLE 3 Characteristic fungal alteration patterns in tumors and their mechanisms.

Cancer type	Characteristic fungal alterations	Mechanism	Clinical relevance	References
GC	Symbiotic fungal imbalance: <i>Malassezia globosa</i> ↑ <i>Saccharomyces cerevisiae</i> ↓	<ul style="list-style-type: none"> Fungal dysbiosis induces chronic inflammation; Disrupts mucosal barrier function. 	Salivary/tongue coating fungal communities as early screening markers for GC.	[214, 215]
CRC	Pathogenic fungal enrichment: <i>Candida albicans</i> ↑ <i>Schizosaccharomyces pombe</i> ↑ <i>Malassezia spp.</i> ↑	<ul style="list-style-type: none"> Activate Wnt/β-catenin pathway to promote proliferation; Secret pro-cancer proteins; Induce cell adhesion gene dysregulation. 	<ul style="list-style-type: none"> <i>Candida</i> abundance correlates with advanced CRC; Fungal translocation to blood indicates metastasis risk. 	[216–218]
PC	3000-fold fungal concentration ↑: <i>Malassezia</i> ↑	<ul style="list-style-type: none"> Complement C3 pathway activation promotes pro-inflammatory microenvironment. 	<ul style="list-style-type: none"> Fungal load correlates with poor prognosis; Potential biomarker for therapeutic resistance. 	[219, 220]
HCC	Opportunistic fungal colonization: <i>Candida albicans</i> ↑ <i>Malassezia furfur</i> ↑	<ul style="list-style-type: none"> Induce oxidative stress; Synergize with HBV/HCV to promote liver fibrosis. 	Fungal-viral co-infection accelerates HCC progression.	[217]
BC	Tumor microenvironment dysbiosis: <i>Candida albicans</i> infection ↑	<ul style="list-style-type: none"> Increase Treg cells to suppress immunity; Promote angiogenesis. 	Antifungal therapy may enhance ICIs efficacy.	[213]
Melanoma	<i>Saccharomycetales</i> ↑	<ul style="list-style-type: none"> T cells recognize melanoma antigens. 	Fungal diversity may correlate with immunotherapy response.	[221]
PCa	Plasma fungal dysbiosis: <i>Sordariomycetes</i> ↑	<ul style="list-style-type: none"> Promote inflammatory microenvironment. 	<ul style="list-style-type: none"> Specific fungi may assist in identifying PCa 	[222]

Abbreviations: ↑, Increased; ↓, Decreased; ICIs, immune checkpoint inhibitors; IL-6, Interleukin-6; PCa, prostate cancer; Treg, regulatory T cells.

compositions in saliva and tongue samples from GC patients undergo significant alterations, characterized by marked enrichment of *Malassezia globosa* (*M. globosa*) and concurrent depletion of the symbiotic fungus *Saccharomyces cerevisiae* (*S. cerevisiae*) [214]. Patients with CRC showed not only significant increases in *S. cerevisiae* and *Malassezia spp.* abundance [226, 227] but also elevated levels of proteins secreted by *Schizosaccharomyces pombe*, including four key proteins strongly implicated in tumor progression [216]. In PC studies, fungal concentrations in tumor tissues were approximately 3000-fold higher than in normal tissues, with *Malassezia spp.* demonstrating significant enrichment and capacity to promote pancreatic tumor growth through the complement pathway. This was particularly pronounced in PC, where genes related to immunity and inflammation exhibited significant upregulation, suggesting a substantial role for *Malassezia* [219, 220] in disease pathogenesis. Additionally, the modulatory role of intestinal fungal microbiota on the TME extends to other cancer types, with melanoma patients demonstrating significantly elevated fungal abundance compared to healthy controls and selective enrichment of *Saccharomycetales spp.* [221].

Pathogenic fungi and tumorigenesis

Extensive research has demonstrated that specific pathogenic fungi promote the development of diverse tumor types through multiple oncogenic mechanisms. Additionally, certain commensal fungi transition to pathogenic phenotypes through interactions with other microorganisms, influenced by host immune status and genetic factors [217]. The fungal microbiome of GC patients exhibits significant dysbiosis compared to healthy controls. *Candida albicans* (*C. albicans*) may promote GC by increasing intestinal inflammation, with significantly elevated proportions of *Malassezia*, *Cutaneotrichosporon*, and *Fusicolla acetilerea*, alongside significantly reduced abundance of *Penicillium arenicola*, *Aspergillus montevidensis*, and *C. glabrata* [215, 217, 228]. Patients with CRC exhibit enrichment of *Basidiomycota* and *Ascomycota*, with significant increases in *C. albicans*, *Malassezia*, and *Rhodotorula* abundance. *C. albicans* promotes intestinal epithelial cell proliferation through activation of Wnt signaling pathway, thereby accelerating tumor progression [218, 226, 227]. Elevated *Candida* abundance in advanced CRC patients may lead to dysregulated expression of cell adhesion genes and facilitate translocation of fungal components into the bloodstream [217]. The observation that *Aspergillus rambellii* significantly enhances cancer cell proliferation in vitro and

accelerates tumor growth in vivo [229] further substantiates the potential causal relationship between fungal dysbiosis and CRC [217].

Studies in HCC have established that aberrant colonization by *C. albicans* and *M. furfur* promotes tumor development, while *Alternaria alternata* contributes to PC progression [217]. Beyond digestive system malignancies, *C. albicans* infection enhances BC growth by expanding regulatory T cell (Treg) populations within splenocytes and the TME [213]. Patients with head and neck squamous cell carcinoma (HNSCC), GC, CRC, and lung cancer have significant intestinal fungal dysbiosis, characterized by enrichment of opportunistic pathogenic fungi (including *Cutaneotrichosporon*, *Malassezia*, and *Trichosporon*) [221]. The diversity of circulating fungal microbiome in plasma of PCa patients differs significantly from healthy controls, with marked *Sordariomycetes* enrichment observed in PCa cases with high pathological grade of tumor [222].

Microbial metabolites and tumorigenesis

Microbial metabolites produced by intestinal microbiota can contribute to tumorigenesis and progression through multiple mechanisms, including modulation of host immune responses, regulation of cell proliferation signaling pathways, and alteration of intestinal barrier integrity. Short-chain fatty acids (SCFAs), secondary bile acids, and tryptophan metabolites represent key microbial products that exert important regulatory effects on the intestinal microenvironment and host health [230–236]. Table 4 summarizes the mechanisms through which these key microbial metabolites influence diverse tumor types and their potential clinical applications, highlighting recent advances in microbial metabolism within oncological research.

Short-chain fatty acids

SCFAs constitute essential intestinal microbial metabolites, primarily consisting of acetic acid, propionic acid, and butyric acid. These compounds exhibit bidirectional regulatory effects on digestive system tumor development through modulation of host immune response, inflammatory processes, and epigenetic modifications [252–255]. SCFAs may play a significant regulatory role in CRC, particularly butyric acid, which modulates tumor cell proliferation, apoptosis, and invasive capacity through receptor-mediated signaling, thereby inhibiting intestinal inflammation and carcinogenesis [237]. Additionally, oral

TABLE 4 Key microbial metabolites: mechanisms of action in different tumor types and their potential clinical significance.

Metabolite type	Metabolite	Associated cancer types	Mechanism	Clinical significance	References
SCFAs	Butyrate	CRC	<ul style="list-style-type: none"> Promotes abnormal proliferation and transformation of colonic epithelial cells; Regulates HDAC activity to induce apoptosis in cancer cells. 	Probiotics (such as <i>C. butyricum</i>) are targeted to deliver butyric acid or as adjunctive therapy.	[237, 238]
	Propionate	BC	<ul style="list-style-type: none"> Inhibits STAT3 pathway; <ul style="list-style-type: none"> Promote the accumulation of ROS; Activates p38; Reverses microbiota dysbiosis induced by psychological stress. 	Sodium propionate combined with chemotherapy enhances efficacy.	[239, 240]
Anti-inflammatory SCFAs		HCC	SCFA-producing bacteria (such as <i>Faecalibacterium</i>) decrease, leading to weakened anti-inflammatory effects and promoting HCC progression.	Fecal microbiota transplantation to restore SCFA levels or inhibit HCC progression.	[91]
Pentanoate	Melanoma	Melanoma	Enhance the anti-tumor effects of CTLs and CAR-T cells.	Synergistic cancer immunotherapy.	[241]
Butyrate	Pancreatic cancer				
Secondary bile acids	Deoxycholic acid	CRC	<ul style="list-style-type: none"> Induces DNA oxidative damage and chromosomal instability; Promotes proliferation of mutagenic bacteria (such as Bilophila). 	Monitor deoxycholic acid levels in high-fat diet patients to prevent adenoma-to-carcinoma transition.	[242, 243]
	Lithocholic acid	BC	<ul style="list-style-type: none"> Induces oxidative stress to inhibit EMT. 	Lithocholic acid analogs as potential therapies for metastatic BC.	[244, 245]
Tryptophan metabolites	Indole derivatives	CRC	<ul style="list-style-type: none"> <i>Akkermansia muciniphila</i> inhibits AhR/β-catenin pathway to reduce risk. 	Indole derivatives (such as indole-3-carbinol) as chemopreventive agents.	[246-249]
	Kynurenone	Pan-cancer	<ul style="list-style-type: none"> Suppresses T-cell function to promote immune evasion; Activates IDO1 pathway to drive tumor progression. 	IDO1 inhibitors combined with ICIs therapy.	[250, 251]

Abbreviations: AhR, aryl hydrocarbon receptor; CTLs, cytotoxic T lymphocytes; HDAC, histone deacetylase; IDO1, indoleamine 2,3-dioxygenase-1; ROS, reactive oxygen species; SCFAs, short-chain fatty acids.

probiotic spores (spores-dex) specifically colonize CRC lesions and generate anti-tumor SCFAs through *C. butyricum*-fermented dextran, achieving targeted intervention within the TME [238]. In HCC patients, the abundance of SCFA-producing commensal bacteria (such as *Faecalibacterium*, *Ruminococcus*, and *Ruminoclostridium*) is significantly reduced, and the decrease in SCFA levels may promote HCC progression through impairment of their anti-inflammatory effects [91]. Disturbances in bacterial metabolites, including SCFAs, lipopolysaccharides (LPS), and lipoproteins, resulting from microbiota dysbiosis constitute established pathogenic mechanisms in PC development [256]. In BC research, sodium propionate (SP) induces apoptosis and suppresses tumor cell proliferation through inhibiting the STAT3 signaling pathway, enhancement of reactive oxygen species (ROS) accumulation, and activating p38 [239]. Concurrently, psychological stressors including social isolation may diminish SCFA production through disruption of the brain-gut-microbiome axis homeostasis, thereby potentially increasing BC risk [240]. Furthermore, SCFAs demonstrate considerable therapeutic potential for neutrophil dysfunction-related conditions, including IBD and various malignancies [257, 258]. As critical mediators at the microbiota-tumor interface, imbalances in SCFA levels and functions may contribute to the pathogenesis of digestive and systemic cancers through diverse molecular mechanisms [259–263].

Microbial-derived SCFAs modulate the activity and function of immune cells, including lymphocytes, macrophages, DCs, and neutrophils, thereby influencing the TIME and exerting complex bidirectional effects on tumor progression [264]. Consequently, SCFAs represent potential therapeutic targets for cancer therapy. In vitro experiments demonstrate that sodium butyrate (NaB) inhibits lung cancer development and progression through suppression of cancer cell proliferation, induction of tumor cell apoptosis, and modulation of immune responses [265]. SCFAs generated through dietary fiber fermentation by gut microbiota enhance host antibody responses, with their capacity to potentiate B cell immune function documented in both mice and humans [266]. Dietary fiber-derived SCFAs regulate immune system hematopoiesis, thereby exerting anti-neoplastic effects [267]. In murine tumor models, SCFAs (pentanoate and butyrate) significantly potentiate the anti-tumor efficacy of cytotoxic T lymphocytes (CTLs) and chimeric antigen receptor T (CAR-T) cells, demonstrating potential for synergistic therapy in cancer immunotherapy [241]. SCFAs are significantly reduced in CRC and supplementation with probiotics that metabolize SCFAs can inhibit tumor cell growth. In both mouse CRC models and CRC patients, SCFAs have been

observed to enhance host responses to chemotherapy and immunotherapy [268]. Therefore, SCFAs are regarded as substances with potential for adjuvant cancer treatment.

Secondary bile acids

Secondary bile acids (including deoxycholic acid [DCA] and lithocholic acid [LCA]) are metabolites generated through microbial transformation of primary bile acid in the gut and may play crucial roles in host immunomodulatory and metabolic networks with complex regulatory effects on digestive system cancers [269–274]. Studies demonstrate significantly elevated secondary bile acid concentrations in the intestines of patients with CRC [242], potentially driving carcinogenesis through induction of cellular damage including membrane disruption, mitochondrial dysfunction, and genomic mutations [275]. High-fat diet (HFD) promotes tumor-promoting properties of mouse colonic mesenchymal stromal cells (MSCs) by increasing primary/secondary bile acid production [276]. Furthermore, secondary bile acid-enriched microenvironments selectively promote the proliferation of bile salt-resistant microorganisms (particularly *Bilophila* and *Desulfovibrio*), which accelerate adenoma-to-CRC transformation through release of pro-inflammatory or mutagenic metabolites including hydrogen sulfide (H_2S) and secondary bile acids [243]. HCC-related studies show that intestinal bacteria suppress hepatic natural killer T (NKT) cell accumulation, thereby attenuating anti-tumor immune responses and facilitating hepatic metastasis through mediation of primary-to-secondary bile acid conversion [277]. Animal experiments demonstrate that in BC, LCA induces oxidative stress, promotes mesenchymal-to-epithelial transformation, inhibits tumor cell proliferation and metastasis, and suppresses cancer cell proliferation [244, 245]. Secondary bile acids may exert context-dependent effects, both oncogenic and tumor-suppressive, in digestive and systemic malignancies through mechanisms including direct genotoxicity, immune microenvironment modulation, and microbial interactions [278–281].

Tryptophan metabolites

Tryptophan metabolites (including indoleacetic acid, kynurenone, and tryptamine), as key molecules generated through microbial tryptophan metabolism, exert complex regulatory effects on digestive cancer development via multiple pathways encompassing immunomodulation, inflammatory response regulation, and epigenetic modifications [282–288]. Tryptophan catabolism, involving this essential amino acid critical for protein synthesis, modulates

cancer-related immune responses and tumor suppression mechanisms [250, 289]. Studies demonstrate that dysregulated microbiota-mediated tryptophan metabolism strongly correlates with impaired intestinal barrier function, while its metabolites (including indole and indole-3-acetic acid) modulate colon cancer progression through regulation of cell proliferation, metastasis, and anti-inflammatory activity via multiple signaling pathways [246, 247]. Notably, mucin-producing *Akkermansia muciniphila* significantly reduces CRC development risk in mice through specific inhibition of tryptophan metabolism-dependent aryl hydrocarbon receptor (AhR)/β-catenin signaling pathway [248]. Additionally, indole derivatives (such as indole sodium analogs) can modulate IL-6 expression in colon tumor cell lines through AhR activation [249]. A comprehensive analysis across five cancer types revealed that alterations in plasma tryptophan and its metabolites (such as GABA and melatonin) in cancer patients may interfere with immune responses and contribute to malignant progression [251]. Research further established that compositional differences in gut microbiota between cancer patients and healthy individuals significantly alter tryptophan metabolite profiles, suggesting these metabolites may serve as biomarkers for cancer screening and detection [251].

Intestinal barrier function alteration and tumorigenesis

Disruption of intestinal barrier function constitutes a critical driver of tumorigenesis and development [290–293]. Studies demonstrate that altered intestinal permeability represents a core feature of impaired intestinal barrier function. Additionally, immune dysfunction serves as a pivotal mediator in intestinal barrier disruption processes [294–298]. Notably, inflammatory response activation constitutes a fundamental molecular mechanism underlying altered intestinal barrier function [299, 300]. Importantly, intestinal barrier disruption resulting from microbiota dysbiosis contributes to cancer development and progression through multiple pathways. In summary, intestinal barrier function disruption establishes a critical link between microbiome and tumorigenesis through multiple interconnected processes, including enhanced intestinal permeability, immune system dysregulation, and inflammatory cascade activation, a complex pathophysiological sequence with molecular mechanisms illustrated in Figure 1.

Intestinal permeability alteration

Increased intestinal permeability represents a cardinal pathological feature of microbe–host interactions in

digestive cancer pathogenesis, operating through multiple mechanisms including facilitation of microbial translocation, induction of inflammatory cascades, and enhancement of carcinogen exposure [301]. Studies show that tight junctions (TJ) between colonic epithelial cells function cooperatively with the epithelial cells to maintain intestinal barrier stability, and increased TJ permeability correlates with CRC development and progression [302]. Regular probiotic supplementation potentially prevents CRC through the reduction of intestinal permeability and diminished carcinogen absorption [303]. Hepatic research demonstrates that obesity-induced intestinal hyperpermeability facilitates dysbiosis, promotes chronic inflammatory responses, and consequently accelerates CRC initiation and progression [304, 305]. Intestinal inflammation induces altered intestinal permeability, while compromised barrier function permits bacterial translocation, thereby exacerbating malignancy through the establishment of chronic inflammatory states [306]. In contrast, SCFAs serve a crucial function in maintaining intestinal barrier integrity. Butyrate protects intestinal epithelial cells, alleviates local inflammatory responses, and enhances barrier function through stabilization of hypoxia-inducible factor-1 (HIF-1) and increasing transcription of Claudin-1 protein (an integral membrane protein present in epithelial and endothelial cells) [307, 308]. Additionally, NaB activates the GPR109A signaling pathway and while concurrently downregulating NF-κB p65 and AKT signaling cascades, thereby suppressing intestinal inflammation and restoring epithelial barrier function [309]. Modulation of intestinal permeability constitutes a critical interface between microbiota dysbiosis and tumorigenesis. Consequently, targeted interventions aimed at intestinal barrier restoration or microbiome manipulation represent promising therapeutic strategies for prevention and treatment of gastrointestinal malignancies.

Immune dysfunction

As a fundamental pathological consequence of dysregulated microbiota–host interactions, immune dysfunction exerts multifaceted influences on digestive cancer development through modulation of immune cell polarization, activation of inflammatory signaling pathways, and orchestration of cross-organ immune responses [310, 311]. Perturbation of the gastric micro-ecosystem, encompassing bacterial, fungal, and viral community dysbiosis, induces immune dysfunction within the gastric mucosa, characterized by diminished commensal microbes and enhanced abundance or virulence of pathogenic microorganisms, consequently promoting carcinogenesis through sustained inflammatory responses and immune dysregulation [312]. Concurrently,

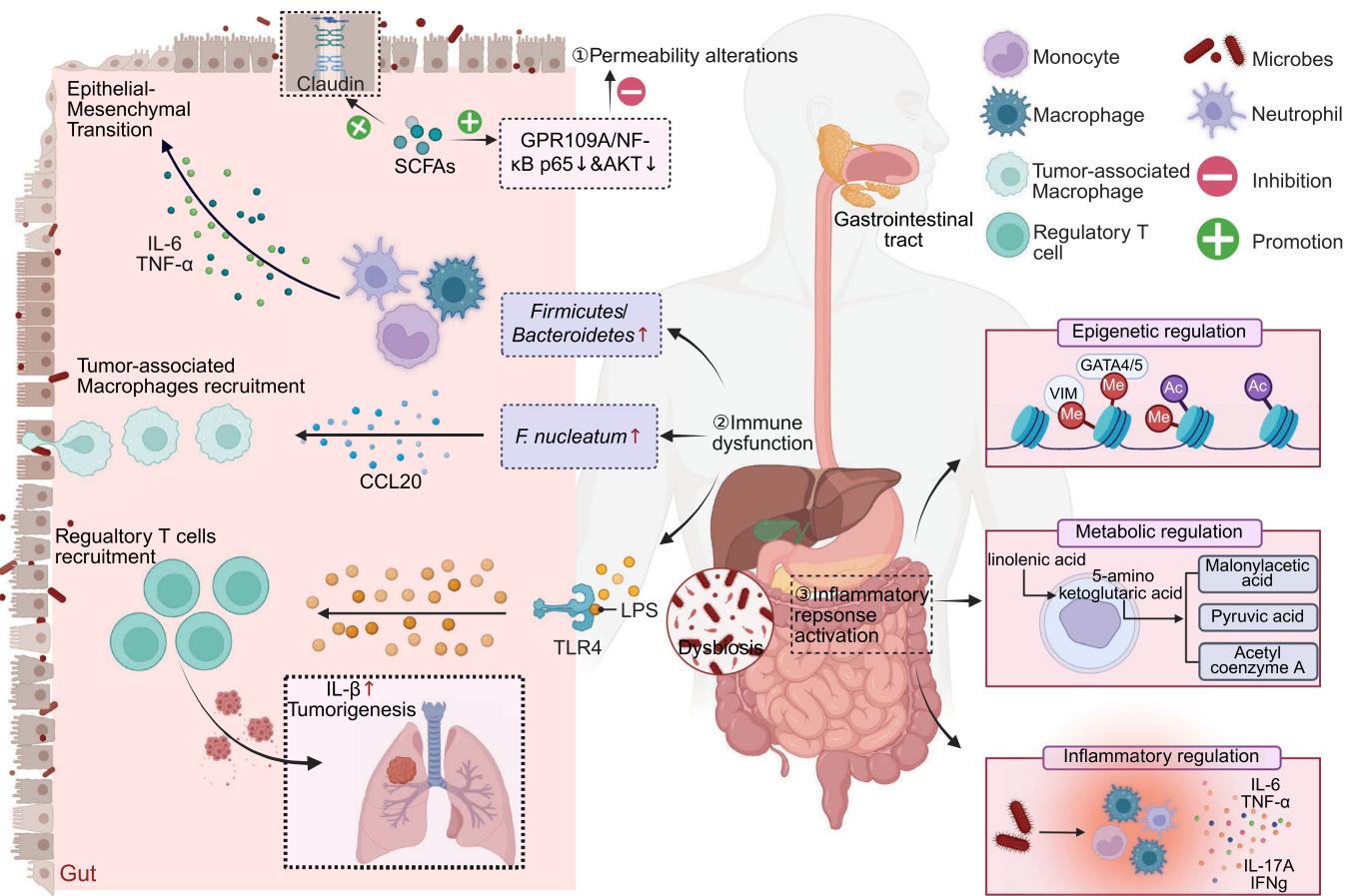


FIGURE 1 Mechanisms and cancer type-specific characteristics of tumor-associated microbiota. Multiple mechanisms induce intestinal barrier function disruption, involving intestinal permeability alteration, immune dysfunction, and inflammatory response activation. Increased intestinal permeability impairs intestinal barrier function and triggers microbial translocation, potentially exacerbating malignancy. SCFAs act as protectors that maintain intestinal barrier integrity through upregulating transcription of Claudin-1 protein and activating the GPR109A signaling to downregulate NF- κ B/AKT inflammatory response signaling. Regarding immune dysfunction, an imbalanced *Firmicutes* and *Bacteroidetes* ratio, along with the secretion of pro-inflammatory factors IL-6 and TNF- α , promotes EMT and tumor invasion. Pathogenic bacteria like *F. nucleatum* recruit TAMs through CCL20 upregulation. Gut microbes of lung cancer patients could indirectly promote malignancy deterioration by mediating LPS transport and Tregs recruitment via the gut-lung axis, while modulating IL-1 β expression in lung tissues. Furthermore, aberrant gene methylation of VIM, GATA4/5, dysregulated histone modifications, abnormal linolenic acid metabolism, and inflammatory microenvironment formation collectively contribute to inflammatory response activation by gut microbes. AKT, protein kinase B; EMT, epithelial-mesenchymal transition; IL-1 β , interleukin-1 beta; IL-6, interleukin-6; LPS, lipopolysaccharide; NF- κ B, nuclear factor-kappa B; SCFAs, short chain fatty acids; TAMs, tumor-associated macrophages; TNF- α , tumor necrosis factor-alpha; Tregs, regulatory T cells.

pathogenic bacteria such as *F. nucleatum* can induce intestinal immune dysfunction, thereby accelerating CRC progression [157]. Additionally, research has established that the gut microbiome of lung cancer patients indirectly promotes tumor development through mediation of LPS transport and Tregs recruitment via the gut-lung axis, modulating IL-1 β expression in pulmonary tissues and disrupting metabolic-immune homeostasis [313]. The altered immune microenvironment and dysregulated immune responses resulting from microbial dysbiosis facilitate the TME establishment and maintenance in gastrointestinal malignancies and distant anatomical sites.

Inflammatory response activation

The bidirectional interplay between chronic inflammation and microbiota dysbiosis exerts sustained influence on gastrointestinal cancer initiation and progression [314–316]. Studies demonstrate that IBD, comprising Crohn's disease (CD) and ulcerative colitis (UC), functions as a significant precursor condition for CRC development [316–321]. The pathophysiological mechanisms underlying progression from IBD to colitis-associated CRC encompass multiple integrated factors. Factors including immune cell dysfunction, intestinal

epithelial cells alterations, and microbial dysbiosis collectively potentiate inflammatory responses and drive carcinogenic processes [322]. Intestinal microbiota dysregulation in IBD patients manifests through epigenetic mechanisms (including aberrant gene methylation of *VIM*, *GATA4/5*, and dysregulated histone modifications) and metabolic pathway perturbations (particularly disrupted linolenic acid metabolism), thereby promoting carcinogenesis [323, 324]. Probiotics, particularly *Lactobacillus bulgaricus* (*L. bulgaricus*), significantly attenuate tumor progression in CAC models through the reduction of pro-inflammatory mediators, including IL-6 and TNF- α [325]. Dysregulation of the *Firmicutes/Bacteroidetes* ratio, especially significantly increased *Bacteroidetes* abundance, promotes EMT and enhances tumor growth, invasion, and metastasis through the induction of pro-inflammatory cytokine secretion, including IL-6 and TNF- α [157]. Meanwhile, *Lactobacillus plantarum* and *Lactococcus lactis* show dual application potential in IBD treatment and CRC prevention by modulating the intestinal immune microenvironment [326]. Concerningly, even in patients with primary sclerosing cholangitis (PSC) without typical IBD symptoms, elevated intestinal inflammatory factors such as *IL-17A* and *IFNG*, along with microbiota dysbiosis, may still increase CRC risk [327]. Additionally, anti-inflammatory diets (especially bioactive substances like flavonoids) exert anti-tumor effects through multiple mechanisms including inflammatory response inhibition, intestinal barrier integrity maintenance, and immune cell function regulation [328, 329]. These findings indicate the central role of inflammatory microenvironment and microbiota interactions in digestive system tumorigenesis, providing an important theoretical basis for developing cross-cancer prevention and treatment strategies.

INTRATUMORAL MICROBIOME

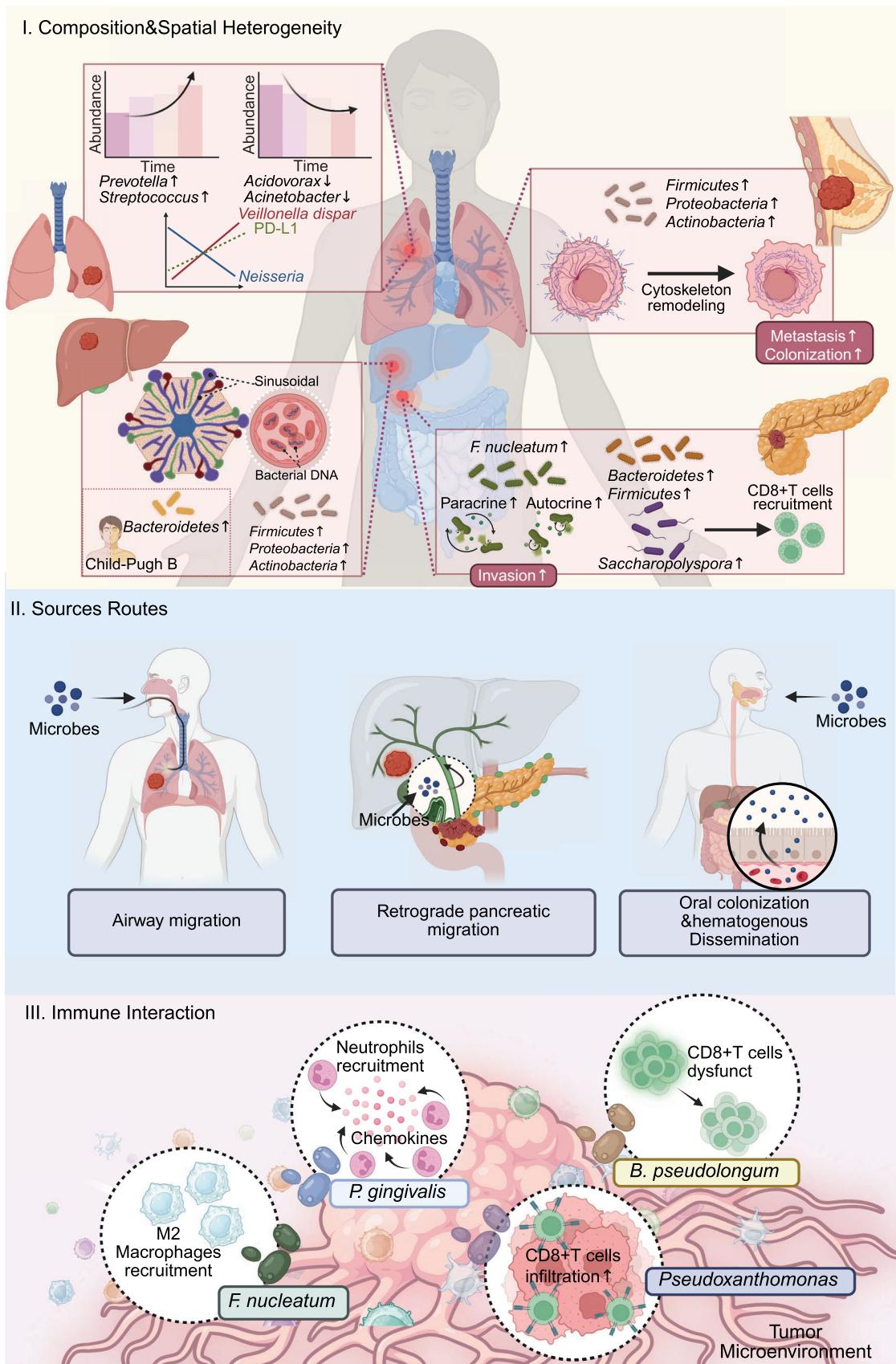
Characterization of bacteria in tumors and mechanisms of tumorigenesis

The characterization of bacteria within tumors and their oncogenic mechanisms reveals a complex multilevel biological regulatory network. Bacterial communities in different tumor types have unique compositional characteristics. The complex interactions between bacteria and the TME, and their involvement in tumor development through multiple signaling pathway regulation [330–332], are outlined in Figure 2. It illustrates the carcinogenesis process from bacterial community compositional heterogeneity to microenvironmental interactions. This framework provides a systematic approach for

understanding the multidimensional role of the microbiome in tumor development.

Characterization of bacterial community composition

The intratumoral microbiome exhibits significant compositional heterogeneity across different cancer types [333]. For instance, the *Firmicutes/Bacteroidetes* ratio is highest in precancerous lesions of gastric cancer (PLGC) mouse models, while GC groups show increased abundance of *Proteobacteria* and *Actinobacteria* [334]. Research indicates that tumor-associated microbiota in HCC patients is predominantly composed of *Actinobacteria*, *Proteobacteria*, and *Firmicutes*, while *Bacteroidetes* shows higher abundance specifically in Child-Pugh grade B HCC [335]. Studies suggest that an elevated *Firmicutes/Bacteroidetes* ratio is associated with favorable responses to nutritional interventions [336]. This microbial diversity closely relates to tumor biological characteristics and patient prognosis. Multiple studies demonstrate that bacteria exhibit specific spatial distribution patterns within tumor tissues. Gram-negative bacteria primarily localize in cancer cells and immune cells, whereas Gram-positive bacteria are mainly detected in melanoma and preferentially appear in macrophages [26]. In HCC, bacterial DNA predominantly enriches in peritumoral hepatic sinusoidal erythrocytes, whereas within the tumor it mainly localizes in the hepatocyte cytoplasm [337]. This spatial distribution difference directly affects biological functions. For example, *F. nucleatum* in PC promotes cancer cell invasion via autocrine/paracrine pathways [159], whereas microbes in BC enhance metastatic colonization of tumor cells by regulating cytoskeletal reorganization [338]. Bacterial load and abundance in BC tissues are significantly higher than in adjacent normal tissues and most other cancer subtypes. This enrichment is particularly evident for viable bacteria of *Firmicutes*, *Proteobacteria*, and *Actinobacteria*, with *F. nucleatum* showing specific enrichment in BC and PC [158]. However, Jeongshin A et al. found that the *Firmicutes/Bacteroidetes* ratio is threefold lower in BC patients compared with healthy individuals and is considered a risk factor for BC [339]. *Corynebacteriaceae* and *Micrococcaceae* abundance is significantly higher in non-gastrointestinal tumors (such as BC and osteosarcoma), whereas *Proteobacteria*, *Bacteroidetes*, and *Firmicutes* dominate the PC microenvironment [26, 110, 158]. In CRC, microbiota community analysis can help determine clinical subtypes and prognostic subgroups. Among stage II/III cases, tumors characterized by *Firmicutes/Bacteroidetes* communities demonstrate better OS

**FIGURE 2** (See caption on next page).

for microsatellite stable tumors compared with other microbial subtypes (*Fusobacterium*/oral pathogens; *Escherichia/Pseudescherichia/Shigella*) [340]. In CRC, mice supplemented with kefir exhibited decreased *Firmicutes/Bacteroidetes* and *Ascomycota/Basidiomycota* ratios, with improved CRC outcomes [341]. For patients with locally advanced non-small cell lung cancer (NSCLC) receiving concurrent chemoradiotherapy, early nutritional intervention can improve host nutritional status and reduce post-treatment adverse reactions. In lung cancer, microbiota compositional features exhibit significant diagnostic and prognostic value. Compared with normal lung tissues, genera such as *Prevotella* and *Streptococcus* show significantly higher abundance in lung cancer, while genera such as *Acidovorax* and *Acinetobacter* show decreasing trends. Particularly, *Thermus* shows cumulative enrichment in patients with advanced (stage IIIB/IV) disease, and *Legionella* are significantly enriched in metastatic cases, suggesting that microbiota compositional dynamic changes are closely associated with disease progression [342, 343]. Regarding prognosis, *Veillonella dispar* in bronchoalveolar lavage fluid (BALF) of lung cancer patients shows positive correlation with high PD-L1 expression, while *Neisseria* is enriched in the low PD-L1 expression group [344].

Notably, intratumoral microbial diversity demonstrates a significant negative correlation with immune microenvironment parameters (such as tumor-infiltrating lymphocytes [TILs] and PD-L1 expression) and exhibits a clear association with shorter overall patient survival [345]. In normal pancreatic tissues, microbial abundance is low and predominantly in extracellular colonization form, whereas *Elizabethkingia* and *Pseudomonas spp.* are significantly elevated, and enrichment of specific genera (such as *Saccharopolyspora*) improves anti-tumor immune responses by enhancing CD8⁺ T cell infiltration in PC

[110, 152, 346]. Together, these findings reveal the critical role of intratumoral microbiota in spatiotemporal heterogeneity, immune regulation, and clinical translation, providing new research directions and ideas for precision oncology.

Bacterial and tumor microenvironment interactions

The origin of tumor microbiota remains controversial, and its distributional characteristics likely vary depending on tumor type. Studies have demonstrated that gut microbes can reach tumors via hematogenous transfer, and oral microbes that colonize tumors through the circulatory system (such as *F. nucleatum* from oral cavity to CRCs) constitute important tumor microbiota sources [347, 348]. Microbiota from adjacent healthy tissues also represents an important source. For example, one study showed that lung tumor microbes originated from the airways [349]. Additionally, bacteria in PC can migrate retrogradely through the pancreatic duct [350].

Intratumoral microbiota forms a complex interaction network with the TME through immune regulation [32, 351–354]. The intratumoral microbiota exhibits a clear double-edged sword effect. Regarding pro-tumor responses, *F. nucleatum* is closely associated with M2 macrophage activation in a specific tumor type; *Porphyromonas gingivalis* (*P. gingivalis*) attracts tumor-associated neutrophils by secreting neutrophil chemokines and stimulates their release of pro-tumorigenic neutrophil elastase [158]. Additionally, *Bifidobacterium pseudolongum* (*B. pseudolongum*) suppresses T-cell immunity, whereas microbes such as *Pseudoxanthomonas* show a significant positive correlation with CD8⁺ T cell infiltration [158].

FIGURE 2 Composition and spatial heterogeneity, invasion routes, and immune interactions of bacterial communities in different tumor types. *Prevotella* and *Streptococcus* show significantly higher abundance in lung cancer, while *Acidovorax* and *Acinetobacter* show decreasing trends. *Veillonella dispar* shows positive correlation with high PD-L1 expression in lung cancer, while *Neisseria* predominates in patients with low PD-L1 expression. In HCC, *Actinobacteria*, *Proteobacteria*, and *Firmicutes* show abundance with *Bacteroidetes* higher in Child-Pugh B classification liver tissue, and bacterial DNA specifically accumulates within peritumoral hepatic sinusoidal erythrocytes. Breast cancer exhibits significant enrichment of *Firmicutes*, *Proteobacteria*, and *Actinobacteria*, which regulate cytoskeletal reorganization and subsequent tumor metastasis. In PC, *F. nucleatum* promotes malignant cell invasion via autocrine/paracrine pathways. Additionally, elevated levels of *Elizabethkingia*, *Pseudomonas spp.*, and specific *Saccharopolyspora* enhance anti-tumor immunity through increased CD8⁺ T cell infiltration. Regarding bacterial colonization routes, colorectal cancer microbiota originates from both oral bacteria via circulation and gut bacteria through hematogenous transfer. Lung tumor microbiota derives from airway microbes, while PC-associated bacteria utilize retrograde migration through the pancreatic duct to trigger metastasis. The intratumoral microbiota exhibits complex cross-talk with the immune microenvironment. Regarding pro-tumor responses, *F. nucleatum* associates with M2 macrophage activation, while *P. gingivalis* triggers tumor-associated neutrophil recruitment through chemokines and elastase secretion. Regarding anti-tumor immunity, *B. pseudolongum* impairs CD8⁺ T cell function, whereas like *Pseudoxanthomonas* positively correlate with CD8⁺ T cell infiltration. *B. pseudolongum*, *Bifidobacterium pseudolongum*; HCC, hepatocellular carcinoma; PD-L1, programmed death-ligand 1.

Mechanisms of viral infection and tumorigenesis in tumors

Investigations of tumor-associated viral infection processes and their oncogenic mechanisms provide critical insights into the complex interactions between microorganisms and their hosts [355–357]. Current studies have identified numerous viruses with established oncogenic potential, including HBV, HCV, EBV, HPV, Kaposi's sarcoma-associated herpesvirus (KSHV), human T-cell leukemia virus type 1 (HTLV-1), and Merkel cell polyposis virus (MCPyV), among others. Notably, initial oncogenic virus infection in humans typically does not directly lead to tumorigenesis. However, under conditions of immunosuppression or in synergy with other oncogenic factors, these viruses can promote malignant cell transformation through multiple mechanisms. Figure 3 comprehensively illustrates the molecular mechanism network and interactions among major oncogenic viruses through three core mechanisms: infection pattern establishment, genome modification, and immune escape to induce tumorigenesis.

Virus infection patterns

Virus-mediated tumorigenesis is intricately linked to the mode of viral infection. The mode involves a systematic biological process comprising host cell invasion, establishment of persistent infection, and induction of malignant transformation. The core mechanisms underlying this process reside in the molecular interactions between viruses and host cells, as well as the dynamic regulation of viral latency. For example, high-risk HPV types (especially types 16 and 18) integrate their viral genome into host cell DNA to induce CC transformation [358]. The oncogenic proteins encoded by these viruses, E6/E7, drive the development of epithelial tumors such as CC through the specific degradation of tumor suppressors, notably p53 and RB. In the B-lymphocyte transformation paradigm, viral infection promotes B-cell immortalization [359], enables evasion of apoptotic regulation, and activates proliferative signaling pathways, ultimately leading to hematological malignancies like lymphomas. HBV infection specifically targets hepatocytes, wherein the virus completes DNA replication via reverse transcription and subsequently integrates into the host genome [360]. Hepatocytes harboring these integrated viral fragments acquire proliferative advantages which, in concert with a chronic inflammatory microenvironment, synergistically promote HCC development. In T-cell leukemia, HTLV-1 induces clonal expansion and genomic instability through infection of CD4⁺ T cells and subsequent integration of its viral genome into host cellular DNA. The

viral Tax protein of HTLV-1 constitutively activates the NF-κB pathway, ultimately triggering adult T-cell leukemia/lymphoma [361, 362]. MCPyV initiates infection through cutaneous transmission, followed by viral DNA integration into the host genome, resulting in expression of the large T (LT) antigen that interacts with tumor suppressor p53 through its C-terminal domain. Truncation of this replicative domain disrupts anti-tumor surveillance, resulting in dysregulated cell cycle control and subsequent Merkel cell carcinoma (MCC) pathogenesis [363]. Although these viruses display tropism for distinct target cell populations, they employ convergent mechanisms to achieve malignant transformation, including genomic integration, expression of viral oncoproteins, and subversion of host signaling pathways, underscoring the fundamental relationship between viral infection dynamics and carcinogenesis.

Virus-mediated genome modifications

Virus-mediated genome modification, as an important molecular mechanism of tumorigenesis, primarily interferes with host cell homeostasis through two pathways: viral genetic material integration and epigenetic regulation, thus promoting abnormal cell proliferation. Among DNA viruses, HPV achieves malignant transformation through integration into host chromosomal DNA, whereby its viral oncoproteins E5, E6, and E7 cooperatively promote carcinogenesis through enhancing aberrant EGFR signaling, causing p53 and RB dysfunction, deregulating microRNA expression, and inhibiting exogenous apoptosis [364]. EBV, with its unique epigenetic regulation in gastric carcinogenesis, including hypermethylation features of EBV-associated GC (EBVaGC), induces aberrant methylation patterns in gastric epithelial cells. This effect silences tumor suppressor genes and cell cycle regulators while concurrently repressing differentiation-associated transcriptional programs, ultimately promoting a poorly differentiated, highly proliferative precancerous cellular state [365]. The oncogenic mechanism of HBV closely relates to its genome integration. During early clonal amplification stages, HBV DNA integration into host genome triggers insertional mutations and drives genome instability which, synergistically with HBV-encoded X protein (HBx)-mediated effects (including impairment of DNA damage repair mechanisms and inactivation of tumor suppressors), collectively accelerates HCC progression [366–370]. RNA viruses lack direct genomic integrative capacity but nevertheless compromise host genome stability through alternative molecular mechanisms. HCV induces genetic and epigenetic disorders through its viral protein repertoire, facilitating both oncogene activation and tumor suppressor silencing. Meanwhile, HCV simultaneously establishes a chronic

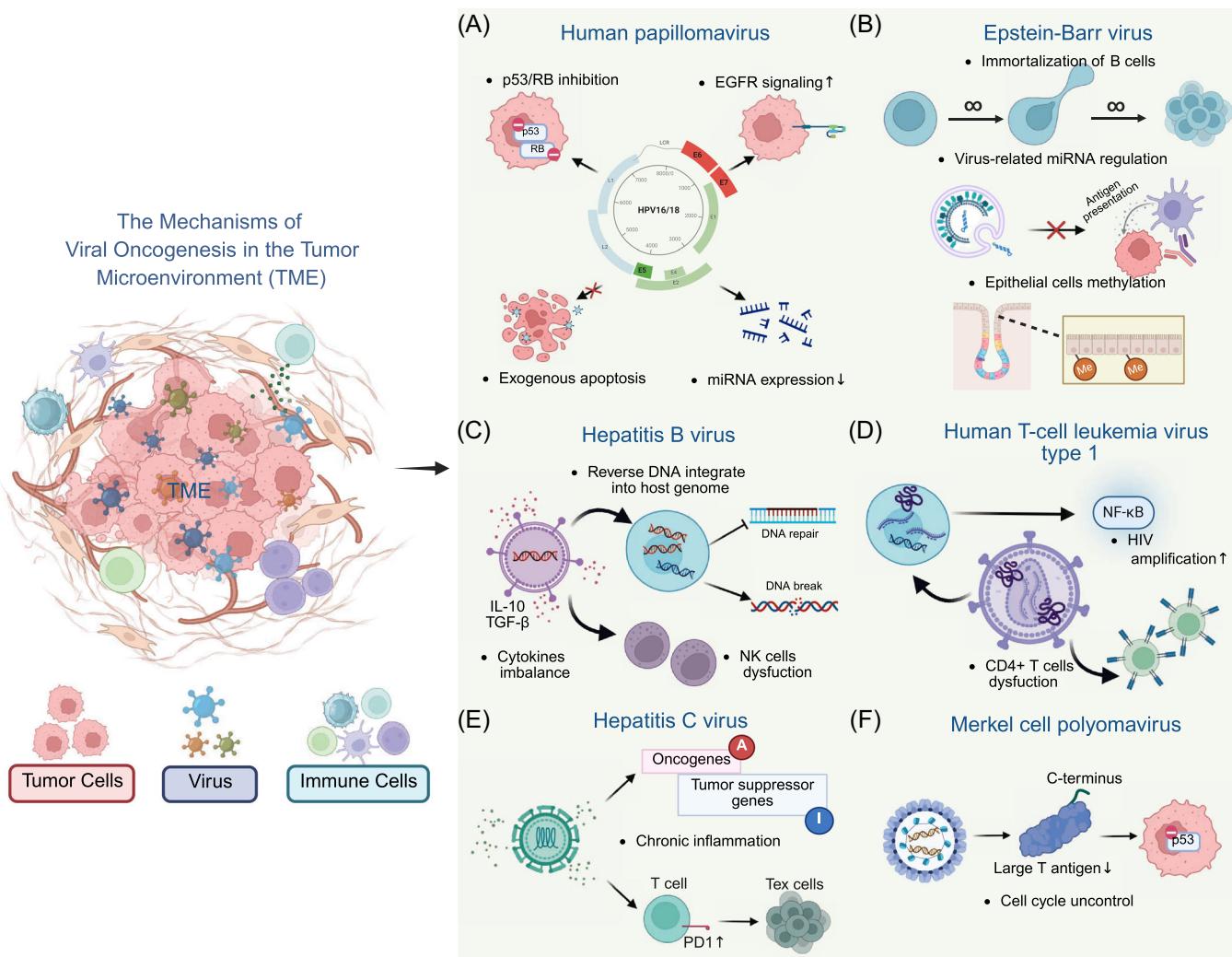


FIGURE 3 Mechanisms of viral oncogenesis in the TME. The schematic illustration demonstrates how different oncogenic viruses modulate the TME to promote carcinogenesis. (A) HPV induces oncogenesis through multiple mechanisms, including p53/RB inhibition, enhanced EGFR signaling, suppression of miRNA expression, and regulation of exogenous apoptosis. (B) EBV promotes tumor development via B cell immortalization, virus-related miRNA regulation inhibiting antigen presentation, and ECs methylation altering the stability of ECs. (C) HBV integrates its reverse DNA into the host genome, triggers DNA breaks, induces cytokine imbalance (IL-10, TGF- β), and leads to NK cell dysfunction. (D) HTLV-1 induces CD4 $^{+}$ T cell dysfunction and activates NF- κ B signaling, resulting in enhanced HIV amplification. (E) HCV contributes to oncogenesis through chronic inflammation, activation of oncogenes, inhibition of tumor suppressor gene expression, and upregulation of PD-1 on T cells, leading to exhausted T cell transformation. (F) MCPyV promotes cell cycle dysregulation through C-terminus-mediated large T antigen reduction and p53 down-regulation. EBV, Epstein-Barr virus; ECs, epithelial cells; EGFR, epidermal growth factor receptor; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HIV, Human immunodeficiency virus; HPV, Human papillomavirus; HTLV-1, Human T-cell leukemia virus type 1; IL-10, interleukin-10; MCPyV, Merkel cell polyomavirus; miRNA, microRNA; NK, natural killing; PD-1, programmed cell death protein 1; Tex, exhausted T cell; TGF- β , transforming growth factor-beta; TME, tumor microenvironment.

inflammatory microenvironment through its persistent infection that constitutes an important factor for HCC development [371, 372]. In summary, whether mediated through direct genomic integration by DNA viruses or epigenetic reprogramming by RNA viruses, virus-mediated genome modification ultimately promotes tumor invasion and metastasis through common pathways such as metabolic abnormalities, cell cycle dysregulation, and genetic instability.

Virus-induced immune escape

Virus-mediated immune escape mechanisms represent critical determinants of oncogenesis, wherein diverse viral pathogens establish persistent infections and induce tumorigenesis by specifically targeting distinct components of immune surveillance networks [373]. HPVs evade host immune clearance mainly through strategies of spatial immune escape. Their viral gene expression and viral

particle production are strictly confined to the most superficial epithelial tissue layer, which is inherently subject to limited immune cell surveillance [374, 375]. EBV evades immunological clearance through expression of specialized viral microRNAs that modulate host immune responses and antigen presentation, effectively circumventing immune surveillance and facilitating lymphomagenesis and other related malignancies [376]. Among HCC-associated viruses, HBV achieves immune evasion through remodeling the TME. Its chronic infection can induce functional exhaustion of intrahepatic immune cells (particularly NK cells) and establish immunosuppressive cytokine networks (characterized by increased IL-10 and TGF- β), thereby promoting malignant hepatocyte clonal expansion while attenuating antiviral immune responses [377]. HCV-induced persistent chronic inflammation and tissue fibrosis accelerate cirrhosis, while concurrent chronic inflammatory signaling drives T cell exhaustion and aberrant upregulation of PD-1, ultimately establishing immune tolerance and promoting HCC progression [371]. These complex molecular mechanisms demonstrate how viruses circumvent host immune surveillance through multidimensional strategies, including immune microenvironment restructuring, subversion of immune signaling networks, and induction of immune tolerance.

Intratumoral fungi and tumor progression

The mechanism by which intratumoral fungi influence tumor progression can be systematically analyzed across three interconnected dimensions: specific distribution patterns of fungal communities within the TME, interaction mechanisms between fungi and the TIME, and fungal-mediated metabolic reprogramming of tumor cells. These mechanistic dimensions exhibit substantial interconnectivity and synergism, collectively orchestrating the complex processes underlying tumor development and progression.

Characterization of fungal communities

Fungal community composition and spatial distribution exhibit significant heterogeneity across diverse tumor types. Macrogenome sequencing-based analyses have demonstrated that various fungi, including *C. albicans*, *Malassezia*, and *S. cerevisiae*, are prevalent across multiple human malignancies, including BC, melanoma, and PC [378]. Fungal abundance is significantly elevated in all examined tumor tissues compared with corresponding normal tissues, with fungal species predominantly

localized within intracellular compartments of tumor cells and tumor-associated macrophages [158]. Each cancer type shows distinct fungal community signatures: *Saccharomyces* abundance is higher in colon cancer, melanoma shows predominant enrichment of *Malasseziomyces* [158], and PC tissues contain approximately 3000-fold higher fungal concentrations compared to normal pancreatic tissues, with *Malassezia* significantly enriched in both human specimens and murine models [219]. Additionally, *Candida* is detected in GC tissues, with its increased abundance correlating with early-stage GC progression, while *Blastomyces* demonstrates a significant association with lung cancer pathogenesis [215].

Interaction between fungi and the tumor immune microenvironment

Intratumoral fungal communities actively modulate tumor–host interactions through direct regulation of the TIME [379, 380]. Studies have demonstrated that *Alternaria alternata* and *M. globosa* induce cancer cell IL-33 secretion through activation of Src-Syk-CARD9-NF- κ B signaling cascade, which subsequently promotes the migration of Th2 cells and type 2 innate lymphoid cells (ILC2) into the TME. The subsequent secretion of pro-tumorigenic cytokines, including IL-4, IL-5, and IL-13, by these activated immune cells further accelerates tumor growth and progression [381, 382]. These findings establish that intratumoral fungi function as critical pro-tumorigenic mediators within tumor-immune interactions through modulation of key signaling pathways and orchestration of cytokine networks [158].

Regulation of the tumor microenvironment by microbial metabolites

Microbial metabolites function as multifaceted regulators within the TME, exerting diverse biological effects across multiple cellular compartments. These metabolites can modulate immune cell phenotype and function, mediating immune responses in the TME that significantly influence tumor progression trajectories [383–387]. Notably, microbial metabolites substantially influence tumor growth, invasion, and metastatic potential through the regulation of angiogenic processes and vascular remodeling. Furthermore, microbial metabolites directly interact with tumor cells and modulate cellular metabolic pathways, underscoring the complexity and diversity of these compounds within the TME regulatory network. As shown in

Figure 4, microbial metabolites establish an intricate regulatory network through modulation of immune cell function, orchestration of angiogenic processes, and reprogramming of tumor cell metabolism, collectively shaping the functional characteristics of the TME and ultimately influencing tumor development.

Metabolites and immune cells

The TME is a dynamic microenvironment system comprising immune cells that infiltrate tumor tissues and their secreted cytokines, chemokines, and other bioactive molecules [388–391]. Evidence indicates that microbial metabolites can regulate immune cell function and phenotype through various pathways, thereby contributing to the TME remodeling processes. SCFAs are produced when gut microbes ferment dietary fiber. Butyrate, a key member of the SCFA family, exhibits

significant immunomodulatory effects and accumulates in tumor tissues. In the TIME, butyrate enhances anti-tumor immune responses through inhibiting HDAC activity, upregulating CCL4 expression, promoting CD8⁺ T cell activation, and enhancing IL-12R signaling pathway activity. Additionally, it also reduces Tregs and promotes anti-PD-L1 effects, thereby augmenting anti-tumor efficacy [392, 393]. In a CRC mouse model, intratumoral *F. nucleatum* was found to affect the TIME through the metabolite-sensing receptor FFAR2 [381]. A study in melanoma demonstrated that after *Lactobacillus reuteri* (*L.reuteri*) colonization of tumor cells, its metabolite indole 3 aldehyde (I3A) promoted CD8⁺ T cell activation and recruitment while elevating interferon γ (IFN- γ) levels through an AhR signaling-dependent pathway, thereby enhancing anti-tumor immune responses and immune checkpoint inhibitor (ICI) efficacy [394]. These findings elucidate the multidimensional regulatory role of microbial metabolites in TIME modulation and

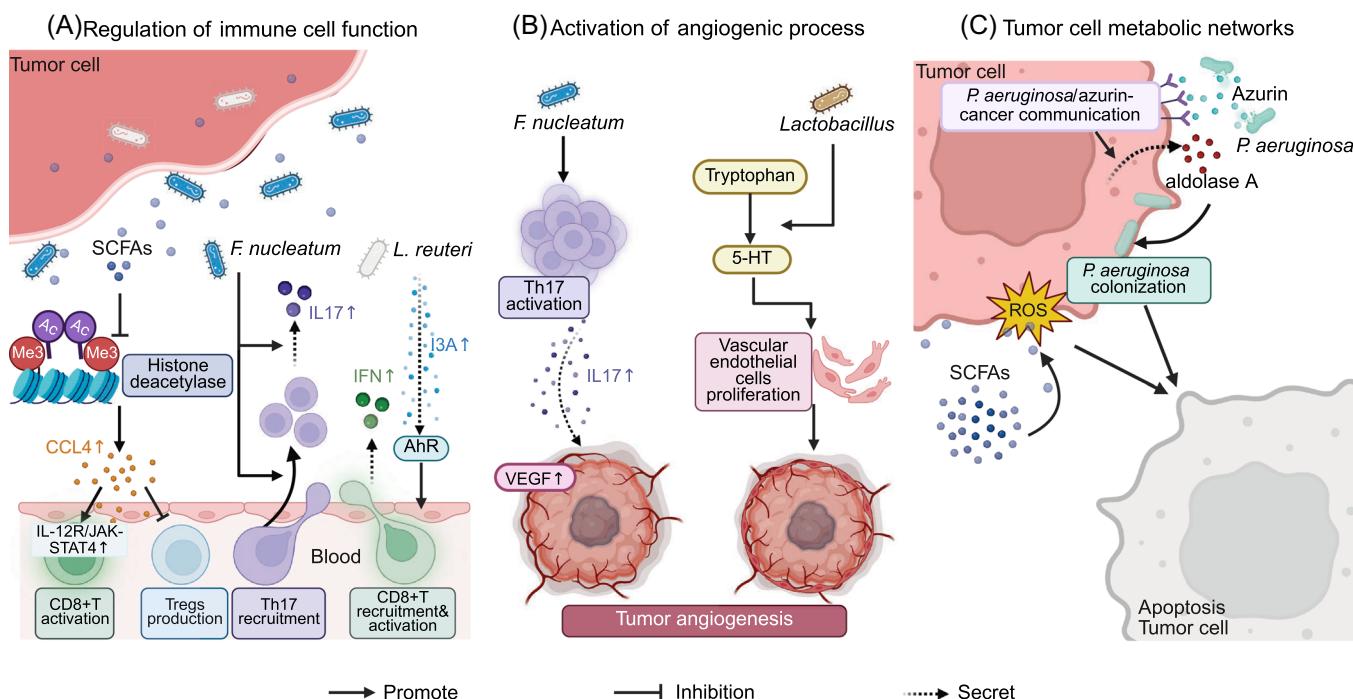


FIGURE 4 Regulation mechanisms of the TME by microbial metabolites. This schematic illustrates three core mechanisms (regulation of immune cell function, activation of angiogenic process, and metabolic networks) by which microbial metabolites modulate the tumor microenvironment. (A) SCFAs inhibit histone deacetylase, leading to increased CCL4 production and subsequent modulation of CD8⁺ T cell activation and Tregs decrease via IL-12/JAK-STAT4 signaling. *F. nucleatum* promotes Th17 cell recruitment and IL17 production, while *L. reuteri* also affects CD8⁺ T cell recruitment and activation through indole 3 aldehyde and IFN- γ pathways mediated by AhR signaling. (B) *F. nucleatum* activates Th17 cells, leading to increased IL17 and VEGF expression. In addition, *Lactobacillus* metabolizes tryptophan to 5-HT, ultimately promoting vascular endothelial cell proliferation and tumor angiogenesis. (C) *P. aeruginosa* enrichment leads to azurin secretion, which triggers tumor cells to produce aldolase A. This creates a feedback loop that further promotes *P. aeruginosa* colonization on the tumor surface, collectively contributing to tumor cell apoptosis. Furthermore, SCFAs generate ROS, which also contribute to tumor cell apoptosis through oxidative stress mechanisms. AhR, aryl hydrocarbon receptor; IFN- γ , interferon γ ; IL12, interleukin-12; IL17, interleukin-17; *L.reuteri*, *Lactobacillus reuteri*; ROS, reactive oxygen species; Th17, T helper 17; VEGF, vascular endothelial growth factor.

establish a theoretical foundation for developing metabolic intervention-based tumor treatment strategies.

Metabolites and angiogenesis

Microbes and their metabolites significantly shape the TME through modulation of angiogenic pathways [395]. In a CRC mouse model, *F. nucleatum* within tumor cells stimulates IL-17 secretion via metabolite receptors, promoting the formation of an inflammatory TME. IL-17 can act on tumor cells to promote angiogenic factor VEGF secretion, which induces tumor angiogenesis and accelerates CRC progression [160, 396]. *Lactobacillus spp.* in tumor cells have shown a strong association with immunosuppression in PC and the immunosuppressive TME in esophageal squamous cell carcinoma (ESCC), significantly correlating with poor patient prognosis [397, 398]. *Lactobacillus* converts tryptophan into an intermediate product, which promotes 5-hydroxytryptamine (5-HT) synthesis, a metabolite that stimulates vascular endothelial cell proliferation and thus promotes tumor angiogenesis [399, 400]. These findings reveal that microbial metabolites influence tumor evolution by regulating tumor vascular homeostasis.

Metabolites and tumor metabolism

Microbial metabolites regulate TME homeostasis through comprehensive remodeling of tumor metabolic networks [268, 401, 402]. Microbial metabolites accumulate within tumor tissues and modulate tumor cell metabolic processes through specific interactions with cancer cell surface receptors, thus establishing a distinct “tumor-microbial microenvironment.” Butyrate directly affects tumor cell metabolic processes independently of its established effects on the immune microenvironment. Studies have demonstrated that butyrate induces lipid peroxidation and promotes ROS generation in HT-29 colon cancer cells, consequently promoting tumor cell apoptosis [403]. Recent investigations have elucidated the bidirectional signaling mechanisms between intratumoral microbes and cancer cells. Azurin protein secreted by *P. aeruginosa* disrupts cancer cell signaling pathways through binding to specific receptor molecules on cellular surfaces, thereby inducing apoptotic cascades. Conversely, cancer cells facilitate *P. aeruginosa* colonization within tumor tissues through aldolase A-mediated metabolic processes [404]. These findings establish that microbial metabolites significantly influence tumor progression and development through direct modulation of tumor cell metabolic pathways.

ORGAN-SPECIFIC MICROBIOME AND TUMORS

Organ-specific microbiomes function as critical determinants in tumorigenesis and development. Studies show that distinct microbial communities at different anatomical sites exhibit specific association patterns with neoplastic transformation in corresponding tissues [405–412]. Microbial dysbiosis at multiple anatomical sites, including the oral cavity, skin, genitourinary system, and respiratory tract, promotes tumor progression through multiple pathways, including induction of inflammatory responses, production of oncogenic metabolites, and activation of immune escape pathways. The oncogenic role of specific pathogenic microorganisms, particularly HPV in cervical and oral cancers, has been extensively documented, while the broader microbiome significantly influences patient responses to immunotherapeutic and chemotherapeutic interventions. Table 5 summarizes the correlated characteristics between major organ-specific microbiomes and corresponding malignancies.

Oral microbiome and oral cancer

Current evidence demonstrates a complex and mechanistic relationship between the oral microbiome composition and oral cancer pathogenesis. Dysbiosis of the oral microbiota represents a significant risk factor for oral cancer development, wherein the aberrant proliferation of specific bacterial communities promotes malignant transformation and progression through inflammatory response activation and dysregulation of critical cellular signaling pathways. Additionally, HPV infection is significantly associated with oral squamous cell carcinoma (OSCC) development, while specific patterns of oral fungal colonization strongly predict clinical outcomes in oral cancer patients. Metabolites produced by oral microorganisms significantly reshape the TME, thereby modulating cancer cell proliferation and metastatic potential and highlighting the microbiome's multifaceted regulatory role in oral carcinogenesis [438, 439].

Association of oral microbial imbalance with oral tumorigenesis

Numerous studies confirm the close association between oral microbiota dysbiosis and oral cancer development. Dysregulation of microbiome is now recognized as an important hallmark of carcinogenesis. The oral microbiota (including bacteria, fungi, archaea, and viruses)

TABLE 5 Characteristics associated with organ-specific microbiome and corresponding tumor.

Organ system	Key microbes	Associated cancer types	Core mechanisms	References
Oral	<i>Porphyromonas gingivalis</i> <i>Fusobacterium nucleatum</i> <i>Streptococcus</i> <i>C. albicans</i> HPV-16/18	OSCC	<ul style="list-style-type: none"> Chronic inflammation (NF-κB activation); Carcinogenic metabolites (such as acetaldehyde) and butyrate; HPV-mediated inhibition of DNA repair and induction of genomic instability. 	[413–418]
Skin	<i>Staphylococcus aureus</i> β-HPV <i>Staphylococcus epidermidis</i>	SCC Melanoma	<ul style="list-style-type: none"> Release of virulence factors and pro-proliferative cytokines; Secretion of 6-N-hydroxylaminopurine to inhibit tumor DNA synthesis. 	[419–422]
Urogenital	HPV <i>Veillonella</i> <i>Bifidobacterium</i> <i>Lactobacillus</i>	CC BCa PCa	<ul style="list-style-type: none"> HPV integration causing genomic instability; Microbiome dysbiosis activating; IGF-1/TLR pathways; SCFAs modulating macrophage polarization; Upregulation of Toll-like receptor expression, inducing chronic inflammation. 	[423–426]
Respiratory	<i>Streptococcus</i> <i>Veillonella</i> <i>C. Pneumoniae</i> <i>Cyanobacteria</i> SCFA-producing bacteria	NSCLC	<ul style="list-style-type: none"> ERK/PI3K pathway activation promoting proliferation; Immune-suppressive microenvironment; Metabolic metabolites inducing apoptosis; Decreased CD36; Increased PARP1; Activate CD4⁺ T cells, inhibit CD8⁺ T cells and NK cells, and induce IFN-γ-R1 in NK cells. 	[265, 427–432]
Breast	<i>Proteobacteria</i> <i>Methylobacterium radiotolerans</i> HPV	BC	<ul style="list-style-type: none"> TLR pathway dysregulation; Induced DNA damage. 	[433–436]
Brain	<i>Fusobacterium</i> <i>Limosilactobacillus</i> <i>Lactobacillus</i>	Glioma	<ul style="list-style-type: none"> <i>Fusobacterium nucleatum</i> promotes tumor proliferation; Microbial metabolites regulating Neuronal genes. 	[80]
Bone Marrow	SCFA-producing bacteria <i>Klebsiella</i>	Multiple myeloma	<ul style="list-style-type: none"> SCFAs inhibit NF-κB-mediated inflammation; Nitrogen-cycling microbiota promoting immune-suppressive microenvironment. 	[437]

Abbreviations: CC, cervical cancer; IGF-1, insulin-like growth factor 1; NSCLC, non-small cell lung cancer; OSCC, oral squamous cell carcinoma; PARP1, poly [ADP-ribose] polymerase 1; PI3K, phosphatidylinositol-3-kinase; SCC, squamous cell carcinoma.

maintains ecological homeostasis through dynamic interactions with the host microenvironment, and its dysregulation can promote carcinogenesis by disrupting these host-microbiota interactions [440]. Pathogenic bacteria such as *P. gingivalis*, *F. nucleatum*, *C. albicans*, *Streptococcus anginosus*, and *Selenomonas* spp. show significant enrichment in cancerous tissues compared to healthy oral mucosa [413, 433, 441]. Further studies have demonstrated that the abundance of *Prevotella*, *Chlamydia*, and *Firmicutes* in the salivary microbiomes of OSCC patients differs significantly from that of healthy controls [442]. Evidence indicates that *C. albicans* demonstrates significant oncogenic potential in OSCC, contributing to tumor progression mainly through multiple

mechanisms, including epithelial damage, production of oncogenic factors, and regulation of the TME [413]. Notably, oral microecological dysbiosis induced by betel nut chewing appears to accelerate carcinogenesis, with the abnormal proliferation of *F. nucleatum*, *P. gingivalis*, *Prevotella melaninogenica*, and other microbes in the saliva of cancer patients being mechanistically linked to their carcinogenic potential [414]. Collectively, these findings elucidate how oral microbial dysbiosis contributes to oral cancer development through diverse molecular mechanisms.

Several systematic reviews and meta-analyses have investigated the relationship between the oral microbiome composition and oral cancer development.

Han et al. observed significantly increased α and β diversity in the salivary microbiota of OSCC patients compared to healthy individuals [443]. The oral microbiota in OSCC patients was predominantly characterized by *Streptococcus*, *Lactobacillus*, and *Prevotella* [443]. A recent meta-analysis summarized the characteristics of oral microbiome across different developmental stages of OSCC, revealing variations in microbial diversity, species, and abundance among different samples [444]. Another meta-analysis indicated that oral microbiome composition is associated with cancer patient prognosis [445]. For instance, patients with lower oral diversity, increased *Fusobacterium* abundance, or *P. gingivalis* colonization were associated with compromised OS [445]. Additionally, established risk factors, including dietary patterns and tobacco exposure, significantly modulate microbiome composition and cancer progression. Cohort studies have demonstrated that increased carbohydrate intake is associated with increased oral bacterial diversity, enrichment of *Fusobacterium* and *Leptotrichia*, and depletion of *Actinomyces* operational taxonomy units (OTUs) [446]. Conversely, dietary patterns characterized by high sugar, processed foods, and alcohol accelerate oral carcinogenesis, whereas diets rich in fruits, vegetables, and fish demonstrate chemopreventive properties against cancer development [447]. In tobacco users, irrespective of conventional combustible cigarettes or electronic nicotine, significant alterations and abundance profiles in oral microbiome composition have been indicated compared to non-smoking controls [448]. Previous research has indicated that approximately 74% of OSCC cases are attributed to tobacco exposure and chronic heavy alcohol consumption [449, 450]. Furthermore, in OSCC pathogenesis, tobacco-derived carcinogens potentially interact with EBV infection [450].

The composition and functional characteristics of the oral microbiome are substantially influenced by modifiable factors, including dietary patterns and smoking behaviors, which subsequently modulate susceptibility to multiple malignancies. Zhang et al. indicate that inadequate oral hygiene practices, including irregular tooth brushing and non-use of dental floss, facilitate dysbiotic microbial overgrowth, and significantly elevate oral carcinoma risk [451]. Another study has established associations between compromised oral hygiene status and elevated risk of NPC, with the oral microbe *Leptotrichia wadei* as a potential mediator connecting quantitative oral hygiene assessments with NPC pathogenesis [452]. Additionally, a tooth brushing frequency of once daily or less (compared with twice or more daily) is independently associated with a 1.8-fold elevated risk of ESCC. Individuals with ESCC exhibit significantly reduced oral bacterial diversity compared to healthy individuals [453].

Mechanisms by specific bacteria promote oral cancer progression

Oral microbiota contributes to oral cancer development through multiple molecular pathways. Substantial evidence demonstrates that oral microbes, including *C. albicans* and *S. aureus*, are significantly associated with increased oral cancer risk. Their oncogenic mechanisms include disruption of oral microenvironment homeostasis and upregulation of critical oncogenes, such as *PI3KCA*, *hRAS*, *mTOR*, and *BRAF*, which can accelerate malignant transformation [40]. Comprehensive microbiome analyses have established that multiple oral microorganisms, including *P. gingivalis*, *F. nucleatum*, and *Streptococcus spp.*, are causally linked to oral carcinogenesis through the induction of chronic inflammatory responses, regulation of cell proliferation, NF- κ B signaling pathway activation, and production of carcinogenic compounds [415, 454]. Microbial components induce β -defensin 2 expression and promote the progression of precancerous lesions through stimulation of mast cell degranulation and establishment of persistent inflammatory responses, a process directly implicated in the pathogenesis of tongue squamous cell carcinoma [455]. Notably, specific oral microbes may diminish chemotherapeutic agent efficacy and exacerbate treatment-related complications [456], suggesting the importance of microbial modulation in oncology treatment strategies. Collectively, these findings delineate a complex molecular network wherein oral microbiota drives oral carcinogenesis through interconnected mechanisms encompassing transcriptional regulation, inflammatory pathway activation, and comprehensive remodeling of the immune microenvironment.

HPV virus infection and the development of oral squamous cell carcinoma

HPV functions as a critical driver in OSCC progression. High-risk HPV genotypes (particularly types 16 and 18) drive oncogenesis by interfering with the DDR system, consequently suppressing tumor suppressor gene function and inducing genomic instability [457–460]. Additionally, viral components of the oral microbiome, principally HPV, contribute to oral mucosal dysbiosis, precancerous lesions, and OSCC progression through activation of inflammatory pathways and dysregulation of cancer stem cell-associated signaling networks [416]. HPV interacts synergistically with diverse microorganisms, including EBV, herpes simplex viruses, HIV, and multiple bacterial species. This interaction promotes persistent viral infection, accelerating cancer development [457].

These mechanisms reveal that HPV both disrupts cellular regulatory processes through genetic material interference and promotes OSCC transformation through remodeling of the local microenvironment, thereby revealing novel therapeutic targets for improved clinical diagnosis and treatment strategies.

Relationship between fungal colonization and prognosis of oral cancer

Recent studies have confirmed significant correlations between patterns of fungal colonization within the oral ecosystem and clinical outcomes in oral cancer patients [461, 462]. Clinical investigations have demonstrated the presence of complex polymicrobial communities, including *Chlamydia* and diverse fungal taxa in salivary samples from OSCC patients [442]. As a representative pathogenic fungus, *C. albicans* promotes oral carcinogenesis and progression through multiple molecular mechanisms. Its cell wall components (especially β -glucan) induce Th17 cell-mediated immune responses and activate the NF- κ B and Wnt signaling pathways, consequently fostering a pro-carcinogenic microenvironment formation and enhancing tumor cell resistance to apoptosis [417, 463, 464]. Additionally, *C. albicans* and yeast upregulate expression of pro-inflammatory cytokines, including IL-6 and IL-8, thereby accelerating oral cancer progression [418]. *C. albicans* also upregulates PD-L1 expression to facilitate tumor immune escape, while simultaneously accelerating HNSCC progression through modulation of acetaldehyde metabolism processes [465]. These findings suggest that alterations in fungal community composition may serve as valuable diagnostic and prognostic biomarkers for oral malignancies.

Impact of oral microbial metabolites on the oral cancer microenvironment

Metabolites derived from oral microorganisms orchestrate the dynamic evolution of the oral cancer microenvironment through complex and interconnected signaling networks. Disruption of oral microbial communities induces aberrant metabolite release, compromises epithelial barrier integrity, and precipitates immune homeostasis dysregulation. These pathological alterations synergistically converge on oral mucosal cells, promoting malignant transformation and dysregulated cellular proliferation [466]. Interactions between microbial metabolites and the host immune system constitute a fundamental driver of tumor progression. Specifically, lactate metabolites attenuate anti-tumor immune responses through recruitment of TAMs, Tregs,

and myeloid-derived suppressor cells [467]. Among microbial metabolites, SCFAs are closely associated with OSCC development. Particularly, NaB produced by *P. gingivalis* promotes OSCC progression through mechanisms that remain incompletely characterized despite intensive investigation [468, 469]. Microbial-host interactions exhibit mutually reinforcing relationships. Oral microorganisms and their metabolites promote tumor progression, while the TME creates favorable conditions for microbial colonization. This mutually reinforcing vicious cycle constitutes an important pathogenic mechanism in oral cancer progression [470].

Skin microbiome and skin cancer

The skin microbiome serves as a critical regulator of cutaneous homeostasis, and disruption of this dynamic balance is strongly associated with skin carcinogenesis and progression [471]. Accumulating evidence has demonstrated that skin microbiome dysregulation promotes cutaneous carcinogenesis through multiple mechanisms, including disruption of epidermal barrier integrity, induction of immune escape, and activation of inflammatory cascade responses. UV radiation, a major causative factor in skin carcinogenesis [472–474], not only directly damages host cells but also increases the risk of photocarcinogenesis by altering the composition and function of skin microbial communities. These multidimensional interaction mechanisms highlight the central regulatory role of the skin microbiome in cancer prevention, occurrence, and treatment, establishing a theoretical foundation for the development of microbiome-targeted preventive and therapeutic strategies.

Relationship between skin microbial imbalance and skin carcinogenesis

Dysbiosis of the skin microbial community contributes to cutaneous carcinogenesis through both direct oncogenic or oncostatic effects and indirect immunometabolic regulatory mechanisms. Among carcinogenesis-associated microbes, *S. aureus* induces carcinogenesis through multiple virulence factors and cytokine release, promoting SCC cells proliferation [419]. This pathogen shows a significantly elevated relative abundance in SCC patients [475]. *Fusobacterium* spp., *Trueperella* spp., and *Corynebacterium* are significantly enriched in melanoma lesions [476, 477]. Notably, *Corynebacterium* demonstrates a significant positive correlation with IL-17 levels, a critical factor in melanoma progression [477]. Mendelian randomization analysis has revealed a bidirectional positive

correlation between class *Bacilli* and malignant melanoma, whereas decreased phylum *Bacteroidetes* abundance may elevate disease risk [478]. *Pseudomonas aeruginosa* also promotes skin cancer cell growth [479]. Among protective microorganisms, *Staphylococcus epidermidis* (*S. epidermidis*) significantly reduces UV-induced skin cancer incidence by inhibiting tumor cell DNA synthesis through the secretion of 6-N-hydroxyaminopurine (6-HAP) [420]. Similarly, *Cutibacterium acnes* contributes to anti-tumor processes through anti-angiogenic effects, and its reduced abundance correlates strongly with SCC disease progression [480]. These findings suggest that the skin microbiota bidirectionally regulates skin cancer progression by directly affecting cell proliferation and indirectly regulating immune metabolism [481], providing new therapeutic targets for microbial intervention-based skin cancer prevention and treatment strategies.

Relationship between microbiome alterations due to ultraviolet exposure and skin cancer

Ultraviolet exposure promotes both the initiation and progression of skin cancer. Beyond directly damaging host cells, ultraviolet radiation can also kill skin microorganisms and induce dysbiosis of the cutaneous microbial community, thereby synergistically promoting skin cancer initiation and progression [482–485]. UV radiation (especially the UVC band) exerts broad-spectrum bactericidal effects by disrupting microbial nucleic acid structure and enzymatic activity [421, 486], resulting in significant alterations to skin microbiome composition. UV irradiation increases the abundance of *Proteobacteria*, impairing anti-inflammatory immune response functions. Similarly, it decreases *Lactobacillaceae* and *Pseudomonadaceae*, compromising cutaneous barrier homeostasis. Abnormal *Cyanobacteria* proliferation may contribute to tumorigenesis, progression, and metastasis through the release of pro-inflammatory metabolites and upregulation of immunosuppressive factors [487, 488]. This microbial dysbiosis synergizes with UV-induced keratinocyte DNA damage, and the dysregulated microbiota exacerbates oxidative stress and chronic inflammatory states, further destabilizing genomic integrity and accelerating non-melanoma skin cancer (NMSC) progression [489]. Additionally, UV radiation and HPV infection show significant synergistic effects in CSCC, with UV-induced damage interacting with HPV oncoproteins through activation of the Wnt/β-catenin signaling pathway, collectively driving malignant cellular transformation [490]. These mechanisms indicate that UV radiation not only directly

damages host cells but also multidimensionally promotes cutaneous carcinogenesis through remodeling the microbe–host interaction network.

Viral infections and the mechanisms of skin cancer development

Viral infections represent critical etiological factors in the pathogenesis and progression of cutaneous malignancies. Studies show β-HPV exhibits significant tropism for cutaneous tissues and is strongly associated with non-melanoma skin cancer development, whereas HPVs of γ, μ, and ν genera mainly induce the formation of benign cutaneous lesions [491]. In states of immunosuppression (including verrucous epidermal dysplasia, HIV infection, or long-term immunosuppressive drug use), β-HPV significantly accelerates cutaneous oncogenesis [422, 492]. Additionally, KSHV has been established as a direct etiological agent in Kaposi's sarcoma (KS) development, evidenced by the persistence of specific viral DNA sequences within KS lesions and the temporal precedence of KSHV infection before tumor formation, further corroborating its pathogenic mechanism [493]. In studies of MCC, Merkel cell polyomavirus (MCV) DNA is detectable in approximately 80% of tumor tissues, suggesting viral genome integration functions as a potential driver of clonal tumor expansion [494]. Together, this body of evidence underscores the pivotal role of oncogenic viruses in cutaneous carcinogenesis through multiple molecular mechanisms, including viral genome integration and host immune evasion.

Microbe-mediated inflammatory response promotes skin cancer progression

The skin microbiota drives the cancer process by activating inflammatory signaling pathways. Pathogenic microbes can abnormally activate Toll-like receptors (TLRs), triggering chronic inflammatory responses that promote skin cancer development [495, 496]. Animal experiments show that TLR-5 signaling pathway activation, through chronic inflammatory responses, plays an important role in regulating tumorigenesis in murine skin cancer models [497]. Additionally, *S. aureus* releases various pro-inflammatory factors that promote tumor development-conducive immune microenvironment formation and induce SCC progression [419]. Conversely, *S. epidermidis* activates immune-inflammatory responses while reducing pathogenic bacteria colonization (such as *S. aureus*) through competitive inhibition, thereby inhibiting cancer cell proliferation [498]. Aberrations in

skin microbiota metabolites also influence tumor progression, for example, reduced levels of the tryptophan metabolite I3A accelerate the malignant transformation of precancerous lesions [499]. These mechanisms suggest that microbe-mediated inflammatory networks participate in skin tumorigenesis and evolution through multiple signaling pathways.

Impact of the microbiome on melanoma immunotherapy

ICI therapy has markedly improved prognosis in melanoma patients; however, substantial heterogeneity exists in individual treatment responses [500–502]. Several studies have confirmed that the microbiome plays a pivotal role in modulating ICI therapeutic efficacy [503, 504]. A clinical investigation found that patients receiving antibiotics during cancer treatment, including those with melanoma, exhibited significantly reduced response rates to ICI therapy [505]. Cutaneous commensal bacteria also show immunomodulatory potential. In a murine model, genetically engineered *S. epidermidis* induced robust T-cell immune responses through expression of melanoma-specific antigens and synergistically enhanced ICI efficacy, resulting in potentiated anti-tumor effects [506]. Notably, synergistic effects between the microbiome and immunotherapy can also be achieved through alternative strategies, such as the combination of oncolytic viruses (OVs) and ICIs. OVs induce both local and systemic immune responses by selectively lysing tumor cells and facilitating antigen release, while the combination of anti-CTLA-4 and anti-PD-1 therapy significantly inhibits primary tumor progression and simultaneously promotes regression of metastatic lesions [507]. Collectively, these findings suggest that the skin microbiome not only directly modulates host immune status but may potentially remodel the TME through synergistic effects with other therapeutic modalities, thereby providing a multifaceted scientific rationale for optimizing melanoma immunotherapeutic strategies [508–512].

Urinary/genital microbiome and urinary tumors

The genitourinary microbiome exhibits complex interactions with urogenital tumorigenesis and progression [513–515]. Studies reveal that dysbiosis of the urogenital microbiota represents a significant risk factor for bladder carcinogenesis, while HPV infection constitutes a key causative factor in CC development and progression. Additionally, numerous studies show that specific bacterial infections are significantly associated with PCa

risk, and the composition and functional profile of the urinary microbiome can markedly influence patients' clinical responses to anti-tumor therapies. With advancing research, microbiome-derived biomarkers are emerging as important molecular tools for the early diagnosis and prognostic assessment of urological malignancies.

Association of urethral microbial imbalance with bladder cancer

Recent studies have progressively elucidated the association between urethral microbial imbalance and BCa through microbial characterization. One study showed microbial richness (α -diversity) was significantly lower in BCa patients compared with healthy controls, suggesting that dysbiosis may contribute to disease progression [516]. Additionally, urinary microbiome β -diversity in BCa patients differed significantly from that of the recurrence-free tumor group, with elevated abundance of *Veillonella* and *Bifidobacterium* in the tumor group, whereas the recurrence-free group exhibited enrichment of *Escherichia-Shigella* and *Helococcus* [423]. Further studies identified significant correlations between bladder carcinogenesis and various microbial taxa, including members of the family *Rikenellaceae* and the genera *Allisonella* and *Senegalimassilia* [517]. Microbial compositional analysis between muscle-invasive bladder cancer (MIBC) and non-muscle-invasive bladder cancer (NMIBC) revealed that there were no significant changes in the relative abundance of major phyla such as *Firmicutes* and *Proteobacteria*. However, *Flavobacteriales*, *Eubacterium CAG-581*, and *Bacteroides* sp. 43-47FAA were enriched in NMIBC and were strongly associated with decreased patient survival [518]. In summary, structural dysbiosis of the urogenital microbiome may promote BCa development through regulation of the local microenvironment, and these characteristic microbial signatures may serve as potential biomarkers, providing new avenues for BCa diagnosis and prognostic assessment.

Association of bacterial infections with prostate cancer risk

A substantial body of evidence confirms a significant association between bacterial infections and PCa development. Several studies show that the prostatic microbiome of PCa patients displays characteristic alterations, with significant differences in the relative abundance of specific bacterial taxa. In a case-control study of patients with benign and malignant prostate lesions, researchers found significant alterations in bacterial communities

within high-grade PCa tissues, with notable enrichment of species including *Streptococcus anginosus*, *Anaerococcus lactolyticus*, and *Actinobaculum schaalii* [519]. SCFAs produced by intestinal microbial communities can induce chronic inflammatory responses through multiple mechanisms: modulation of the IGF-1 signaling pathway, promotion of M2-phenotype macrophage polarization, and upregulation of TLR expression, collectively creating a microenvironment conducive to PCa progression [424]. In summary, urinary tract bacterial infections promote PCa development through modulation of key signaling pathways and induction of chronic inflammatory responses that alter the TME.

Mechanisms of HPV infection and the development of cervical cancer

The vast majority of CC cases are attributable to persistent HPV infection [520–522]. The mechanisms underlying HPV infection and subsequent CC development encompass multifaceted molecular and pathological processes, including effects on the cervicovaginal microbiota, which represents an emerging frontier in gynecologic oncology research. During the progression of cervical lesions from premalignant to malignant states, HPV infection significantly alters the composition and abundance of vaginal microbial communities. Specifically, commensal bacteria such as *Lactobacillus crispatus* and *Lactobacillus iners* exhibit significant decreases in abundance, whereas potentially pathogenic bacteria including *Prevotella* and *Gardnerella* demonstrate significant proliferation [425, 523–526]. Other viruses (such as HIV, EBV, and herpes simplex virus) are also closely associated with HPV infection, collectively promoting malignant transformation and tumor progression [527]. Importantly, increased cervicovaginal microbiome (CVM) diversity, together with decreased *Lactobacillus spp.*, is significantly associated with elevated risk of tumorigenic intraepithelial lesions resulting from persistent HPV infection, ultimately accelerating progression to invasive carcinoma [528]. Notably, HPV infection not only alters the compositional structure of the vaginal microbiota but also collaboratively establishes a tumor-promoting microenvironment through complex interactions with microbial metabolic activities [426]. Additionally, HPV maintains its infection status through dual mechanisms: inducing dysbiosis of the CVM and simultaneously suppressing the expression of host antimicrobial peptides essential for innate immunity, further exacerbating vaginal microecological imbalance. HPV-associated perturbations in the cervicovaginal microenvironment exhibit distinctive metabolomic signatures and

inflammatory responses that correlate with the extent of HPV infection, collectively facilitating tumorigenesis and disease progression [426].

Impact of the urinary microbiome on response to treatment

Distinct compositions of the urinary tract microbiome exhibit significant heterogeneity in their responses to therapeutic interventions. A growing body of evidence confirms that the microbiota plays a pivotal role in renal cell carcinoma (RCC) pathogenesis, progression, and therapeutic responsiveness, with the underlying mechanism mainly realized through immune system function modulation, host metabolism, and drug response [529]. Microbiome diversity is significantly reduced in RCC tissue specimens compared to adjacent non-neoplastic renal parenchyma. The end-stage renal disease-associated microbiome demonstrates decreased abundance of putatively beneficial bacteria (such as *Roseburia*) and concurrent enrichment of potentially oncogenic microbes (such as *Escherichia*, *Fusobacterium*, and *Bacteroides*) compared to control specimens [530]. Together, these findings underscore the potential contributory role of urinary microbiome alterations in renal disease pathogenesis, thereby providing a critical theoretical foundation for the development of novel microbiome-targeted therapeutic strategies in RCC management.

Microbial markers in predicting prognosis of urologic tumors

Microbiome-derived biomarkers demonstrate significant clinical applications in urologic tumor diagnosis. Numerous studies confirm dynamic alterations in specific microbial communities exhibit significant correlations with PCa development and prognostic assessment. The β -diversity of circulating fungal microbiomes in peripheral blood significantly differs between PCa patients and healthy controls, with particularly pronounced distinctions in patients with high pathological tumor stages (pT3 or pT4). Notably, the abundance of *Sordariomycetes* is significantly elevated in advanced PCa and has emerged as a promising biomarker for identifying high-grade disease [222]. Additionally, in post-digital rectal examination urine samples and post-prostatectomy prostatic secretions, alterations in the abundance of five strictly anaerobic bacterial genera (including *Fenollarria*) show significant correlation with PCa aggressiveness and biochemical recurrence risk, suggesting their potential utility as non-invasive urinary diagnostic and prognostic biomarkers [531]. These findings

suggest that specific microbiome markers may not only participate in urologic tumor pathogenesis but also serve as potential diagnostic tools, providing new approaches for early detection, risk stratification, and therapeutic monitoring of urologic malignancies.

Respiratory microbiome and lung cancer

A complex bidirectional relationship exists between the respiratory microbiome and lung cancer development [532–534]. Emerging evidence demonstrates that respiratory microbiome dysbiosis is significantly associated with lung cancer development, involving molecular mechanisms that may contribute to lung cancer progression through interconnected signaling pathways, revealing the critical role of microbial community alterations in lung cancer pathogenesis. Additionally, the respiratory microbiome significantly modulates key lung cancer biological behaviors, including proliferation, invasion, and metastasis, through regulation of the TME. Notably, respiratory microbiome composition and temporal dynamics correlate strongly with treatment responses and clinical outcomes in lung cancer patients, offering promising avenues for the development of microbiome-based precision medicine strategies.

Association of respiratory microbial imbalance with lung carcinogenesis

Substantial evidence now establishes that respiratory microbiota dysbiosis is causally linked to lung cancer pathogenesis. Clinical investigations confirm that the respiratory microbiome composition and community structure in lung cancer patients differ significantly from those of healthy individuals. Lower respiratory microbial α -diversity is slightly reduced in lung cancer patients [427, 535]. In patients with central lung tumors, *Streptococcus* constitutes the predominant bronchial microbes at both the lesion site and contralateral bronchus, whereas *Pseudomonas* predominates in the bronchial microbiome of healthy controls [428]. Significant taxonomic overlap exists between the oral and pulmonary microbiomes of lung cancer patients, whose salivary samples demonstrate significantly altered bacterial abundance (*Streptococcus*, *Lactobacillus*, etc.) and fungal composition (*Candida*, *Malassezia*, etc.) compared to control individuals [428]. Distinct lung cancer histological subtypes exhibit characteristic microbial signatures: lung adenocarcinoma (LUAD) demonstrates predominance of *Propionibacterium*, whereas lung squamous cell carcinoma (LUSC) shows enrichment of *Enterobacteriaceae*, with significantly higher microbial diversity observed in LUSC patients

[313]. In early-stage I/II NSCLC patients, *Firmicutes*, *Bacillus*, and *Actinobacteria* demonstrate significant enrichment, whereas *Actinobacteria* predominates in patients with advanced-stage (III/IV) disease [313]. Respiratory microbiota dysbiosis drives lung cancer progression through multiple interconnected mechanisms, including metabolic reprogramming, inflammatory cascade modulation, and establishment of an immuno-suppressive TME. For example, elevated *Veillonella parvula* (*V. parvula*) abundance correlates with reduced CD4 $^{+}$ T cell infiltration and upregulation of PD-1 and IL-17 expression, collectively fostering an immuno-suppressive TME [429]. These findings suggest respiratory microbial dysbiosis functions not only as a critical driver of lung carcinogenesis but also provides novel research directions for developing innovative diagnostic biomarkers and therapeutic interventions.

Molecular mechanisms underlying the association between specific bacteria and lung cancer progression

Current evidence elucidates distinct molecular mechanisms connecting specific bacterial taxa to lung cancer initiation and progression. Specific bacterial genera, including *Veillonella* and *Streptococcus*, modulate lung cancer cell proliferation and survival through activation of key oncogenic pathways, particularly ERK and PI3K, thereby contributing to lung cancer development and progression [536]. Studies confirm specific bacterial groups significantly correlate with distinct lung cancer histopathological subtypes, with *Cyanobacteria* exhibiting significant enrichment in LUAD, which correlates with decreased CD36 expression and elevated poly[ADP-ribose] polymerase 1 (PARP1) levels. These inflammatory mediators are mechanistically linked to carcinogenic processes and tumor-promoting effects [430]. LUSC demonstrates significant associations with distinct bacterial families, particularly *Enterobacter* and *Serratia* [537, 538]. These specific bacterial taxa contribute to tumorigenesis and malignant progression through modulation of multiple cancer-associated signaling networks. Interestingly, microbial diversity within lung cancer lesions exhibits modest reduction compared to adjacent normal lung parenchyma, while specific bacterial taxa associated with SCFA production demonstrate significant predictive value for lung cancer risk and progression [427, 538]. SCFAs (particularly NaB) modulate immune cell function and immunoregulatory molecules, including activation of CD4 $^{+}$ T cells, Tregs, and Th2 cells; inhibition of CD8 $^{+}$ T cells and NK cells, and induction of IFN- γ -R1 in NK cells, thereby suppressing lung cancer

development and progression [265]. Comprehensive analyses have identified several bacterial taxa, including *Actinomycetota*, *Bacteroidota*, and *Cyanobacteria*, that are significantly associated with lung cancer progression, while respiratory microbiome dysbiosis contributes to pulmonary tumorigenesis through multiple interconnected mechanisms, including metabolic network perturbation, inflammatory pathway modulation, and immune response alteration [535].

Microbiome regulation of the immune microenvironment in lung cancer

The mechanisms by which the microbiome regulates the lung cancer immune microenvironment exhibit remarkable complexity and diversity, with profound implications for tumorigenesis, progression, and therapeutic response [539]. Existing studies show oral microorganisms and their metabolites (such as proteins and endotoxins) translocate to pulmonary tissues through either direct respiratory tract inhalation or hematogenous dissemination. Subsequently, they influence lung cancer initiation and progression through multiple mechanisms, including chronic inflammatory response induction, host immune system reprogramming, and activation of oncogenic signaling pathways [431]. Specifically, oral *H. pylori* can translocate across lung endothelium, establishing persistent inflammatory microenvironments that ultimately promote malignant transformation and tumor growth through modulation of DC function and suppression of CD8⁺ T cell cytotoxicity [431]. Additionally, dysregulation of oral microbiota can modulate lung cancer cell survival through interference with p53-dependent apoptotic pathways [540]. Pulmonary microorganisms contribute to lung cancer development and progression through multiple integrated pathways, including directly affecting local immune microenvironment, modulating tumor-associated signaling pathways promoting cell cycle dysregulation and genomic instability, and bacterial metabolite-mediated effects involving bacteriocin production, TLR signaling activation, and TNF release [541]. Recent studies identified *Chlamydia pneumoniae* infection and HPV types 16 and 18 infection as potential lung cancer-associated risk factors that contribute to disease progression through profound remodeling of the local immune microenvironment [432]. In summary, the microbiome plays pivotal roles in regulating the TIME regulation of lung cancer, offering novel insights and potential therapeutic targets for comprehensive lung cancer prevention, early detection, and personalized treatment approaches.

Relationship between respiratory microbiome and prognosis of lung cancer treatment

Studies show respiratory microbiome composition and diversity are strongly associated with therapeutic outcomes in patients with lung cancer. A comprehensive study of never-smoking female LUAD patients revealed that the relative abundances of *Faecalibacterium*, *Fusicatenibacter*, and *Bacteroides* correlate with tumor size, and *Fusicatenibacter* relative abundances also correlate with tumor stage, suggesting that specific microbial signatures may play pivotal roles in lung cancer progression and treatment response [542]. Additionally, alterations in the abundance of butyrate-producing bacteria in NSCLC patients have garnered significant scientific attention [543]. These commensal microorganisms may favorably influence lung cancer treatment outcomes through multiple mechanisms, including inhibition of pathogenic bacterial growth, enhancement of nutrient absorption, modulation of immune responses, and maintenance of intestinal barrier integrity [543]. Recent investigations confirm that physiological concentrations of SCFAs can significantly inhibit lung cancer cell proliferation by inducing cell cycle arrest and promoting apoptosis, further substantiating the potential modulatory role of the gut-lung axis in lung cancer treatment efficacy [544, 545].

Other organ microbiomes and tumors

Microbial communities in other organs also demonstrate significant associations with tumorigenesis and progression in their respective tissues. Emerging evidence indicates that dysbiosis of the breast microbiome significantly correlates with BC initiation and progression; similarly, aberrant alterations in the brain microbiome increase brain tumor (BT) risk and promote disease progression, while interactions between the bone marrow microbiome and hematological malignancies are increasingly recognized as an important research focus.

Breast microbiome and breast cancer

Recent studies have demonstrated a significant association between breast microbiome and BC development [546, 547]. Breast tissue harbors a distinct microbial ecosystem with characteristic taxonomic distribution patterns, predominantly dominated by members of the *Proteobacteria* and *Firmicutes* [434]. Comparative metagenomic analyses revealed significant differences in breast tissue microbial composition and functional profiles between healthy individuals and BC patients [434]. Quantitative microbiome

profiling has demonstrated an overall elevation in microbial biomass within BC tissues, concurrent with a significantly reduced taxonomic diversity index compared to adjacent normal tissues [548]. In BC patients, total bacterial load is significantly elevated, with characteristic enrichment of specific microbial species such as *Methylobacterium radiotolerans*, while the relative abundance of *Sphingomonas yanoikuyae* is significantly depleted compared to non-malignant tissues [435]. Additionally, the TLR signaling pathway is significantly dysregulated in BC tissues, a phenomenon closely associated with microbial pattern recognition and immune response modulation [433]. At the molecular mechanism level, breast microbiome may contribute to mammary carcinogenesis. Key biological pathways implicated in this process include DNA damage mediated by toxins from *Escherichia coli* (*E. coli*) and other bacteria, and cancer susceptibility mediated by HPV [434]. Furthermore, the composition and functional status of the breast microbiome significantly influence BC treatment outcomes. For example, *Lactobacillus iners* is significantly associated with poor patient prognosis and may lead to decreased chemotherapy and radiotherapy sensitivity [436]. In summary, breast microbiome plays complex and important regulatory roles in BC occurrence, development, and therapeutic response. However, the precise molecular mechanisms underlying these interactions and their potential translational applications in clinical oncology warrant further comprehensive investigation [549–552].

Brain microbiome and brain tumor

Research exploring the association between BTs and the microbiome has faced considerable challenges due to the blood-brain barrier's (BBB) intrinsic function in preventing direct microbial invasion into the central nervous system. However, recent studies have revealed the critical role of specific microbiomes in modulating the brain TME. For example, comprehensive metagenomic analyses have demonstrated significant differences in microbial composition between glioma tissues and adjacent non-neoplastic brain parenchyma, with the phyla *Firmicutes* and *Fusobacteria* exhibiting significantly higher abundance in gliomas. In-depth analysis showed that genera including *Fusobacterium*, *Limosilactobacillus*, and *Pasteurella* are significantly enriched within glioma tissues [80, 553]. Notably, integrated multi-omics analyses have indicated that the intratumoral microbiome may regulate neuron-related gene expression networks through bacterial-derived metabolites. Both *in vivo* and *in vitro* experimental models have confirmed that key bacterial species enriched in gliomas influence tumor growth. *F. nucleatum* significantly

promotes tumor cell proliferation [80]. These findings suggest that although microorganisms rarely directly penetrate the intact BBB, resident microbial communities within the brain TME may significantly influence tumor progression through metabolite production or immune regulation, thereby providing novel direction for exploring the complex “microbiome-tumor” interaction mechanisms.

The gut-brain axis represents a bidirectional communication network through which the gut microbiota and central nervous system reciprocally regulate each other, influencing the progression of neurological malignancies and gastrointestinal neoplasms [554]. Research using a neurofibromatosis type 1-associated low-grade glioma mouse model has elucidated the molecular mechanisms by which intestinal *Bacteroides* species regulate optic pathway glioma progression through the TGF- β signaling pathway within the gut-brain-tumor axis, suggesting that targeted manipulation of gut microbiota could represent a novel therapeutic strategy for neurological malignancies [555]. Through integrated multi-omics analysis and experimental validation in mouse models, Lin et al. have identified a gut-brain-tumor axis regulatory network involving enrichment of *Clostridium* species and consequent purine metabolism dysregulation, which collectively mediate target organ redox imbalance. These molecular alterations synergistically contribute to disease pathogenesis, potentially mediating the initiation and progression of craniopharyngioma-associated hypothalamic complications [556]. The loss of intestinal epithelial interleukin-17 receptor A (IL17RA) signaling induced by aberrant expansion of Th17 cells can influence brain tumor growth by regulating the gut microbial community ecology [557]. Additionally, the microbiome may participate in regulating immune responses, modulating metabolite secretion, and influencing therapeutic efficacy to affect tumor development [558].

Bone marrow microbiome and hematologic neoplasms

The bone marrow microbiome has emerged as a critical factor influencing the initiation, development, and progression of hematologic malignancies [559–561]. Numerous investigations have confirmed that the microbiota significantly influences the bone marrow microenvironment through the synthesis of various bioactive metabolites. SCFAs exert bidirectional immunomodulatory effects within the bone marrow niche by inhibiting the expression of pro-inflammatory factors, including NF- κ B, IL-6, and TNF- α , while concurrently promoting anti-inflammatory factor IL-10 production and enhancing Th17 and Th1 cell activities [562–564]. Clinical studies have revealed a

significant decrease in the abundance of SCFA-producing bacterial taxa in multiple myeloma (MM) patients, concurrent with significant proliferation of bacterial groups involved in the nitrogen cycle, such as *Klebsiella* [437]. These findings reveal that microbiome affects hematologic malignancies by modulating immune microenvironments and altering metabolic profiles, thereby providing potential targets for related disease treatment.

MICROBIOME IN TUMOR DIAGNOSIS

Microbiome markers

Microbiome markers have demonstrated significant clinical utility in tumor diagnostics. Comprehensive studies have established that microbial signatures can serve as robust diagnostic bioindicators, encompassing (including specific microbes, diversity indicators, and metabolites), viral markers (including infection status, viral load quantification, and viral oncoproteins), and fungal markers (including mycobiome community structures and fungal-derived metabolites) [565–569]. Among these, bacterial marker research has been more extensively characterized, with compelling examples including *F. nucleatum* serving as a specific bacterial marker in CRC, GC, and oral cancer; gut microbiota diversity indices and SCFA metabolic profiles showing value for early detection, risk stratification, and prognostic assessment in CRC. Specific viral biomarkers demonstrate exceptionally high diagnostic value for particular malignancies, exemplified by high-risk HPV for CC, HBV for liver cancer, and EBV for NPC. Additionally, liquid biopsy techniques show advantages for non-invasive diagnosis in liver and PCs, particularly suitable for early screening and therapeutic monitoring. These microbiome-derived biomarkers offer multifaceted clinical applications, including population-based early screening, minimal residual disease detection, enhancement of conventional diagnostic accuracy, and provision of novel strategies for precision oncology diagnostics. Table 6 summarizes recent progress and the clinical application value of microbiome biomarker research in different tumor types.

Bacterial markers

Specific microbes: The human microbiome has demonstrated significant value in cancer diagnostics, with the biomarker potential of specific microbial taxa attracting substantial research interest [582–587]. Numerous studies have confirmed that specific microbiota, when utilized as tumor diagnostic biomarkers, has significant

clinical utility. In colorectal neoplasia studies, comparative analyses between patients with colorectal polyps and healthy controls have revealed significant differences in both salivary and fecal microbiota composition and diversity, characterized predominantly by increased abundance of potentially pathogenic bacteria and concurrent decreased representation of beneficial microbial taxa [588]. Additionally, intestinal microorganisms like *Veillonella*, *Bifidobacterium dentium*, and *Lactobacillus salivarius* have demonstrated good diagnostic value for GC [143]. *F. nucleatum* has emerged as a promising biomarker for CRC [161]. In familial adenomatous polyposis studies, researchers found intratumoral *E. coli*, as a precancerous lesion, could serve as an early microbial biomarker for CRC risk detection [589]. Additionally, peripheral blood CRC-associated microorganisms, such as *B. fragilis* and *S. gallolyticus*, have shown bacterial marker potential in CRC prediction [570]. In GC diagnostics, specific microbial signatures, including *Fusobacterium*, *Streptococcus*, and *Pseudomonas*, have been identified as important discriminatory indicators differentiating malignant from non-malignant conditions [575]. In BC research, investigators have observed a significant inverse correlation between tumor tissue total bacterial load and tumor stage, providing novel insights into microbiome-based approaches for BC diagnosis [580]. These collective findings confirm the significant potential of microbiome-based biomarkers in cancer screening and diagnosis. In conclusion, the human microbiome demonstrates extensive clinical potential for oncological diagnostics, with microbial-based biomarkers representing a promising frontier that warrants further mechanistic investigation.

Indicators of bacterial diversity: As microbiome research has advanced, bacterial diversity metrics have emerged as particularly promising diagnostic indicators with significant clinical potential across multiple cancer types. Extensive investigations have confirmed that quantitative assessments of microbial abundance and community compositional characteristics provide innovative approaches for cancer detection and classification [588]. Different cancer types present unique bacterial compositional features. Tissue-associated microbiome across various cancer types has demonstrated prognostic value for predicting disease recurrence, with a specific combination of nine bacterial genera significantly enhancing the accuracy of patient survival prediction [590]. Gut microbiota characterization has evolved as an effective non-invasive assessment methodology for evaluating HCC risk. Through microbial sequencing technology, investigators have successfully identified optimal combinations of microbial markers demonstrating significant diagnostic potential for both early-stage and

TABLE 6 Advances and clinical applications of microbiome biomarkers in tumor diagnosis.

Tumor type	Biomarker category	Representative biomarkers	Related research	Clinical utility	References
CRC	Bacteria & Metabolites	<i>Fusobacterium nucleatum</i> <i>Bacteroides fragilis</i> γ -aminobutyric acid L-aspartic acid phenylacetic acid	Enrichment of <i>Fusobacterium nucleatum</i> in tumor tissue correlates positively with tumor stage.	• Non-invasive fecal screening (sensitivity 85%); • Recurrence monitoring.	[161, 570, 571]
Viruses		<i>Bacteroides phage</i> <i>Streptococcus phage</i>	Viral biomarker panel distinguishes CRC from healthy controls (AUC 0.89).	Differentiation of adenoma vs. carcinoma (specificity 79%).	[572, 573]
Fungi		<i>Rhodotorula dairenenensis</i> <i>Cutaneotrichosporon curvatus</i>	Reduced fungal diversity in CRC, enrichment of specific taxa.	TME profiling: predicting immunotherapy response.	[574]
GC	Bacteria	<i>Fusobacterium</i> <i>Streptococcus</i>	<i>Streptococcus</i> ↑ <i>Lactobacillus</i> ↑	Non-invasive salivary screening (AUC 0.76).	[575, 576]
Fungi		<i>Candida albicans</i> <i>Malassezia globosa</i>	<i>C. albicans</i> promotes nitrosamine synthesis, correlates with GC risk.	Tissue biopsy support: risk stratification.	[43, 214]
HCC	Viruses	HBV viral load miR-122	The viral load of HBV is negatively correlated with mi-R122.	Stratified monitoring in hepatitis patients: antiviral efficacy assessment.	[577]
CC	Viruses	HPV-16/18 ctDNA	HPV-ctDNA positivity predicts recurrence risk.	Minimal residual disease monitoring, survival prognosis.	[578]
PC	Bacterial metabolites	Polyamine metabolites (spermine, spermidine)	Elevated serum polyamine levels precede imaging abnormalities.	High-risk population screening: improved diagnosis with CA19-9.	[579]
BC	Bacteria	Total bacterial load in tumor tissue	Load inversely correlates with tumor stage.	Prognostic assessment (low load indicates advanced risk).	[580]
NPC	Viruses	EBV antibodies	Combined detection AUC 0.93 (vs. healthy controls).	Screening in high-risk regions.	[581]
PCa	Fungi	<i>Sordariomycetes</i>	Increased in plasma abundance ($p < 0.01$).	Non-invasive diagnosis of advanced PCa; Biochemical recurrence prediction.	[222]

Abbreviations: AUC, area under curve; CA19-9, carbohydrate antigen 19-9; ctDNA, circulating tumor DNA; LFS, lipopolysaccharide.

advanced HCC. Concurrently, blood microbiome profiling-based diagnostic models have achieved high accuracy in distinguishing HCC from healthy controls [591, 592]. In a comparative study, bacterial diversity was determined through OTUs analysis and represented by Shannon index, Simpson index, and Invsimpson index [591]. This study demonstrated that all three indices of fecal microbial diversity were significantly reduced in cirrhosis patients compared to the control group. Conversely, compared to cirrhosis, all three indices were significantly elevated, suggesting a characteristic microbial diversity pattern associated with hepatocarcinogenesis. The study concluded that indices based on OTU markers possess good diagnostic value [591]. A cross-sectional study indicated that α -diversity of circulating microbiota was significantly reduced in HCC patients. At the genus level, seven bacterial taxa demonstrated significantly differential abundance between HCC and control subjects. Among these, a diagnostic index composed of five genus-level microbial signatures could characteristically distinguish HCC [592]. Additionally, gut microbiota-based prediction models incorporating 37 specific strains have accurately identified advanced fibrosis status in non-alcoholic steatohepatitis (NASH) patients, further substantiating the important clinical application of microbial signatures in early disease detection [593]. The diagnostic potential of microbial diversity metrics has also been extensively demonstrated in oral microbiome studies. Studies confirm characteristic alterations in tongue microbiota are significantly associated with GC development, potentially becoming novel non-invasive biomarkers [576]. This study represented microbial α - and β -diversity using multiple indices, finding that GC patients exhibited significantly increased tongue coating bacterial richness metrics concurrent with decreased overall bacterial diversity indices compared to non-cancer controls. Specifically, GC patients demonstrated significantly reduced relative abundance of *Bacteroidetes*, *Fusobacteria*, *Proteobacteria*, and *Actinobacteria* [576]. In summary, microbial taxonomic signatures and bacterial diversity metrics demonstrate substantial clinical potential and research value in tumor diagnosis.

Bacterial metabolites: Bacterial metabolite markers play an increasingly important role in tumor diagnosis. Studies confirm intestinal microbial metabolites can accurately reflect the homeostatic state of the gut microbicosystem and serve as key biomarkers for cancer diagnosis [571]. In non-invasive diagnostic approaches, the combination of specific metabolite markers (such as γ -aminobutyric acid, L-aspartic acid, and phenylacetic acid) and bacterial markers (such as *F. nucleatum* and *P. anaerobius*) has significantly improved discriminatory

accuracy between CRC, pre-existing lesions (CRA), and healthy controls [571]. Metabolomic analysis has revealed primary microbial metabolites associated with tumor progression, particularly polyamine metabolites. These metabolites demonstrate significant elevation in the serum of PC patients, with notably preceding detectable histologic changes [579]. This suggests intestinal microbes analysis and microbial metabolite detection (such as polyamines) could serve as potential non-invasive PC detection biomarkers [579]. In HCC studies, bacterial population compositional alterations and their metabolites demonstrate strong mechanistic correlations with tumorigenesis. Specifically, decreases in beneficial butyrate-producing bacterial populations and increases in LPS-producing bacteria are strongly associated with early HCC development. Consequently, researchers have developed and validated relevant microbial profiles that demonstrate excellent diagnostic performance in independent case-control validation cohorts, further confirming the significant promise of microbiome in tumor diagnosis [591].

Viral markers

Indicators of viral infection: Viral infection-related biomarkers represent a critical category of microbial signatures with important application value in cancer diagnosis [594–598]. Various oncogenic viruses, including HBV, high-risk HPV, and EBV, can infect host cells and integrate their genomic material into the cellular genome, thereby serving as biomarkers for assessing minimal residual diseases (MRDs) through detection of viral circulating tumor DNA (ctDNA) or viral oncoproteins in liquid biopsies. For example, persistent detection of HPV ctDNA in CC patients following completion of radiotherapy strongly correlates with inferior progression-free survival (PFS), and MRDs can be quantified through HPV-ctDNA detection [578]. In CRC diagnosis, viral markers have demonstrated significant clinical applications. Studies have shown specific gut virome signatures, including Phage FAKO27_000271F, *Faecalibacterium* virus *Toutatis*, and *Faecalibacterium* virus *Lugh* markers, can effectively differentiate CRC patients from healthy individuals. Furthermore, distinct patterns of *Faecalibacterium* virus *Brigit*, *Streptococcus* phage *Javan191*, and *Streptococcus* phage *YMC-2011* abundance can discriminate between CRC and CRA with clinically relevant sensitivity and specificity [572]. Additionally, a multi-component viral signature comprising 14 novel viruses has been shown to significantly differentiate CRC patients from healthy controls, with several viral species enriched in CRC patients [573].

Moreover, phages not only participate in CRC pathogenesis but also show potential in diagnosis. Studies have confirmed specific phage prevalence in early, intermediate, and advanced CRC patients, potentially serving as CRC biomarkers [599]. In summary, viral components of the human microbiome and relative infection indicators demonstrate potential as biomarkers for cancer diagnosis.

Viral loads: Viral load and related molecular markers hold valuable diagnostic and prognostic indicators in tumor diagnosis. HBV and HCV, as major hepatotropic viral pathogens, not only significantly disrupt normal liver physiological functions but also demonstrate clear etiological associations with HCC initiation, development, and progression. MicroRNA-122 (miR-122) promotes HCV replication, while HBV viral load demonstrates a significant inverse correlation with miR-122 expression. Dysregulated miRNAs mediate complex interactions at the host–virus interface and can promote viral persistence in HCC, thereby potentially serving as novel detection biomarkers [577]. Other viruses like HPV demonstrate well-established etiological associations with malignancies. In cervical pre-cancer (CIN) and CC, HPV viral load serves as an important risk assessment parameter [600]. Therefore, viral components of the microbiome and viral load represent important molecular tools in cancer diagnosis. In-depth investigation of virus-related molecular signatures and their mechanistic connections to carcinogenesis will provide critical theoretical foundations and innovative research directions for early cancer diagnosis, prognosis assessment, and personalized therapeutic strategy development.

Viral antigens: Viral antigens and their corresponding host-derived antibody responses represent critical viral biomarkers in cancer diagnosis. Current studies explore diverse predictive biomarkers incorporating viral antigens, with the objective of enhancing diagnostic sensitivity and specificity [601]. Viral markers demonstrate particular significance in NPC diagnosis and monitoring. Serological analyses have demonstrated that five EBV-specific antibodies, including BLRF2-IgA, BLRF2-IgG, and BDLF1-IgG5, exhibit significantly elevated levels in NPC patients compared to healthy controls, highlighting their potential as biomarkers for early disease detection [581]. Follow-up studies have confirmed that integrating these five EBV-associated antibodies with EBNA1-IgA significantly enhances the diagnostic accuracy for NPC [581]. Viral antigens exhibit significant clinical utility beyond NPC, contributing to diagnostic approaches for various other malignancies. In China, chronic hepatitis B and hepatitis B carriers (HBsAg positive) are correlated with significantly elevated PC risk [602], suggesting that HBsAg screening may facilitate early risk assessment and inform preventive interventions. In summary, viral

components of the microbiome, particularly viral antigens and their corresponding antibody responses, play an increasingly important role in tumor diagnosis.

Fungal markers

Characterization of fungal communities: Studies have shown that alterations in fungal abundance and community composition within tumor tissues and associated samples correlate significantly with cancer development [603]. For example, *C. albicans* exhibits significant enrichment in GC tissues and demonstrates potential utility as a fungal biomarker [43]. Additionally, oral *M. globosa* has emerged as a candidate fungal biomarker species for GC diagnosis [214]. Another study revealed that 14 fungal biomarkers effectively distinguished CRC patients from healthy individuals across different racial populations, highlighting the significant diagnostic potential of fungal signatures in CRC [227]. In a tongue microorganism study, 14 fungal taxa, including *Ampelomyces sp IRAN 1* and related species, demonstrated significant abundance increases in GC patients and exhibited potential as diagnostic biomarkers, further expanding the taxonomic scope of fungi in cancer diagnosis [604]. Linear discriminant analysis effect size (LEfSe) analysis further revealed significant differences in fungal taxonomic profiles among patients with CRC, colorectal polyps, and healthy controls. Several fungal taxa, including *Rhodotorula dairensis* and *Cutaneotrichosporon curvatus*, exhibited significant enrichment in CRC patients and may contribute to the formation of a tumor-permissive microenvironment [574]. Additionally, other studies have reported the significant correlation between specific fecal fungal signatures and GC, providing rationale for the application of fecal mycobiome profiling as a non-invasive cancer screening approach [143]. Notably, disease progression stages demonstrated significant correlation with characteristic patterns of fungal microbiota [605].

Fungal metabolites: Fungi play important roles in tumorigenesis and progression through metabolite regulation, with both fungal taxa and their secreted metabolites demonstrating significant potential as clinical biomarkers. Fungal biomarkers and metabolites potentially exhibit diagnostic potential across multiple cancer types. For example, *Candida spp.*, identified as potential fungal biomarkers for OSCC, synthesize carcinogenic metabolites including nitrosamines that participate in oncogenic transformation and progression. This mechanistic relationship provides a scientific foundation for the utilization of fungal-derived metabolomic signatures as diagnostic indicators [606]. Recent studies have identified

fecal fungi, including *Sordaria pseudoproxies*, *Gibellulopsis*, and *Cercophora*, significantly correlate with elevated GC risk. They also demonstrate significant correlations with altered serum amino acid profiles, particularly methionine, L-alanine, and L-threonine levels, suggesting these metabolic signatures may serve as complementary biomarkers for enhanced GC detection [607].

Microbial metabolite markers

As the field of cancer metabolomics advances, microbial-derived metabolite signatures demonstrate significant diagnostic potential across multiple cancer types. Evidence indicates that intestinal microbial communities and their associated metabolites (including bile acid) undergo significant alterations during PC development, affecting chemotherapeutic efficacy and clinical outcomes while potentially serving as discriminatory biomarkers for PC [608]. Additionally, metabolites derived from gastrointestinal microorganisms, particularly SCFAs, demonstrate significant associations with diverse malignancies and exhibit potential as reliable biomarkers for cancer type differentiation [609]. In CRC investigations, researchers have documented significant differences in gut microbial composition and metabolic functions between healthy individuals and patients across the colorectal neoplasia continuum, from adenomas to invasive adenocarcinomas, providing novel metabolic biomarker candidates for early-stage CRC detection [610]. Quantitative analysis of eight gut microbiota-derived serum metabolites has validated their high diagnostic accuracy for distinguishing CRC and precancerous adenomas [611]. In lung cancer studies, specific metabolites including cysteinyl valine, 3-chlorobenzoic acid, and 3,4-dihydroxyphenyl ethanol effectively discriminated lung cancer patients from controls and exhibited enhanced diagnostic performance when analyzed as a composite signature, suggesting potential utility as clinically relevant biomarkers for lung cancer diagnosis [612]. Various intestinal microorganism metabolites (such as secondary bile acids) demonstrate significant associations with gastrointestinal carcinogenesis, most notably in CRC, and represent promising non-invasive biomarkers [613]. Of particular clinical significance, early detection of PC may be achieved through analysis of intestinal microbial community alterations and metabolites (such as polyamines). These aberrant patterns exist prior to histologically detectable disease [579]. In conclusion, microbial-derived metabolites demonstrate considerable potential as cancer biomarkers, offering novel avenues for early detection and therapeutic strategy development.

Inflammation-related markers

In recent years, inflammation-related markers have emerged as promising biomarkers for cancer detection. Multiple investigations have demonstrated significant enrichment of *Parvimonas micra* (*P. micra*) in both the intestinal mucosal tissues and fecal samples of CRC patients compared to healthy controls [614]. Notably, *P. micra* colonization significantly upregulates the expression of several pro-inflammatory mediators, including IL-5, IL-8, CCL20, and CSF2, which collectively contribute to the establishment and maintenance of a pro-tumorigenic inflammatory microenvironment in CRC [614]. Therefore, *P. micra* abundance and its associated inflammatory signature may serve as clinically relevant biomarkers for CRC, providing new strategies for early detection and treatment of CRC. Additionally, *C. albicans* promotes cytokine production, particularly through Th17 cell response induction, and enhances adhesion molecule expression, thereby mediating pro-inflammatory responses that contribute to cancer progression [417]. This mechanistic relationship suggests that *C. albicans* colonization patterns and associated inflammatory signatures may represent valuable biomarkers for cancer.

Organ-specific microbial markers

Applications of microbiome analysis in cancer diagnostics demonstrate distinct organ-specific signatures, with site-specific microbial markers offering novel approaches for early cancer detection and characterization. Existing studies have explored microbial markers in the oral cavity, skin, urinary system, and respiratory tract, collectively establishing a comprehensive framework for microbiome-based cancer diagnosis. Table 7 summarizes different organ system key microbial markers and their clinical applications and research progress in corresponding tumor types, providing an important reference for advancing precision oncology and individualized treatment strategies.

Oral microbial markers

Oral microbiome signatures represent a critical subset of organ-specific microbial markers with demonstrated utility in disease diagnosis, prognostic stratification, and therapeutic response prediction across multiple cancer types. Recent studies have revealed that enrichment of periodontal pathogens, including *F. nucleatum*, *P. gingivalis*, and *T. denticola*, correlates with oral potentially malignant diseases and oral cancer [40, 162]. The magnitude of

TABLE 7 Organ-specific microbial biomarkers and their association with tumor characteristics.

Organ system	Key microbial biomarkers	Associated cancer types	Related research	Clinical utility	References
Oral cavity	<i>Fusobacterium nucleatum</i> <i>Porphyromonas gingivalis</i> <i>Alloprevotella</i> <i>Streptococcus</i> <i>Malassezia globosa</i>	Oral cancer GC Lung cancer	• <i>Fusobacterium nucleatum</i> correlates with oral cancer gene expression; • Reduced <i>Streptococcus</i> abundance indicates GC risk; • Decreased oral α -diversity predicts LC risk.	• Non-invasive oral swab screening; • Pre-cancerous lesion monitoring; • Prognostic stratification.	[162, 214]
Skin	<i>Staphylococcus aureus</i> <i>Ralstonia</i> <i>Diaphorobacter</i> <i>Streptococcus</i>	Melanoma SCC	<i>Staphylococcus aureus</i> virulence factors promote carcinogenesis.	• Skin swab diagnostic biomarkers; • High-risk lesion.	[480, 615]
Urogenital	<i>Bacteroides</i> <i>Porphyrobacter</i> <i>Herbaspirillum</i> <i>Acinetobacter</i> <i>Fusobacterium</i> <i>Fenollarria/Ezakiella</i>	BCa PCa	• High prevalence of <i>Acinetobacter</i> in BCa; • <i>Fusobacterium</i> positively correlates with PCa invasiveness.	• Urine microbiome non-invasive diagnosis; • Recurrence risk prediction; • Personalized therapy response assessment.	[531, 616]
Respiratory	<i>Streptococcus</i> <i>Prevotella</i> <i>Veillonella</i> <i>Akkermansia muciniphila</i>	Lung cancer	• <i>Streptococcus</i> enrichment correlates with poor prognosis; • <i>Akkermansia muciniphila</i> predicts immunotherapy response.	• Sputum/ bronchoalveolar lavage fluid testing; • Immunotherapy efficacy prediction; • Survival period assessment.	[429, 617]

pathogenic bacterial enrichment is strongly associated with oncogenic genes and coincides with a significant reduction in commensal bacteria, particularly *Streptococcus*, suggesting these distinctive microbial signatures may serve as novel biomarkers for oral cancer [162]. Meta-analytical studies have established significant correlations between oral microbiome profiles and multiple cancer types. Specifically, taxonomically diverse microorganisms, including *Alloprevotella*, *Streptococcus*, and *M. globosa*, have been characterized as potential oral biomarkers for GC [214, 618]. Notably, reduced α -diversity within the oral microbiome has emerged as a predictive marker for lung cancer risk. Although the direct causal relationship between periodontal pathogens and lung cancer requires further mechanistic elucidation, specific microorganisms, particularly *F. nucleatum*, demonstrate potential utility as non-invasive biomarkers for lung cancer [163]. Alterations in oral microbial composition, particularly changes in the abundance of five genera including *Bacillus* spp. and *Enterococcus* spp., effectively discriminate between patients with epithelial precursor lesions and those with invasive carcinoma, potentially serving as clinically relevant biomarkers for monitoring oral carcinogenesis progression [619]. In summary, oral microbial signatures represent

essential components of the organ-specific microbiome landscape with substantial clinical applications in cancer diagnosis, prognostic assessment, and longitudinal disease monitoring across diverse malignancies.

Skin microbial markers

Emerging evidence indicates that cutaneous microbiome signatures demonstrate significant diagnostic, prognostic, and risk stratification potential across various dermatological malignancies. Multiple studies have confirmed significant differences in microbiome composition and abundance (especially *S. aureus*) between melanoma and non-melanoma skin carcinomas compared to site-matched healthy controls [615]. Researchers have identified novel microbial markers associated with actinic keratosis (AK) or SCC, including AK-associated *Ralstonia* and *Diaphorobacter*, as well as SCC-associated *Ralstonia* and *Streptococcus* [480]. Host factors including immunosuppression, chronic inflammatory conditions, and oncogenic viral infections significantly increase cutaneous susceptibility to malignant transformation, while their complex interactions with the resident

microbiome further modulate disease initiation and progression. Despite the significant potential of cutaneous microbial signatures as biomarkers, in-depth exploration in this field remains relatively limited. With increasing research investment, cutaneous microbiome markers are anticipated to provide innovative strategies for early diagnosis, personalized treatment, and prognostic stratification of skin cancer.

Microbial markers of the urinary system

Urinary microbiome signatures represent an emerging class of non-invasive biomarkers with significant utility in the diagnosis, molecular classification, risk stratification, and prognostic assessment of genitourinary malignancies. Recent comprehensive studies targeting urinary microbiota have systematically identified several bacterial genera with statistically significant associations with urinary tumors. The relative abundance of *Bacteroides*, *Porphyrobacter*, and *Herbaspirillum* shows significant increases in BCa patients characterized by high recurrence and progression risk, suggesting their potential value as risk stratification biomarkers [616]. To thoroughly elucidate the core microbiome characteristics of BCa, researchers integrated multiple data sets and identified 31 characteristic bacterial genera, including *Acinetobacter* [620]. The detection frequency of *Acinetobacter* was significantly higher in tumor patients, highlighting its potential value as a microbial marker for BCa.

Additionally, urinary microbial signatures have demonstrated significant clinical potential in the non-invasive diagnosis, molecular classification, staging, and prognostic assessment of PCa. Comprehensive metagenomic analysis of post-prostate massage urine specimens and post-prostatectomy prostate secretions revealed that alterations in five strictly anaerobic bacterial genera, including *Fusobacterium* and *Fenollarria/Ezakiella*, significantly correlate with PCa aggressiveness and recurrence risk. This suggests their potential utility as urinary cancer biomarkers [531]. This emerging evidence not only emphasizes the important role of the urinary microbiome in the clinical management of PCa but also provides new research directions for developing novel liquid biopsy approaches and precision medicine strategies.

Respiratory microbial markers

The respiratory microbiome represents a complex ecological niche with emerging diagnostic, prognostic, and therapeutic implications in pulmonary malignancies.

Comprehensive metagenomic analyses have demonstrated that elevated abundance of specific microbial communities within the lower respiratory tract, particularly oral commensals including *Streptococcus*, *Prevotella*, and *Veillonella*, is significantly associated with poor prognosis in lung cancer patients [429]. Furthermore, a clinical study encompassing patients with colorectal, breast, and lung malignancies demonstrated that intratumoral microbial diversity exhibits a significant negative correlation with immunohistopathological markers, including TILs and PD-L1 expression. These immunological relationships are strongly associated with unfavorable clinical outcomes [345]. Additionally, the abundance of the intestinal mucinophilic bacterium *Akkermansia muciniphila* has emerged as a significant predictive biomarker for immunotherapeutic response in lung cancer patients [617]. In summary, respiratory microbiome signatures demonstrate substantial clinical utility in lung cancer detection and prognostic assessment, advancing our mechanistic understanding of lung cancer biology while establishing novel biomarker platforms and potential therapeutic targets for precision oncology approaches in pulmonary malignancies.

Combined application of liquid biopsy and microbiome markers

The integration of microbiome analysis with liquid biopsy technologies represents a rapidly evolving frontier in cancer diagnosis, with this multimodal approach demonstrating exceptional potential. The detection of circulating microbial DNA offers the possibility of non-invasive monitoring of tumor microbiome changes, while microbial-derived exosomes function as biological couriers, conveying specific markers of the tumor microbiome. This combinatorial approach establishes novel paradigms for early cancer diagnosis, treatment efficacy monitoring, and recurrence surveillance across tumor types.

Circulating microbial DNA testing

The integration of liquid biopsy methodologies with microbiome analysis, particularly through the detection and characterization of circulating microbial DNA (cmDNA), demonstrates remarkable diagnostic and prognostic potential across diverse malignancies [621–623]. Circulating microbial DNA encompasses free DNA fragments of microbial origin detectable in peripheral blood and has demonstrated significant diagnostic value across various malignancies, particularly CRC [624]. In HCC research, significant changes in the abundance of seven bacterial

species were detected in the serum of HCC patients compared to patients with cirrhosis and healthy controls, with particularly notable enrichment of *Staphylococcus*. Investigators subsequently developed a multivariate scoring model based on the abundance profiles of five bacterial species that successfully discriminated HCC patients, strongly suggesting the potential application of cmDNA in HCC diagnosis [592].

Beyond HCC, cmDNA has demonstrated significant diagnostic and prognostic value in other cancer types. For instance, consistently detected HPV-ctDNA following chemoradiotherapy (CRT) for CC correlates with inferior PFS. Assessment of MRD through HPV-ctDNA has demonstrated substantial clinical utility [578]. In oropharyngeal cancer (OPC) studies, detection of HPV-16 DNA in plasma and saliva serves as a highly sensitive predictor of disease recurrence [625]. These collective findings not only underscore the critical role of HPV in cancer diagnosis and prognostic assessment but also establish scientific foundations for the clinical application of cmDNA detection technology across a diverse spectrum of malignancies.

Exosomes of microbial origin

Extracellular Vesicles (EVs) of microbial origin have demonstrated significant value as novel biomarkers in disease diagnosis. A systematic analysis of bacterial EVs isolated from both peripheral blood and tissues of patients with BTs revealed significant differences in bacterial EV distribution between BT patients and healthy controls. Specifically, *Saccharibacteria*, *Prevotellaceae*, and *Dialister* demonstrated significant depletion in both circulation and tissue microenvironments of BT patients, and *Erysipelotrichia* was significantly increased in both circulation and tissue microenvironments of BT patients. *Lachnospiraceae* NK4A136 exhibited divergent compartment-specific alterations, showing significant enrichment in peripheral blood yet concurrent depletion in tumor tissues of BT patients [626]. This finding elucidates the potential value of bacterial EVs for BT diagnosis, particularly for detecting early-stage lesions that conventional imaging modalities fail to identify [626]. Furthermore, bacterial EVs in serum have important applications in HCC diagnosis [592]. A study developed a diagnostic method based on detecting glycan-1 (GPC1), a membrane-anchored proteoglycan enriched on the surface of EV. This approach effectively differentiates patients with benign pancreatic disorders from those with premalignant pancreatic lesions and demonstrates superior sensitivity for identifying patients with advanced

PC, offering significant advantages over conventional PC marker carbohydrate antigen 19-9 (CA19-9) [627]. In cancer biology research, EV-based microRNA characterization provides novel concepts for developing clinical diagnostic algorithms applicable to early detection of various gastrointestinal cancers, including CRC [628]. In summary, the application of microbial-derived EVs, representing a combination of liquid biopsy and microbiome markers, has demonstrated significant diagnostic advantages across various malignancies, including biliary tract tumors, HCC, and gastrointestinal cancers. This multidisciplinary approach has established innovative research directions for early disease diagnosis and treatment plan development.

Standardization of microbiome diagnostic methods

The analytical validity and reproducibility of microbiome-based diagnostic applications depend critically on rigorous standardization of sample collection protocols. Consequently, implementation of standardized operating procedures for specimen acquisition represents a fundamental prerequisite for generating reproducible, clinically actionable microbiome data.

Specifications for sample collection and handling

Implementation of standardized microbial sample collection and processing protocols represents a critical determinant of analytical accuracy and reliability. Acknowledging the spatial heterogeneity of microbial community distribution across anatomical niches [629], standardization efforts must ensure consistent sampling site selection with precise anatomical localization and documentation. Specimens must be collected in statistically sufficient quantities to ensure adequate representation of microbial diversity and biomass, with optimal sampling preferably performed during the acute phase of disease and before initiating antimicrobial therapy. Sampling procedures must follow standardized aseptic protocols to minimize environmental and cross-site contamination from commensal microbiota. Acquired specimens should avoid contact with disinfectants or preservatives and be promptly submitted for testing [630]. Samples should be collected in sterile, sealed, specialized containers to maintain microbial viability during transportation [630]. Additionally, sample-specific processing workflows must be established based on the unique biological characteristics and

stability profiles of distinct specimen types. Specimens from sterile sites, including cerebrospinal fluid and body fluids, require expedited processing protocols. Fecal and urinary specimens, however, demonstrate microbiome stability and can be maintained under validated preservation conditions for extended periods. For sensitive organisms such as *Shigella spp.* and *Neisseria gonorrhoeae*, immediate sample processing is necessary to ensure testing accuracy [631]. A standardized system for microbiome research requires establishing evidence-based standard operating procedures, encompassing critical elements including sampling site consistency, aseptic protocol implementation, appropriate collection method selection, suitable transport media, and differentiated sample processing strategies.

Standardization of detection methods

The standardization of microbiome characterization methodologies represents a fundamental challenge in translating microbiome research. Currently, microbial taxonomic classification primarily employs two complementary analytical approaches, targeted amplicon sequencing of phylogenetic marker genes and metagenomic shotgun sequencing analysis, which collectively provide robust technical frameworks for systematic microbiome investigation [632]. Establishing standardized processes is equally essential for implementing rapid detection techniques. These techniques include immunofluorescence, agglutination tests, immunochromatography (ICT), enzyme immunoassays (EIA), and molecular microbiology techniques, all widely implemented in clinical microbiome analysis due to their rapid turnaround time, operational simplicity, and diagnostic performance characteristics [631]. However, advanced assays alone cannot guarantee diagnostic performance; systematic optimization of the entire analytical workflow remains indispensable. Laboratories typically adopt selective testing strategies, including taking a cautious approach to culture results of suspected contaminants and avoiding unnecessary antimicrobial susceptibility tests. These practices collectively represent critical strategies for enhancing diagnostic specificity and optimizing antimicrobial stewardship [633]. The standardization of microbiome diagnostic methods requires not only harmonization of testing techniques but also optimization of testing processes and standardized application of rapid testing detection methods. Collectively, these measures constitute vital components of a standardized microbiome diagnostic framework, establishing a solid foundation for improving diagnostic accuracy, optimizing antimicrobial use, and advancing microbiome research.

MICROBIOME IN TUMOR PROGNOSIS AND EFFICACY PREDICTION

The microbiome has emerged as a crucial bioindicator for tumor prognosis assessment and treatment efficacy prediction. Evidence indicates that alterations in microbial diversity, taxonomic composition, and metabolite profiles correlate significantly with clinical outcomes in cancer patients. The microbiome influences therapeutic outcomes through multiple mechanisms, including modulation of tumor response to chemotherapy, radiotherapy, and immunotherapy, while also contributing to treatment-related adverse events. Table 8 summarizes current evidence regarding microbiome-based biomarkers for tumor prognosis prediction and treatment response assessment, along with their potential clinical applications.

Microbiome and tumor prognosis

Microbial diversity and prognosis

Microbial diversity and its influence on tumor prognosis have emerged as a critical focus in contemporary oncological research [646]. Evidence suggests that microbiota from both oral cavity and intestinal tract are associated with PC prognosis, with *Streptococcus spp.*, *Prevotella spp.*, or *Veillonella spp.* showing significant negative correlations with survival outcomes [429, 634]. These findings indicate that microorganisms from multiple anatomical sites have potential as prognostic biomarkers for PC. Previous studies have revealed significant alterations in the microbiome composition of patients with HNSCC before and after surgery. Microbial α -diversity significantly decreases following surgery but subsequently increases in patients experiencing tumor recurrence [635], indicating that microbiota diversity patterns may serve as predictive indicators for HNSCC prognosis. Additionally, higher gut microbiome diversity consistently correlates with favorable clinical responses in NSCLC patients undergoing immunotherapy [636].

Specific microbial species and prognosis

Accumulating evidence highlights the prognostic significance of specific microbial species in predicting tumor progression and treatment outcomes. Multiple investigations have confirmed that oral mucositis (OM), a common adverse effect of cancer treatment. It exhibits variations in microbial composition that correlate with

TABLE 8 Key roles and clinical applications of the microbiome in tumor prognosis and treatment response prediction.

Application direction	Tumor type	Key microbes/metabolites	Key roles	Clinical application strategies	References
Prognostic prediction					
Microbial diversity	PC	<i>Streptococcus</i> <i>Prevotella</i> <i>Veillonella</i>	Reduced microbial diversity correlates with shorter survival (HR = 1.8).	Multi-site microbial detection (oral& gut) to guide postoperative management.	[429, 634]
HNSCC		Postoperative microbial dynamics	Increased α -diversity in recurrent patients ($p = 0.006$).	Postoperative microbiome monitoring to predict recurrence risk.	[635]
NSCLC		Gut microbial diversity	High diversity linked to better immunotherapy response.	Stratification of immunotherapy patients.	[636]
Specific microbial biomarkers	CRC	<i>Fusobacterium nucleatum</i>	Tumor-enriched <i>F. nucleatum</i> shortens OS and promotes pro-inflammatory microenvironment.	Fecal testing to identify high-risk patients guiding adjuvant chemotherapy intensity.	[164]
	BC	<i>Tissierella</i>	Higher abundance correlates with prolonged OS ($p < 0.01$) and inhibits metastasis.	Development of probiotic formulations to enhance anti-tumor efficacy.	[44]
	GC				
	LUAD				
HCC		<i>Lachnospiridium</i> ↑ <i>Prevotella</i> 9 ↓	Combined signature predicts high response to ICI.	FMT to optimize immunotherapy.	[637]
Lung cancer		<i>Prevotella</i> <i>Streptococcus</i> <i>Veillonella</i>	Enrichment correlates with poor survival prognosis ($p < 0.05$).	Sputum testing to guide prognosis management.	[429]
CC		<i>Microbacterium</i> <i>Streptococcaceae</i>	Higher abundance correlates with reduced OS/ RFS ($p < 0.001$).	Identification of high-risk patients; Recurrence monitoring.	[638]
NSCLC		<i>Bacteroides dorei</i> <i>Parabacteroides distasonis</i>	Enrichment linked to prolonged OS (>6 mo).	Gut microbiome testing to identify patients likely to benefit from immunotherapy.	[639]
Metabolite biomarkers	HCC	Galanthaminone (bacterial metabolite)	High levels correlate with prolonged OS in ICI therapy, Inhibits PD-1/PD-L1 pathway.	Dynamic serum metabolite monitoring to guide ICI treatment timing.	[640]
		Bile acids (fecal metabolites)	Specific bile acid profiles correlate positively with ICI efficacy.	Personalized immunotherapy strategy development.	[637]
	HCC	Butyrate	Activates T cell anti-tumor activity; Enhances PD-1 efficacy.	Oral butyrate supplementation combined with immunotherapy.	[641]
Efficacy prediction					
Drug resistance	PC	<i>Escherichia coli</i>	Enzyme-mediated gemcitabine inactivation.	Antibiotics (such as ciprofloxacin) combined with chemotherapy to reverse resistance.	[642]

TABLE 8 (Continued)

Application direction	Tumor type	Key microbes/metabolites	Key roles	Clinical application strategies	References
	Pan-Cancer	High butyrate/proprionate levels	Suppresses CTLA-4 efficacy ($p = 0.01$), promotes Treg expansion.	Low-fiber diet to reduce SCFAs and enhance immunotherapy response.	[643]
Adverse effects	CRC	<i>Escherichia coli</i> β -glucuronidase	Converts irinotecan to toxic metabolites.	β -glucuronidase inhibitors (such as nicsyn) to reduce intestinal toxicity.	[644]
	Melanoma	<i>Bifidobacterium</i>	Supplementation reduces colitis incidence.	Probiotic formulations to support immunotherapy and reduce toxicity.	[47]
	Radiation Dermatitis	Reduced skin microbiome diversity	Post-radiation dysbiosis exacerbates inflammation.	Topical probiotic ointments to restore skin barrier.	[645]

Abbreviations: CTLA-4, cytotoxic T lymphocyte associate protein-4; FMT, fecal microbiota transplantation; HNSCC, head and neck squamous cell carcinoma; IL-17, Interleukin-17; LUAD, lung adenocarcinoma; OS, overall survival; PD-1, programmed death 1; PDL1, programmed cell death ligand 1; RFS, recurrence-free survival.

disease severity, specifically decreased abundance of *Prevotella*, *Leptotrichia*, and *Actinomyces* alongside increased prevalence of *Treponema* [647]. In CRC, the abundance of *F. nucleatum* in tumor tissues may have the potential to serve as a prognostic biomarker [164]. In vivo experiments have established that *E. coli* significantly reduces gemcitabine's anti-tumor effect, resulting in increased tumor burden and compromised patient survival [46]. Conversely, co-administration of *Lactobacillus* with cisplatin significantly suppresses tumor growth and improves survival in mouse models of lung cancer [648].

Notably, a potentially anti-cancer microbiome genus, *Tissierella*, has been significantly associated with improved prognosis across various tumors, including breast, lung, and gastric cancers, further confirming the critical role of specific microbial species in tumor prognosis [44]. Additionally, the salivary microbiota of PC patients exhibits unique prognosis-related features. Poor oral hygiene and periodontal disease caused by microbial dysbiosis represent independent risk factors for PC, underscoring the oral microbiome's significant role in PC prognosis [429, 649]. Moreover, differential abundances of *Neisseria elongata* and *Streptococcus mitis* in saliva samples from PC patients compared to healthy controls demonstrate potential as non-invasive biomarkers for PC prediction [650].

In lung cancer studies, enrichment of *Prevotella spp.*, *Streptococcus spp.*, and *Veillonella spp.* consistently correlates with inferior survival outcomes [429]. Specifically, bacterial abundance in normal tissues adjacent to lung cancer correlates with recurrence-free survival (RFS). Significant positive correlations exist between *Koribacteraceae* family enrichment and RFS, while inverse correlations are observed between *Bacteroidaceae*, *Ruminococcaceae*, and *Lachnospiraceae* family enrichment and RFS [651].

Viral-microbial interactions play equally important roles in tumor prognosis. HPV has been demonstrated to be a potent prognostic biomarker, with HPV-positive patients typically experiencing better prognosis, while the presence of HPV DNA in plasma and saliva serves as an effective predictor of OPC recurrence [601, 652]. In HPV-independent cervical adenocarcinoma, the abundance of *Microbacterium* and *Streptococcaceae* family microorganisms significantly correlates with diminished OS and RFS, further validating the utility of specific microbial signatures as prognostic indicators [638].

In patients with HCC undergoing immunotherapy, substantial evidence demonstrates significant associations between fecal microbiome composition and patients' OS and PFS [637]. Specifically, *Lachnoclostridium* enrichment coupled with *Prevotella* 9 depletion correlates

with improved OS, while patients harboring favorable microbial signatures exhibit extended PFS [637]. Enrichment of *Bacteroides dorei* and *Parabacteroides distasonis* in NSCLC patients treated with ICIs significantly correlates with prolonged OS, whereas abundance of *Chaetosphaerales*, *Cortinarius davemallochii*, and *Helotiales* associates with shorter OS. These findings illuminate the complex interplay between the microbiome and therapeutic efficacy in cancer patients [639]. Consequently, the broad application of microbiome analysis in tumor prognosis prediction, while elucidating the relationships between specific microbial taxa and clinical outcomes, provides novel avenues for developing precision oncology approaches for cancer patients.

Microbial metabolites and prognosis

Microbial metabolites play crucial roles in modulating tumor progression and treatment outcomes. Investigations have identified the bacterial metabolite galanthamine as a biomarker for predicting outcomes in HCC patients treated with ICIs. It provides novel insights for clinical applications of microbial metabolites in tumor prognosis assessment [640]. Further studies have demonstrated that fecal microbiota and their metabolites, especially bile acids, are closely associated with clinical efficacy and prognosis in HCC patients undergoing immunotherapy [637]. These observations substantiate the prognostic and predictive value of gut microbial communities and their metabolic derivatives in predicting ICI therapeutic responses in HCC patients. A study has revealed that the gut microbial metabolite butyrate plays a pivotal role in modulating CD8⁺ T cell functionality and phenotype, significantly potentiating anti-PD-1 immunotherapy efficacy. This important finding establishes butyrate as a potential prognostic biomarker for enhancing anti-tumor immune responses [641]. Collectively, microbial metabolites, as functional mediators of the microbiome, demonstrate potential for integration into tumor prognostication frameworks and therapeutic response prediction.

Microbiome and tumor treatment efficacy

The relationship between the microbiome and tumor treatment efficacy has been comprehensively investigated. The composition and abundance of the microbiome closely correlate with treatment outcomes while simultaneously exerting significant impacts on tumor therapy resistance. Furthermore, perturbations in microbiome structure and function significantly contribute

to treatment-related toxicities observed during oncologic interventions.

Microbiome and drug resistance

The contribution of tumor-associated microbiota to chemoresistance mechanisms has emerged as a critical focus in translational oncology research. Studies have confirmed that colonizing bacteria present in the PC microenvironment can induce gemcitabine resistance and attenuate its cytotoxic efficacy through expression of specialized cytidine deaminase enzymes [642]. Further research has found that antibiotic therapy can effectively inhibit this drug inactivation pathway, consequently restoring gemcitabine's therapeutic efficacy [642]. Beyond gemcitabine, the intestinal microbiota demonstrates the capacity to mediate resistance to diverse chemotherapeutic agents, including cyclophosphamide, 5-fluorouracil (5-FU), and oxaliplatin [653]. However, high concentrations of SCFAs (butyrate and propionate) in the microenvironment have demonstrated significant associations with resistance to CTLA-4 blockers [643].

Microbiome and adverse effects

Investigating the interplay between the microbiome and tumor therapy outcomes (including efficacy and toxicity) has emerged as a central paradigm in cancer research. Extensive research has confirmed that gut microbiota directly modulates the efficacy of chemotherapeutic agents via metabolic regulation. Specifically, *E. coli* converts irinotecan into toxic metabolites through β-glucuronidase expression, resulting in severe diarrhea. A clinical investigation has found that co-administration of β-glucuronidase inhibitors significantly attenuates intestinal epithelial damage [644]. Additionally, *E. coli* possesses nitroreductase activity that bioactivates the prodrug CB 1954, enhancing its cytotoxic effects while concurrently compromising gemcitabine's anti-tumor activity, resulting in increased tumor burden and diminished survival outcomes [46]. In tumor immunotherapy, perturbations in intestinal microbial homeostasis significantly exacerbate immune-mediated adverse events. For instance, antibiotic therapy worsens anti-CTLA-4 therapy-induced colitis, whereas *Bifidobacterium* supplementation mitigates intestinal inflammatory pathology through suppression of pro-inflammatory cytokine cascades [47, 654]. Cutaneous microbiome perturbations strongly correlate with treatment-related toxicity. Significant reductions in cutaneous microbial diversity and alterations in taxonomic proportions during radiotherapy or EGFR inhibitor treatment combined with chemotherapy

potentiate localized inflammatory response. This condition may precipitate adverse effects including radiation dermatitis, palmar–plantar erythrodysesthesia syndrome, and papulopustular eruptions [645, 655]. Notably, specific microbial characteristics demonstrate utility as predictive biomarkers for treatment-associated toxicities. For example, in metastatic RCC patients treated with vascular endothelial growth factor tyrosine kinase inhibitors (VEGFTKI), the elevated abundance of *Bacteroides* spp. shows a significant positive correlation with diarrhea incidence, while *Prevotella* spp. demonstrates a protective effect [656]. These insights suggest that precision microbiome modulation strategies, including microbial transplantation or combination with specific enzyme inhibitors, may constitute innovative approaches to optimize the safety window of oncologic interventions.

MICROBIOME AND TUMOR THERAPY

Microbiome and chemotherapy

The relationship between microbiome and tumor therapy, with particular emphasis on chemotherapeutic modalities, has emerged as a rapidly expanding research domain. Bacteria, viruses, and fungi all significantly impact chemotherapy efficacy, while chemotherapeutic agents simultaneously affect microbiome composition and function. Furthermore, microbiome alterations may mediate toxic effects during chemotherapy, impacting therapeutic tolerability and health-related quality of life. Consequently, microbiome modulation strategies to enhance chemotherapy efficacy while attenuating treatment-limiting toxicities represent an emerging direction in cancer therapy. As illustrated in Figure 5, this framework encompasses the bidirectional regulatory networks between microbial ecosystems and chemotherapeutic agents, including influences exerted by bacterial, viral, and fungal constituents, chemotherapy-induced alterations in the microbiome, microbe-mediated toxicity mechanisms, and microbiome-based intervention strategies.

Impact of the microbiome on chemotherapy

Role of bacteria: The regulatory influence of microbiota on antineoplastic agent pharmacodynamics, particularly intestinal microbial communities, has emerged as a central focus in translational oncology research. Certain bacteria, such as *Akkermansia muciniphila*, enhance chemotherapy efficacy [657]. In CRC, the intestinal microbiota closely relates to chemotherapeutic efficacy and

resistance. *F. Nucleatum* can induce chemotherapy resistance and reduce the therapeutic effect [165–167], while butyric acid and its derivatives can alleviate the chemotherapy resistance induced by *F. Nucleatum* [165]. The microbial-derived butyrate, beyond glucose metabolism inhibition, targets the G protein-coupled receptor 109a-AKT signaling pathway and enhances chemotherapeutic anti-tumor effects [658]. In PC, *Gammaproteobacteria* enhance chemotherapeutic agent inactivation, including gemcitabine, substantially diminishing therapeutic efficacy [642, 659]. However, certain probiotics or microbiota metabolites may benefit CRC treatment. For example, *Lactobacillus plantarum*-derived metabolites augment butyrate-mediated tumor suppression and reverse multiple drug resistance [660]. Additionally, specific oral bacterial species diminish chemotherapeutic efficacy while simultaneously exacerbating treatment-induced oral mucositis [456]. In summary, bacterial effects on chemotherapeutic drug metabolism exhibit remarkable complexity, playing crucial roles in tumor chemotherapy.

Role of viruses: Viruses, particularly bacteriophages, have emerged as remarkable mediators of chemotherapeutic efficacy. Experimental evidence demonstrates that engineered bacteriophages conjugated with chemotherapeutic-loaded nanoparticles significantly potentiate cytotoxic activity against malignant cells [661]. Additionally, several studies have hypothesized that HPV-positive HNSCC exhibits better responses to radiotherapy [662, 663]. Therefore, bacteriophages represent promising biological vectors for modulating microbiome-mediated chemotherapeutic metabolism, offering remarkable application prospects for enhancing anti-neoplastic efficacy.

Role of fungi: Fungal communities have emerged as critical mediators of chemotherapeutic pharmacokinetics and treatment response through diverse metabolic and immunological mechanisms. Studies show that *Candida tropicalis* (*C.tropicalis*) is closely associated with CRC and promotes chemotherapy resistance through dual mechanisms, including lactate production and suppression of MLH1 expression. In this process, lactate, as a critical signaling metabolite, regulates MMR protein expression levels through activation of the GPR81-cAMP-PKA-CREB signaling pathway, enhancing tumor cell chemoresistance [664]. To further elucidate fungal mechanisms in chemotherapeutic responses, investigators employed amphotericin B to selectively deplete the mycobiome, demonstrating that fungal ablation significantly enhanced gemcitabine cytotoxicity [219]. These findings reveal the critical contribution of fungi to chemotherapeutic agent metabolism and treatment efficacy, identifying potential

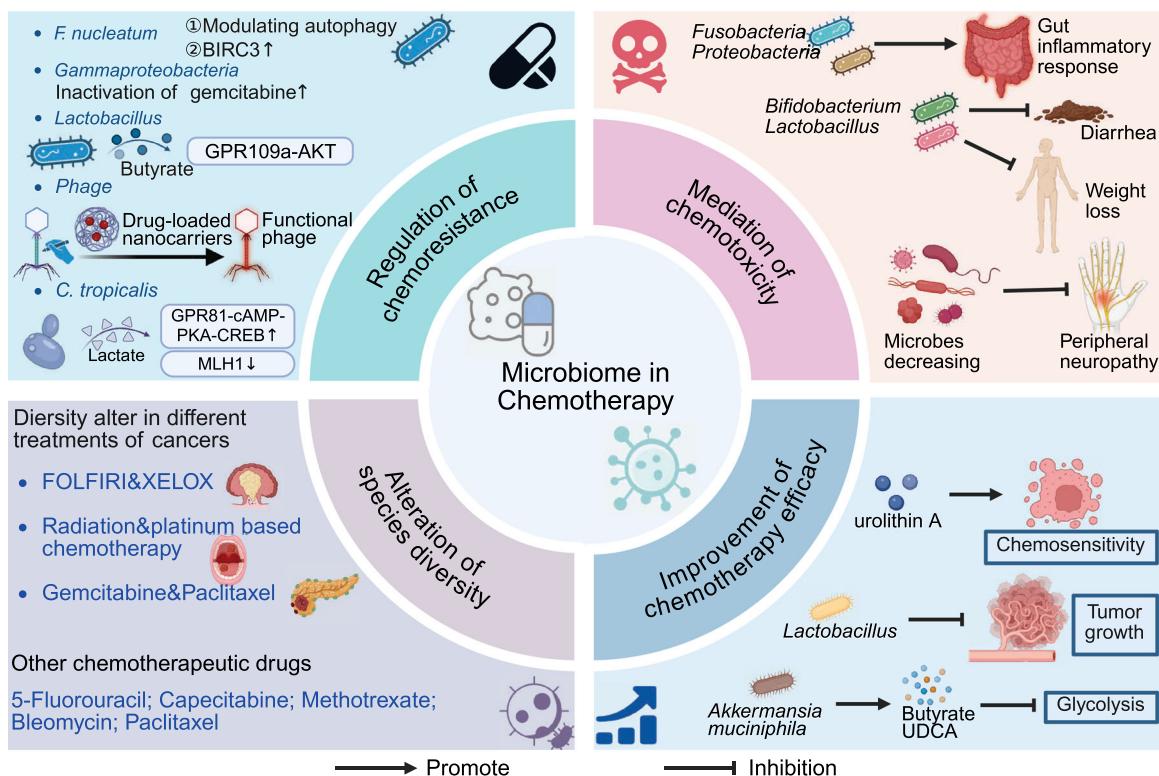


FIGURE 5 The role of microbiome in chemotherapy. This figure illustrates four key aspects of microbiome-chemotherapy interactions. Regulation of chemoresistance (upper left): Various microorganisms, including *F. nucleatum*, *Gammaproteobacteria*, *Lactobacillus*, Phage, and *C. tropicalis*, influence drug resistance through different mechanisms. Mediation of chemotoxicity (upper right): Specific microorganisms (*Fusobacteria*, *Proteobacteria*, *Bifidobacterium*, and *Lactobacillus*) influence chemotherapy side effects, including gut inflammatory responses, diarrhea, and weight loss. Additionally, decreases in specific microbial populations may contribute to chemotherapy-induced peripheral neuropathy. Alteration of species diversity (lower left): This section demonstrates different chemotherapy treatments' effects on microbial populations, including FOLFIRI/XELOX in CRC, radiation with platinum-based chemotherapy in head and neck squamous cell carcinoma, and combinations of gemcitabine and paclitaxel in PC. Additional chemotherapeutic agents contributing to microbial community alterations include 5-Fluorouracil, capecitabine, methotrexate, bleomycin, and paclitaxel. Improvement of chemotherapy efficacy (lower right): *Akkermansia muciniphila* influences tumor response through UDAC and butyrate production, subsequently inhibiting tumor glycolysis. Furthermore, urolithin A enhances chemosensitivity, while *Lactobacillus* species exhibit tumor growth inhibition. (Red text for anti-chemoresistance; Black text for pro-chemoresistance). CRC, colorectal cancer; *C. tropicalis*, *Candida tropicalis*; FOLFIRI, folinic acid (leucovorin), fluorouracil (5-FU), and irinotecan; UDAC, ursodeoxycholic acid; XELOX, capecitabine (Xeloda) and oxaliplatin.

interventional targets for novel adjunctive strategies to optimize chemotherapeutic outcomes.

Effect of chemotherapy on the microbiome

Chemotherapeutic interventions induce profound and heterogeneous alterations in microbial communities, exhibiting notable variability across malignancy types and chemotherapeutic agents. In HNSCC patients, chemotherapy and radiotherapy significantly alter the salivary microbiome, evidenced by substantially increased *Candida* and reduction in overall bacterial and fungal diversity [665]. In CRC patients, different chemotherapy regimens

(including FOLFIRI[fluorouracil, leucovorin, and irinotecan] and XELOX[capecitabine and oxaliplatin]) induce significant taxonomic restructuring of intestinal microbial communities, with characteristic alterations in bacterial and fungal population dynamics [666]. PC patients treated with different chemotherapeutic agents (gemcitabine and paclitaxel) exhibit differentiable patterns of intestinal microbiome perturbation [667, 668]. Additional chemotherapeutic agents, including pyrimidine analogs (5-fluorouracil) and platinum compounds (oxaliplatin), similarly induce characteristic microbial compositional shifts [669, 670]. 5-FU treatment induces significant restructuring of intestinal microbial communities, decreasing abundance of *Streptococcus* spp. and

Bacteroides spp. while increasing enrichment of *Clostridium hathewayi* and *Lachnospiraceae* [671]. Gemcitabine significantly decreases the proportion of *Firmicutes* and *Bacteroidetes* [667]. Additionally, capecitabine, methotrexate, bleomycin, and paclitaxel modulate the composition and abundance of gut microbiome [671]. Furthermore, chemotherapeutic interventions exert modulatory effects beyond intestinal microbial communities, significantly influencing intratumoral microbiome composition and ecological diversity. Comprehensive analyses reveal significant reductions in intratumoral bacterial diversity and characteristic shifts within the post-treatment TME [548, 672]. This microbial community restructuring demonstrates substantial correlations with therapeutic response parameters and treatment-associated adverse effects profiles.

Microbiome-mediated toxicities of chemotherapy

Accumulating evidence establishes the microbiome as a critical mediator of chemotherapy-induced toxicities. During irinotecan administration, gut microbial structure experiences profound alteration, characterized by decreased microbial diversity with elevated proportions of *Fusobacteria* and *Proteobacteria* phyla. This dysbiosis positively correlates with intestinal inflammatory responses, potentially exacerbating chemotherapy-induced toxicity [673]. Studies demonstrate that specific bacterial strains (including *Bifidobacterium* and *Lactobacillus*) significantly alleviate irinotecan-induced weight loss and diarrhea, further confirming the microbiome's critical role in modulating chemotherapy-induced adverse effects [674]. Additionally, Shen et al. demonstrated that transient intestinal microbial depletion through targeted antibiotic intervention significantly attenuates oxaliplatin-induced peripheral neuropathy in preclinical models, providing mechanistic evidence for understanding gut microbiome's role in oxaliplatin toxicity [675]. These findings elucidate the microbiome's role in modulating chemotherapeutic agent efficacy and reveal its important mechanisms in mediating chemotherapeutic toxicity, providing new research directions for developing precision microbiome-targeted interventions to minimize therapeutic adverse effects [676].

Microbiome modulation strategies to improve chemotherapy outcomes

Microbiome-based therapeutic interventions demonstrate considerable potential for enhancing chemotherapeutic efficacy. Accumulating evidence indicates

that intestinal microbial communities significantly influence chemotherapeutic outcomes through both direct effects and metabolite modulation. Specifically, commensal bacteria with immunomodulatory properties like *Akkermansia muciniphila* significantly potentiate chemotherapeutic efficacy [657]. Additionally, gut microbiota-produced metabolites such as butyrate and ursodeoxycholic acid (UDCA) enhance chemotherapeutic efficacy through multiple mechanisms, including glucose metabolism inhibition, specific signaling pathway modulation, and intestinal microbial community reconfiguration [677]. Metabolites like ursolic acid can enhance cancer cell chemosensitivity and ameliorate chemotherapy-induced systemic toxicities [678]. Furthermore, microbiome-targeted modulation influences gemcitabine metabolism, generating synergistic therapeutic effects in specific cancer types [642]. Experimental studies demonstrate that cisplatin combined with *Lactobacillus* supplementation yields enhanced therapeutic responses in murine pulmonary carcinoma models, manifesting as significant tumor growth inhibition and prolonged survival intervals. The outcome closely relates to alterations in oncogene expression profiles and notable augmentation of anti-tumor immune responses [648]. In summary, microbiome modulation strategies provide promising adjunctive therapeutic approaches to enhance chemotherapeutic efficacy. Through optimizing microbial communities and their metabolic outputs, these strategies may offer potential for significantly improved therapeutic outcomes while concurrently mitigating treatment-associated adverse events, ultimately enhancing quality of life metrics for oncology patients.

Microbiome and radiotherapy

Host-associated microbial communities demonstrate significant bidirectional interactions with radiotherapeutic outcomes across diverse malignancies. Microbial ecosystems influence tumor radiosensitivity while concurrently, ionizing radiation significantly perturbs microbial community structures. Additionally, the microbiome may mediate radiotherapy's toxicities, potentially exacerbating treatment-related burdens in patients.

Within the interaction between radiotherapy and the microbiome, distinct hierarchical patterns emerge regarding the clinical relevance of various bacteria, viruses, and fungi. Bacteria occupy a predominant position due to their extensive involvement in regulating radiotherapy sensitivity and mediating radiation-induced toxicities. For example, *Lactobacillus iners* modulates CC and *Bacteroides vulgatus* influences rectal cancer response to

radiotherapy [436, 679], with targeted probiotic interventions already demonstrating clinical efficacy for mitigating radiation-induced enteropathy [680]. Among viruses, HPV demonstrates a well-established role in HNSCC radiotherapy sensitivity. It induces immunomodulation significantly enhancing control rates, though its effects remain restricted to virus-associated malignancies [662]. Fungal research primarily focuses on the bidirectional regulation between intestinal commensal fungi and the post-radiotherapy immune microenvironment, though mechanistic understanding and clinical translation remain insufficient. In summary, bacterial research is the most systematic and has the greatest value in clinical translation in radiotherapy. Viral factors provide established clinical guidance in specific malignancy subtypes, while fungal contributions to radiotherapeutic outcomes warrant further mechanistic investigation.

Consequently, the development of targeted microbiome modulation strategies to potentiate radiotherapeutic efficacy while attenuating radiation-induced normal tissue complications represents an emerging paradigm in precision radiation oncology. As illustrated in Figure 6, the microbiome-radiotherapy interaction manifests in four key aspects: microbial community contributions to tumor radiosensitivity modulation, radiotherapeutic effects on microbial composition, microbiome-mediated radiotherapy-induced toxicities, and microbiome modulation intervention to improve radiotherapeutic outcomes.

Effect of microbiome on sensitivity to radiotherapy

The regulation of tumor radiosensitivity by the microbiome has emerged as a critical research area. Preclinical investigations utilizing murine models demonstrate that radiotherapeutic efficacy is determined by an intricate interplay between intrinsic tumor characteristics and intestinal microbial community composition, encompassing bacterial and fungal constituents [681]. Across diverse cancer types, gut microbes significantly modulate radiotherapy efficacy and influence radiotherapy-induced adverse effects [681]. For instance, *Lactobacillus iners* produces L-lactic acid, which is significantly associated with unfavorable clinical outcomes and induces radiotherapy resistance in CC cells [436]. Additionally, intestinal microbial dysbiosis may constitute an important mechanism of primary radiotherapeutic resistance through impairing anti-tumor immune responses via inhibition of antigen presentation and effector T cell function [682].

The microbiome's clinical significance is particularly prominent in rectal cancer treatment. Specific microbes and metabolic pathway indicators serve as biomarkers for predicting efficacy and adverse effects in rectal cancer patients undergoing neoCRT [683]. A prospective longitudinal investigation confirmed that there are remarkable differences in the microbiome between responders and non-responders to treatment. For example, butyrate-producing bacteria dominated in radiotherapy-sensitive individuals, whereas *Fusobacterium* and *Coriobacteriaceae* predominated in non-responders [684]. Recent investigations have revealed that *Bacteroides vulgatus* inhibits rectal cancer radiosensitivity. Through modulating the nucleotide biosynthesis pathway, *Bacteroides vulgatus* substantiates the critical regulatory role of specific bacterial taxa in regulating radiotherapeutic responses [679]. Collectively, diverse bacterial taxa demonstrate remarkable modulatory effects on tumor radiosensitivity. Elucidation of these regulatory pathways will provide a basis for developing novel microbiome-targeted strategies to enhance tumor radiotherapy efficacy.

Viral components of the microbiome have garnered increasing attention in tumor radiosensitivity regulation. Studies show that HPV-positive patients with HNSCC exhibit higher radiotherapeutic sensitivity [662]. Clinical data confirms that HPV-positive HNSCC patients demonstrate significantly higher local control rates following radiotherapy, representing a principal factor of improved OS [685]. Further mechanistic studies have revealed that HPV-positive HNSCC patients exhibit significantly prolonged OS following radiotherapy compared to HPV-negative cohorts [685]. These favorable prognostic distinctions appear related to HPV-mediated alterations in HNSCC.

Recent comprehensive investigations have examined mycobiome-mediated regulatory mechanisms influencing tumor response to radiotherapy. Intestinal fungal communities significantly modulate post-radiotherapy anti-tumor immune responses in murine models of BC and melanoma, demonstrating regulatory patterns contrast with those observed in bacterial communities [686]. Specifically, antifungal interventions enhance tumor radiotherapy efficacy by eliminating commensal fungi, while triggering a decrease in commensal bacterial abundance is associated with poor efficacy. Furthermore, elevated expression of Dectin-1 in BC is associated with unfavorable survival outcomes. In murine radiotherapy models, Dectin-1 demonstrated essential functionality for mediating commensal fungi-induced biological effects. It provides that molecular mechanistic insights into the mycobiome contribute to radiotherapeutic response modulation [686], further establishing fungal

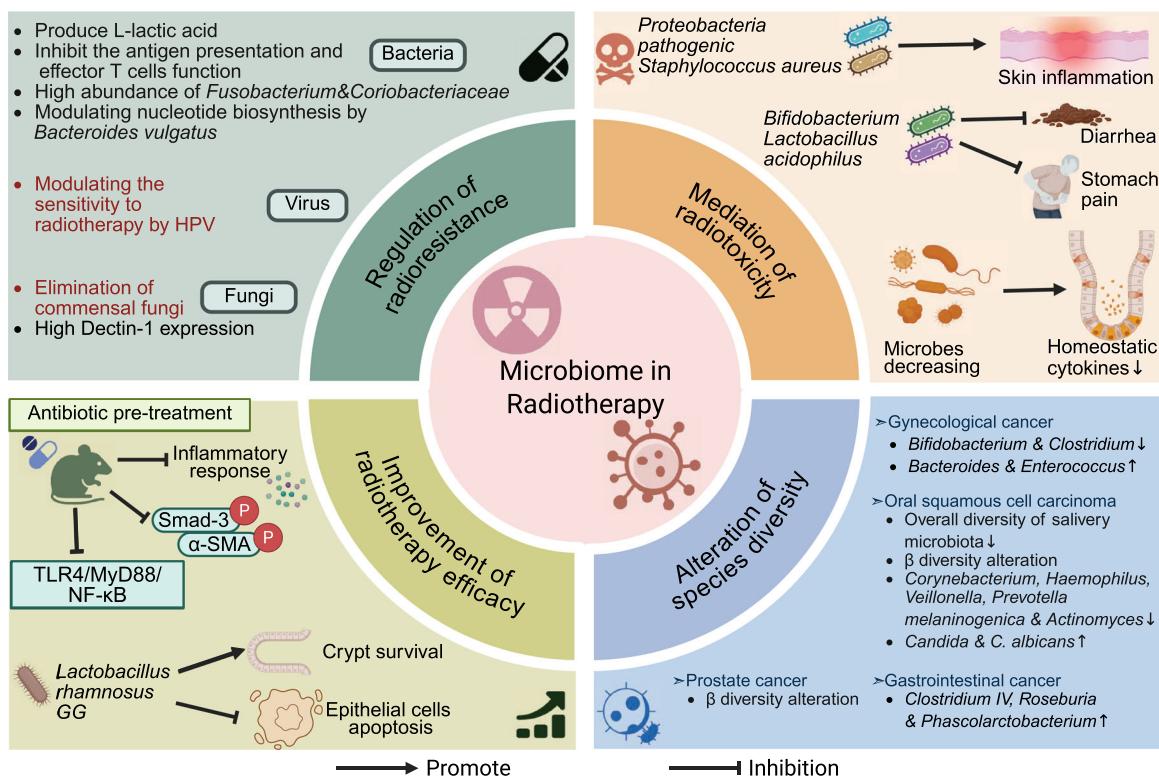


FIGURE 6 The role of microbiome in radiotherapy. This figure illustrates four key aspects of microbiome-radiotherapy interactions. Regulation of radioresistance (upper left): Key mechanisms related to bacteria include L-lactic acid production, affecting antigen presentation and effector T cell function, elevated abundance of *Fusobacterium* and *Coriobacteriaceae*, and nucleotide biosynthesis modulation by *Bacteroides vulgatus*. HPV enrichment or commensal fungi elimination improves radiotherapy sensitivity, whereas high Dectin-1 expression of fungi contributes to resistance mechanisms. Mediation of radiotoxicity (upper right): Microbes including *Proteobacteria pathogenic Staphylococcus aureus* trigger skin inflammation. *Lactobacillus acidophilus* plus *Bifidobacterium* supplementation correlates with reduced diarrhea and abdominal pain. Radiation-induced decreases in microbial populations are associated with reduced homeostatic cytokine levels. Alteration of species diversity (lower right): Distinct microbial community changes occur across different anatomical sites. Gynecological cancer patients after radiotherapy show intestinal *Bifidobacterium* and *Clostridium* reduction concurrent with *Bacteroides* and *Enterococcus* increases. In OSCC, β -diversity shows differences, particularly in *Corynebacterium*, *Haemophilus*, *Veillonella*, *Prevotella melaninogenica*, *Actinomyces*, and *Mycoplasma* populations. Additionally, *Candida* and *C. albicans* increased following radiotherapy. Only gut microbiome β -diversity alterations were found in prostate cancer patients during radiotherapy. Likewise, gut microbiota diversity in CRC patients undergoing radiotherapy shows elevation with significant enrichment of *Clostridium IV*, *Roseburia*, and *Phascolarctobacterium*. Improvement of radiotherapy efficacy (lower left): Antibiotic pre-treatment suppresses inflammatory responses, TLR4/MyD88/NF- κ B pathway signaling, and Smad-3/pSMAD pathway activation to improve radiotherapy efficacy. Furthermore, *Lactobacillus rhamnosus GG* promotes intestinal crypt survival while inhibiting epithelial cell apoptosis. (Red text for anti-radioresistance; Black text for pro-radioresistance). OSCC, oropharyngeal cancer; OSCC, oral squamous cell carcinoma; pSMAD, phosphorylated SMAD; TLR4, Toll-like receptor 4.

communities as critical factors in tumor radiotherapy. In summary, fungal components significantly influence radiotherapeutic response.

Effects of radiotherapy on the microbiome

Radiotherapy exerts complex and multifaceted effects on host-associated microbial ecosystems, with differential impacts observed across diverse anatomical niches and microbial kingdoms. In HNSCC patients, salivary microbial communities undergo substantial compositional

restructuring following radiotherapy, characterized by substantial reductions in taxonomic diversity and concurrent enrichment of *Candida* [665]. Similarly, oral microbiome composition undergoes reconfiguration during radiotherapy in OSCC patients. While α -diversity remains statistically unchanged between pre-treatment and immediate post-treatment timepoints, β -diversity reveals significant divergence at 6 months post-radiotherapy [441]. Specific species including *Corynebacterium*, *Haemophilus*, *Veillonella*, and *Actinomyces* decrease in OSCC patients, while concurrent enrichment of *Selenomonas* and *Mycoplasma* is observed [441]. Investigations confirm

significant dynamics in oral microbial communities during and following OSCC radiotherapy, with notable depletion of *Prevotella melaninogenica* abundance in post-radiotherapy samples [687]. Conversely, *C. albicans* demonstrates notable expansion following radiotherapy in HNSCC [688].

In gastrointestinal and pelvic malignancies, radiotherapy induces profound perturbations in intestinal microbial ecosystems. Pelvic radiotherapy for gynecological malignancies induces substantial intestinal dysbiosis, characterized by selective depletion of *Bifidobacterium* and *Clostridium*, and remarkable enrichment in *Bacteroides* and *Enterococcus* [660]. A prospective study of PCa patients has found substantial alterations in gut microbiome β -diversity without corresponding changes in α -diversity during radiotherapy [689]. Ferreira et al. similarly observed significantly reduced gut microbiota diversity in patients undergoing radiotherapy, characterized by depletion of *Clostridium perfringens* alongside enrichment of *Clostridium IV*, *Roseburia*, and *Phascolarctobacterium*, which may contribute to the pathogenesis of radiation-induced enteropathy [690].

Notably, radiotherapeutic interventions modulate not only microbial community structure and ecological diversity but also alter the bacterial functional capacity and virulence expression. For example, neoadjuvant radiotherapy can convert inoculated *Pseudomonas aeruginosa* into a highly pathogenic phenotype that destroys anastomotic sites [691]. During HPV-associated OPC radiotherapy, substantial reductions in microbial α -diversity with concurrent alterations in specific taxonomic abundances have been demonstrated [692]. These radiation-induced microbial perturbations reflect both direct effects on host physiology and clinical prognosis of patients.

Microbiome-mediated radiotherapy toxicities

The microbiome represents a critical role in radiation-induced normal tissue complication pathogenesis and progression. Clinical investigations demonstrate that radiotherapeutic intervention induces significant taxonomic shifts within microbial communities. These alterations are strongly, negatively correlated with homeostatic cytokine expression in the intestinal mucosa, potentially exacerbating radiotherapy-induced mucosal injury [693]. In cutaneous tissues, radiation-induced dermatitis demonstrates a marked association with diminished microbial diversity and characteristic taxonomic alterations, particularly elevated *Proteobacteria/Firmicutes* ratios and *pathogenic S. aureus* proliferation [645]. However, probiotic interventions offer novel therapeutic strategies to alleviate radiotherapy-related

tissue complications. Studies confirm that probiotics effectively attenuate multiple radiation-induced toxicities through downregulating pro-inflammatory cytokines [680]. Specifically, clinical studies have demonstrated that the prophylactic and therapeutic administration of *Lactobacillus acidophilus* plus *Bifidobacterium* supplements can alleviate radiation-induced gastrointestinal toxicity symptoms, including diarrhea and abdominal pain. That concurrently improves health-related quality of life during radiotherapy [680]. In summary, microbial communities represent critical mediators of radiotherapy-induced toxicities, establishing a crucial theoretical basis for developing novel therapeutic strategies.

Microbiome modulation strategies to improve radiotherapy outcomes

Emerging evidence demonstrates that targeted microbiome manipulation strategies hold significant clinical potential in improving radiotherapy outcomes. *Lactobacillus rhamnosus GG* effectively attenuates radiotherapy-induced epithelial damage by enhancing crypt survival and reducing epithelial cell apoptosis [694]. Further studies show that altering microbiota composition through antibiotic interventions significantly modulates radiotherapy outcomes. For example, preclinical studies showed that antibiotic pretreatment before radiotherapy partially reversed microbiota dysbiosis and accelerated recovery from radiation-induced intestinal damage [690]. This process is associated with multiple factors, including the TLR4/MyD88/NF- κ B signaling pathway, macrophage polarization, and inflammatory mediator regulation, demonstrating novel mechanisms of microbiota modulation in improving radiotherapy efficacy [695, 696]. Additionally, prophylactic antifungal interventions appear more beneficial, as commensal fungal species may influence the TIME through pattern recognition receptor-mediated interactions with macrophages and T cells, potentially enhancing radiotherapy efficacy [686].

Microbiome and immunotherapy

Host-associated microbial communities represent critical determinants of immunotherapeutic efficacy. They are strongly associated with ICI efficacy and significantly influence CAR-T cell therapeutic outcomes and cancer vaccine efficacy. Modulation of the microbiome shows therapeutic potential for enhancing immunotherapy efficacy and strengthening anti-tumor immune responses. Figure 7 summarizes the principal mechanistic pathways

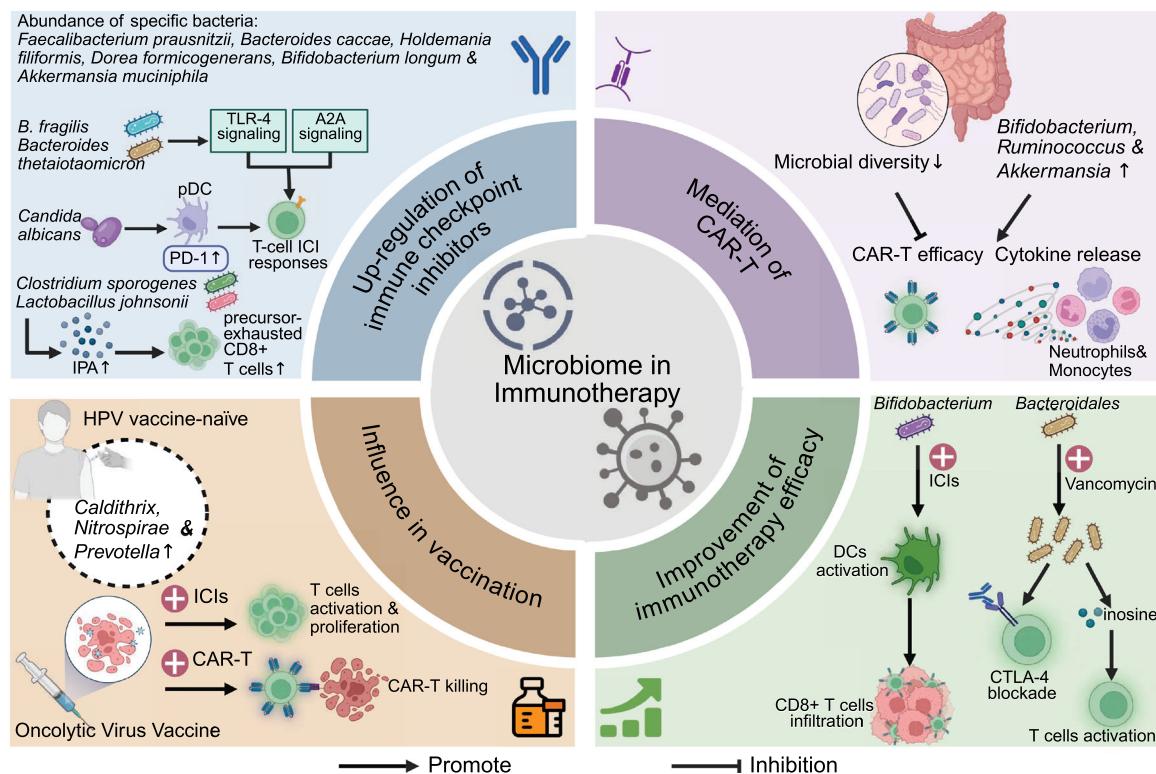


FIGURE 7 The role of microbiome in immunotherapy. This figure illustrates four key aspects of microbiome-immunotherapy interactions. Upregulation of immune checkpoint inhibitors (upper left): Specific bacterial species (*Faecalibacterium prausnitzii*, *Bacteroides caccae*, *Holdemania filiformis*, *Dorea formicogenerans*, *Bifidobacterium longum*, and *Akkermansia muciniphila*) modulate immune responses. *B. fragilis* and *Bacteroides thetaiotaomicron* activate TLR4 and A2A receptor signaling pathways. *Candida albicans* influences PD-1 expression during pDC activation, while *Clostridium sporogenes* and *Lactobacillus johnsonii* enhance precursor-exhausted CD8⁺ T cell responses via increased IPA production. Mediation of CAR-T therapy (upper right): Decreased microbial diversity correlates with reduced CAR-T therapy efficacy. Specifically, *Bifidobacterium*, *Ruminococcus*, and *Akkermansia* populations significantly influence CAR-T treatment outcomes. Improvement of immunotherapy efficacy (lower right): *Bifidobacterium* species combined with ICIs enhance immune responses through DC activation and increased CD8⁺ T cell infiltration. Additionally, vancomycin treatment enhances CTLA-4 blockade therapy and T cell activation to show anti-tumor effects by inducing *Bacteroidales* overexpression with subsequent inosine secretion. Influence in vaccination (lower left): In HPV vaccine-naïve individuals, specific microbiota (*Caldithrix*, *Nitrospirae*, and *Prevotella*) exhibited enrichment. Additionally, immunotherapy including ICIs and CAR-T shows enhanced efficacy when combined with oncolytic virus vaccines, through promoting T cell activation, proliferation, and cytotoxic efficiency. A2A, adenosine 2A; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DC, dendritic cell; ICIs, immune checkpoint inhibitors; IPA, indole-3-propionic acid; pDC, plasmacytoid dendritic cell.

through which the microbiome modulates tumor immunotherapeutic outcomes, including bacterial and fungal effects on ICI efficacy, interactions between the microbiome and CAR-T cell therapy, and microbiome-mediated effects in vaccine therapy. Collectively, these mechanisms provide a theoretical foundation and practical direction for microbiome modulation strategies to optimize tumor immunotherapy.

Microbiome and immune checkpoint inhibitors

Immunomodulatory effects of bacteria: The gut microbiome exerts a significant influence on ICI responses through diverse immunomodulatory pathways,

representing a critical focus in contemporary immuno-oncology research. Studies demonstrate that specific bacterial species, including *Bacteroides thetaiotaomicron*, *B. fragilis*, and *Bifidobacterium*, promote CD8⁺ T cell immune responses through activation of TLR-4 signaling pathway or adenosine 2A (A2A) receptor signaling pathway, consequently enhancing anti-tumor immunosurveillance and regulating anti-tumor immune responses [66]. Intestinal *Lactobacillus johnsonii* abundance demonstrates remarkable positive correlations with ICI efficacy. Specifically, indole-3-propionic acid (IPA), synergistically produced through intestinal probiotics *Clostridium sporogenes* and *Lactobacillus johnsonii*, promotes the generation of precursor-exhausted CD8⁺ T cells, thereby enhancing ICI responses in

diverse malignancies including CRC, BC, and melanoma [697].

Clinical investigations suggest intestinal microbial community is strongly associated with anti-tumor effects across ICI classes [698–700]. Cohort studies indicate that in advanced melanoma, specific intestinal microbial signatures, characterized by enrichment of *Bifidobacterium pseudocatenulatum*, *Roseburia spp.*, and *Akkermansia muciniphila*, demonstrate notable associations with favorable immunotherapeutic response profiles [701]. In patients with metastatic melanoma, intestinal microbiota enriched with *Faecalibacterium* and other *Firmicutes* tend to show enhanced response to ipilimumab treatment [702]. Meanwhile, elevated *Bacteroidetes* phylum demonstrates remarkable negative correlations with ICI-induced colitis incidence and severity [703]. Additional investigations have confirmed that metastatic melanoma patients exhibiting favorable responses to combined ICIs (nivolumab plus ipilimumab therapy) show fecal enrichment of *Faecalibacterium prausnitzii*, *Bacteroides caccae*, and *Holdemania filiformis* strains, while patients responding to pembrolizumab exhibit selective enrichment of *Dorea formicgenerans* [704].

Preclinical investigations suggest that gut microbiome diversity and composition significantly impact PD-1 blockade therapy efficacy. Specific strains including *Bifidobacterium longum*, *Akkermansia muciniphila*, and *Faecalibacterium spp.* are strongly associated with enhanced anti-PD-1 therapeutic efficacy [681]. In summary, the gut microbiome exerts a significant immunomodulatory influence on ICI therapeutic outcomes through modulation of immune cell functionality and regulation of drug metabolism and effects.

Immunomodulatory effects of fungi: Complex immunoregulatory networks exist between mycobiome components and ICIs, with fungus-mediated immunomodulation demonstrating particular research value and clinical significance. A study exploring the relationship between the mycobiome and immunotherapy response demonstrated that predictive algorithms based on fungal taxonomic signatures exhibited superior predictive performance (mean AUC of 0.87), outperforming models relying solely on bacterial biomarkers. Further studies found that integration of fungal and bacterial taxonomic signatures into predictive models substantially enhanced discriminatory accuracy (AUC = 0.89), strongly establishing fungi's important regulatory role in ICI responses [705]. Additionally, *C. albicans* colonization induces upregulation of PD-1 pathways in monocytes and plasmacytoid DCs (pDCs), and also CTLA-4 pathways in both CD4⁺ and CD8⁺ T cells [706]. These findings provide a scientific foundation

for understanding the contribution of the mycobiome to immune checkpoint regulation and ICI efficacy.

Microbiome and CAR-T cell therapy

Emerging clinical evidence establishes the microbiome as a critical factor in CAR-T cell therapy efficacy [707–712]. Studies show diminished intestinal microbial diversity indices are strongly and negatively correlated with CAR-T cell therapeutic response [713]. Specific bacterial taxa abundance, including *Bifidobacterium spp.*, *Ruminococcus spp.*, and *Akkermansia spp.*, demonstrates a remarkable positive association with favorable CAR-T cell therapeutic outcomes [681]. These findings provide new research trajectories for elucidating microbiome-mediated regulation of CAR-T cell therapeutic efficacy. Additionally, OVs as innovative therapeutic vectors demonstrate notable synergistic anti-tumor activity when strategically combined with ICIs, including CAR-T cells and anti-PD-1/PD-L1 or anti-CTLA-4 [714]. In conclusion, microbial communities significantly influence CAR-T cell efficacy through multiple immunomodulatory mechanisms, establishing rationale for developing precision microbiome modulation methods as adjunctive strategies to cellular immunotherapy.

Microbiome modulation strategies to improve immunotherapy outcomes

As research advances, microbiome modulation strategies exhibit considerable promise for enhancing the efficacy of cancer immunotherapy. Intestinal commensal bacteria exert particularly significant roles in immunotherapy. Studies show *Bifidobacterium* combined with PD-L1 therapy exhibits significant therapeutic effects on solid tumors through enhancement of DC activity and augmentation of CD8⁺ T cell infiltration [715]. Vancomycin enhances the anti-tumor effects of CTLA-4 blockade therapy by inducing the expansion of *Bacteroidales* [716]. Additionally, the metabolite inosine promotes T cell activation in the gut, leading to enhanced efficacy of ICIs [717]. Notably, therapeutic strategies specifically targeting distinct microbial populations may provide new research directions for improving immunotherapy efficacy [171]. In summary, microbiome modulation strategies, including microbiome remodeling through antibiotic treatment, probiotic supplementation, or specific microbe-targeted therapies, present promising research avenues for improving immunotherapy efficacy and mitigating treatment-related adverse effects.

Microbiome and vaccine therapy

The complex interplay between the host microbiome and cancer vaccine efficacy represents an emerging focus in tumor immunology research. Recent studies investigating HPV therapeutic vaccines reveal associations between cervical microbiome and vaccine-induced immune responses. Research systematically has analyzed cervical microbiomes of patients with high-grade squamous intraepithelial lesions (HSIL) before and after administration of HPV therapeutic vaccination. Results showed that five bacterial groups, including *Caldithrix*, *Nitrospirae*, and *Prevotella*, exhibited enrichment in vaccine non-responders, suggesting these bacterial communities may suppress vaccine-induced immune responses [718]. These findings provide new insights into the role of the local microbiome in immune responses in patients with HSIL. Notably, enrichment of *Prevotella* may promote persistent HPV infection, thereby potentially conferring resistance to therapeutic vaccination [718]. Furthermore, OVs can be combined with anti-tumor vaccines to synergistically enhance therapeutic efficacy [714]. In summary, the regulatory mechanisms by which the microbiome influences vaccine immunotherapy and their potential clinical application value require further in-depth study.

Microbiome and targeted therapies

The microbiome engages in complex bidirectional interactions with targeted anti-tumor therapeutics. It influences the efficacy of targeted agents through various mechanisms. Concurrently, alterations in microbiome composition are associated with the development of resistance to targeted therapies, with specific microbial species potentially contributing to resistance. Integration of microbiome-modulating interventions with targeted therapeutic strategies represents innovative approaches for cancer treatment.

Mechanisms in microbiome influence the efficacy of targeted drugs

The microbiome influences the efficacy of targeted drug therapeutic through multiple pathways, with bacterial-mediated molecular mechanisms emerging as particularly significant mediators of treatment response. Studies indicate that in CRC cells, *Leuconostoc mesenteroides* regulates the NF- κ B/AKT/PTEN/MAPK signaling pathway to induce apoptosis [719], while *P. gingivalis* activates the MAPK signaling pathway to promote tumor cell

proliferation [720]. BRAF mutations activate the MAPK pathway and trigger oncogenic effects, which can be effectively suppressed by BRAF and MEK inhibitors [721]. These findings demonstrate that microorganisms can affect tumor proliferation and survival via directly modulating cancer cell signaling networks, potentially altering the efficacy of therapeutic agents that target these signaling pathways.

Microbiome and targeted therapy resistance

The microbiome appears to play a significant role in the development of resistance to targeted anti-tumor therapies. Accumulating evidence demonstrates *F. nucleatum* can activate the E-cadherin/ β -catenin signaling pathway [156], and the β -catenin signaling pathway is related to the development of resistance to lenvatinib in HCC [168–170]. Therefore, the modulation of β -catenin expression by *F. nucleatum* may affect the sensitivity of tumor cells to lenvatinib. Additionally, NaB, a metabolite produced by specific gut microbes including *Roseburia cecalis* and *Roseburia intestinalis*, inhibits expression of sorafenib-targeted miR-7641 and miR-199. A combination approach using NaB with anti-miR-7641 or anti-miR-199 enhances apoptotic signaling and reduces the survival of drug-resistant cells [722]. These findings suggest modulating the composition and metabolites of gut microbiota may provide novel intervention strategies to overcome resistance to targeted anti-tumor agents.

Targeted therapeutic strategies for combined microbiome interventions

Research advances in integrating microbiome-modulating interventions with targeted therapeutic strategies have established promising new avenues for cancer treatment. Studies show microbial metabolite butyrate significantly enhances the therapeutic efficacy of sorafenib in HCC, though its lack of target specificity limits clinical translation. To overcome this limitation, researchers developed nanoparticles (NPs) encapsulating both butyrate and sorafenib, significantly enhancing HCC therapeutic efficacy [723]. Researchers are intensively exploring strategies to optimize targeted therapy efficacy through gut microbiota modulation [724]. Hahn et al. found antibiotics targeting *Bacteroides spp.* modulation improved PFS in patients treated with VEGF-TKI [725]. Conversely, FMT significantly alleviates diarrhea in metastatic RCC patients treated with TKIs, while simultaneously promoting favorable alterations in gut

microbiome composition [726]. This suggests while antibiotics and microbiome modulation offer promising strategies for improving targeted therapeutic response, specific microbiota intervention strategies require careful selection to minimize potential adverse effects.

Microbiome and surgery

The microbiome influences the outcome and prognosis of surgical treatment of tumors. Strategic preoperative microbiome modulation through targeted antimicrobial therapy or evidence-based probiotic administration may enhance therapeutic efficacy and substantially reduce the incidence of postoperative complications. Additionally, surgical stress affects microbial homeostasis, while post-operative complications are associated with microbiome composition and metabolism. Therefore, microbiome modulation strategies may accelerate postoperative recovery, mitigate perioperative complications, and optimize outcomes following surgery.

Preoperative microbiome preparation

Targeted microbiome modulation approaches in colorectal surgery, particularly preoperative microbiome optimization protocols, significantly influence long-term surgical prognosis. Numerous studies demonstrate colorectal anastomotic leak (AL) occurrence is associated with reduction in intestinal microbial diversity, whereas oral antibiotic preparations in elective colorectal surgery significantly reduce the incidence of postoperative complications, particularly AL risk [727, 728]. These findings underscore the critical importance of maintaining gut microbiota homeostasis in preventing postoperative complications. Probiotic supplementation demonstrates promise as a prophylactic measure in preoperative microbiome modulation. Studies demonstrate probiotic interventions effectively reduce inflammatory factor levels, attenuate chemotherapeutic side effects, prevent severe diarrhea, reduce postoperative infectious complication incidence, and shorten antibiotic treatment cycles [729]. Accumulating evidence suggests that preoperative probiotic or synbiotic interventions effectively improve surgical outcomes in patients with CRC. Additionally, preoperative mechanical bowel preparation (MBP) combined with antibiotics has garnered substantial clinical interest. Large-scale retrospective analyses have demonstrated that MBP with oral antibiotics significantly reduces the incidence of postoperative complications, including surgical site infection (SSI), bowel obstruction, and AL [730]. These findings further substantiate

preoperative microbiome optimization strategies, particularly evidence-based probiotic interventions, in improving clinical prognosis following colorectal surgery.

Effect of surgical stress on the microbiome

Surgical stress effects on body microbiome represent key research issues in microbiome and surgical therapy. Studies show significantly reduced diversity in fecal microbiota of postoperative CRC patients, with significant compositional differences compared to healthy controls and preoperative CRC patients [731]. Pre-clinical animal models have confirmed significantly altered gut microbial composition following small bowel surgery, with marked reductions in the relative abundance of *Bacteroidetes* and *Proteobacteria* phyla [732]. Further studies systematically evaluating the effects of surgical resection and chemotherapy on intestinal microbiota in CRC patients have demonstrated significant decreases in obligate anaerobes, tumor-associated microbial signatures, and butyric acid-producing bacteria, with significant increases in opportunistic pathogens when comparing postoperative versus preoperative fecal samples [733]. Additionally, hepatectomy can induce gut microbial dysbiosis in HBV-associated HCC patients, with elevated abundance of *Klebsiella* emerging as a potential predictive biomarker for postoperative liver failure (PHLF) in this patient population [734]. In conclusion, surgical stress modulating effects on microbiome deserve an in-depth study and attention.

Postoperative complications and the microbiome

Current evidence reveals that the complex associations between postoperative complications following oncologic surgery and the patient microbiome are receiving increasing investigative attention. AL represents one of the most common life-threatening postoperative complications in patients treated with gastrointestinal resection with primary anastomosis, with its pathogenesis strongly linked to gut microbiome regulation. Studies find gut microbiome influences AL development through two distinct molecular mechanisms. First, specific gut bacteria, notably *Enterococcus faecalis* and *Pseudomonas aeruginosa*, dissolve collagen and activate matrix metalloproteinases, potentially contributing to AL initiation and progression. Second, bacterial communities demonstrate protective effects on maintaining anastomotic integrity and promoting tissue healing [653].

Experimental studies have confirmed *Pseudomonas aeruginosa* inoculation significantly increased AL incidence following radiotherapy combined with low colonic anastomosis construction [691]. Additionally, patients developing postoperative pulmonary infections following GC surgical treatment exhibited significant alterations in the functional gene profiles of gut microbes, with enrichment of potentially pathogenic genera including *Klebsiella* and *Enterobacter* [735]. In summary, complex regulatory networks exist between the microbiome and postoperative complications, and comprehensive elucidation of these mechanistic interactions holds significance for improving patient prognosis.

Microbiome modulation for postoperative recovery

Microbiome modulation may play a fundamental role in optimizing postoperative recovery. Clinical studies confirm that high-fat, high-cholesterol (HFHC) dietary patterns significantly exacerbate gut microbiota dysbiosis and subsequently induce intestinal inflammatory responses in post-cholecystectomy patients, providing a mechanistic rationale for targeted probiotic intervention strategies to restore microbiome homeostasis and accelerate postoperative recovery [736]. Specifically, gut microbiota significantly regulates surgical incision healing. Studies show gut microbiota stimulates vagus nerve-mediated oxytocin release through lactic acid fermentation, subsequently promoting T cell recruitment and accelerating incision-healing processes [737]. Microbiome modulation represents an important therapeutic avenue for enhancing postoperative recovery, and patients may benefit from more optimized post-surgical care protocols through evidence-based nutritional intervention, strain-specific probiotic supplementation, and precision microbiome-targeted therapies.

Microbiome-based strategies for tumor therapy

Microbiome-targeted therapeutic approaches in oncology are being systematically investigated across multiple experimental and clinical platforms with accelerating momentum. Current microbial intervention approaches include probiotic, prebiotic and symbiotic interventions, FMT, precision antibiotic modulation, dietary modification, microbiome-targeted drugs, OVs therapy, engineered bacterial therapy, and fungal therapeutic strategies. These options significantly expand the

therapeutic landscape and offer promising avenues for improving therapeutic outcomes. Figure 8 provides a comprehensive mechanistic framework illustrating dual approaches for optimization of host microbiome and targeted methods with microbes.

Probiotic, prebiotic, and symbiotic interventions

Probiotics, prebiotics, and symbiotics, as established modulators of gut microbial ecology, play fundamental roles in maintaining intestinal microecological homeostasis. Specifically, probiotics are defined as live microorganisms, primarily *Bifidobacterium* and *Lactobacillus*. Prebiotics are non-digestible substrates that selectively promote the growth and metabolic activity of beneficial microbial communities. Symbiotics represent strategic combinations of probiotics and prebiotics. With advancing mechanistic understanding of host-microbiome interactions, probiotic interventions demonstrate significant therapeutic potential in cancer treatment paradigms, particularly in enhancing anti-tumor efficacy and mitigating treatment-associated adverse effects. Preclinical investigations have confirmed that oral multi-strain probiotic preparations significantly improve chemotherapy-related symptoms, including weight loss, adipose tissue depletion, and increased intestinal permeability, while effectively reducing pro-inflammatory cytokine levels. These implications further demonstrate the therapeutic potential of targeted probiotic interventions in alleviating chemotherapy-related adverse effects [738]. Diverse probiotic strains, predominantly within the *Bifidobacterium* and *Lactobacillus* genera, exhibit anti-tumor effects through multiple mechanisms, including enhancement of anti-tumor immune responses and inhibition of tumor invasion [715, 739]. In the context of chemotherapeutic potentiation, probiotics enhance chemotherapeutic efficacy and reduce toxicity through SCFAs production, which is further enhanced through the synergistic application of prebiotics [677]. Specific *Lactobacillus* strains modulate intestinal microbiome homeostasis and metabolite profiles through dual mechanisms, favorably remodeling the TME, collectively demonstrating significant potential for suppressing CRC progression [740]. In PC models, *Lactobacillus* specifically regulates intestinal microbial homeostasis through inhibition of TLR4 signaling pathway, potentially effectively inhibiting PC progression [48]. In IBD patients, probiotics like *Lactobacillus plantarum* and *Lactococcus lactis* are proposed as potential therapeutic agents for both IBD management and associated CRC prevention through modulating intestinal microbial composition and rebalancing dysregulated mucosal immune responses [326]. In CRC prevention and treatment, probiotic/symbiotic interventions significantly reduce

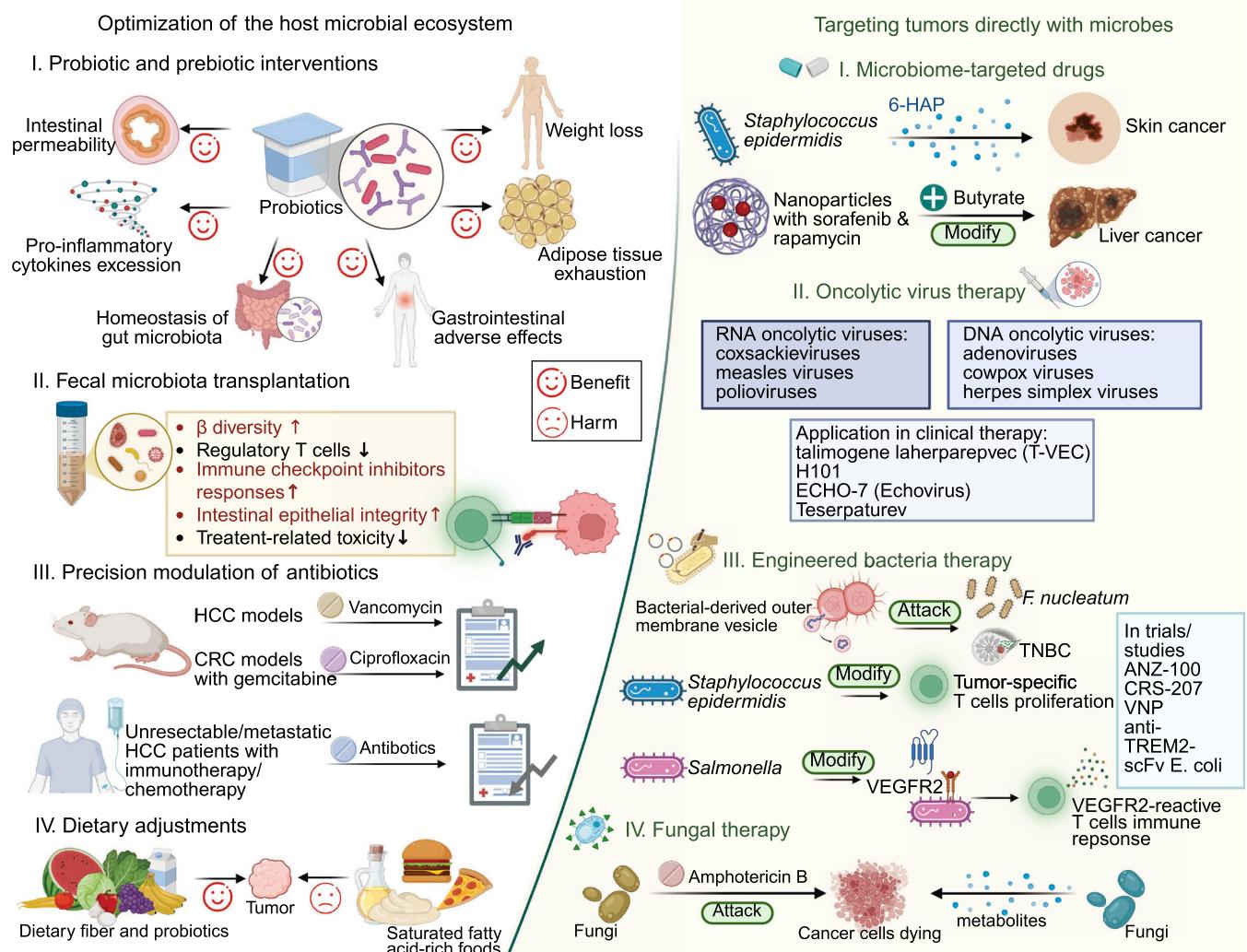


FIGURE 8 Therapeutic strategies for microbiome modulation in cancer treatment. On the one hand, optimize the host microbial ecosystem (Left). (I). Probiotic and prebiotic interventions show the beneficial effects on intestinal permeability, pro-inflammatory cytokine expression, gut microbiota homeostasis, weight loss, adipose tissue exhaustion, and gastrointestinal adverse effects. (II). FMT shows outcomes including increased β -diversity, decreased regulatory T cells (Tregs), enhanced ICI responses, improved intestinal epithelial integrity, and reduced treatment-related toxicity. (III). Precision antibiotic interventions (vancomycin, ciprofloxacin) in HCC and CRC mouse models improve prognosis, while antibiotics for unresectable/metastatic HCC patients receiving immunotherapy/chemotherapy show the converse affects. (IV). Dietary options represent the key modifier in microbiome-mediated tumor treatment. Dietary fiber and probiotics serve as protectors, whereas the role of saturated fatty acid-rich foods is strongly associated with tumorigenesis and microbial dysbiosis. Alternatively, targeting tumors directly with microbes (Right). (I). Microbiome-targeted drug development provides new therapeutic directions. *S. epidermidis* produces 6-HAP with demonstrated efficacy against skin cancer, while engineered nanoparticles containing sorafenib/rapamycin facilitate delivery of microbial metabolites (butyrate) for liver cancer therapy. (II). Oncolytic virus therapy, including RNA oncolytic viruses (coxsackieviruses, measles viruses, polioviruses), DNA oncolytic viruses (adenoviruses, cowpox viruses, herpes simplex viruses), and particularly clinical applications (T-VEC, H101, ECHO-7, and Teserapurev), shows potential for improvement in anti-tumor therapeutic strategies. (III). Engineered bacteria therapy involves bacterial-derived outer membrane vesicles, which can target *F. nucleatum* and attack triple-negative breast cancer cells. *S. epidermidis* promotes tumor-specific T cell proliferation. Engineered bacteria, including *Salmonella typhimurium* expressing vascular endothelial growth factor receptor 2 ($VEGFR2^+$), and *Listeria monocytogenes* attenuated live vaccine (ANZ-100, CRS-207) have progressed to Phase I trials. Additional bacterial candidates under investigation, including facultative anaerobic *Salmonella typhimurium* (VNP) conjuncted with $CaCO_3$ and *E. coli* expressing anti-TREM2 single-chain antibody fragments (scFv), exert anti-cancer activity and promote tumor radioimmunotherapy. (IV). Fungi-based therapeutic approaches, when combined with amphotericin B or specific fungal-derived metabolites, can induce cancer cell death. 1scFv, single-chain antibody fragments; 6-HAP, 6-N-hydroxylaminopurine; FMT, Fecal microbiota transplantation; VEGFR2, vascular endothelial growth factor receptor 2.

aberrant crypt foci formation while promoting the restoration of beneficial microbes, enhancing SCFA production, and modulating expression of key inflammatory mediators [741]. In patients with advanced lung cancer receiving platinum-based combination chemotherapy regimens, clinical studies show probiotic complexes significantly attenuate chemotherapy-related gastrointestinal adverse effects [742]. However, context-dependent effects have been observed wherein *Lactobacillus* may exert potential protumorigenic activities by increasing lactic acid concentrations of the TME and subsequently suppressing anti-tumor immune responses. This suggests that it is critical to consider the TME complexity when developing therapeutic probiotic interventions [743]. In RCC patients receiving ICIs, probiotic preparation of CBM588 containing *Clostridium butyricum* has demonstrated strong correlations with enhanced therapeutic responses through promoting proliferation of *Bifidobacterium spp.* and facilitating acetate and butyrate metabolism [744]. Additionally, probiotic spores (spores-dex) specifically demonstrate selective accumulation within colon cancer tissues, exerting anti-tumor effects through local production of SCFA and modulation of gut microbiota composition, collectively, significantly inhibiting tumor growth [238]. In conclusion, the strategically designed probiotic intervention represents a cornerstone of microbiome-targeted therapeutic approaches, showing considerable promise across multiple clinical applications. However, the mechanistic complexity and context-dependent efficacy of these interventions underscore the importance of rigorous investigation.

Fecal microbiota transplantation

FMT exhibits significant therapeutic potential across diverse malignancies [745–749]. In a primary HCC murine model, FMT significantly altered intestinal microbial β -diversity while concurrently reducing Treg density, indicating FMT efficacy in modulating gut microbiota and immune microenvironment [750]. Subsequent investigations revealed FMT potentially enhances clinical outcomes following ICI administration in advanced or metastatic CRC treatment, particularly among CRC patients with poor immunotherapy response [751]. Mechanistically, FMT combined with lactic acid-producing bacteria and their metabolic products (post-probiotics) synergistically restructures intestinal microbial ecosystems and modulates the TME, conferring both prophylactic and therapeutic benefits against CRC [7]. Interestingly, FMT from ICI-responsive cancer patients significantly enhanced anti-PD-1 efficacy when administered to germ-free or antibiotic-treated murine models [24]. Additionally, FMT efficacy in the treatment of

recurrent *Clostridium difficile* infections (CDI), coupled with its capacity to enhance survival, restore gastrointestinal function, and preserve intestinal epithelial barrier integrity in radiation-exposed animal models, supports its therapeutic potential to improve clinical outcomes in patients with cancer [752]. In summary, FMT represents a central component of microbiome-targeted therapeutic strategies with the potential to modulate the gut microbiota, enhance immunotherapeutic responses, and mitigate treatment-associated toxicities.

Multiple clinical investigations are systematically evaluating FMT efficacy across diverse oncological contexts [753]. Randomized controlled trials show significantly higher rates of TKI-induced diarrhea symptom relief in healthy donors treated with FMT compared to vehicle-only controls [726]. A recent study suggests this process correlates with enhanced mucosa-associated invariant T cell functionality [754]. A retrospective case series demonstrated that for cancer patients receiving chemotherapy who developed CDI, the majority of them experienced significant improvement without recurrence following FMT administration, supporting FMT as an effective and well-tolerated intervention for chemotherapy-associated complications [755]. Similarly, a recent study analyzing patients with ICI-induced refractory immune-mediated colitis found 83% achieved remission following FMT treatment [756]. A clinical trial exploring FMT to overcome ICI resistance in melanoma utilized fecal samples from melanoma patients exhibiting partial or complete ICI responses as donors. They have observed a 30% objective response rate in 10 melanoma patients receiving FMT combined with ICI therapy, a substantial improvement compared to ICI rechallenge response rates (<10%) [757]. Another study conducted a similar trial combining FMT with pembrolizumab in 15 immunotherapy-refractory melanoma patients, documenting clinical benefit in three patients and disease control exceeding 1 year in three patients [758]. Administration of FMT derived from healthy donors to 20 melanoma patients concurrently receiving anti-PD-1 therapy yielded a 65% objective response rate [759]. For urothelial and prostate cancer patients developing colitis after ICI treatment, FMT from healthy donors effectively restructured intestinal microbial communities, resulting in rapid and significant improvement of refractory immune-related colitis [760]. These clinical observations suggest that FMT holds promise for improving remission rates and reducing treatment-associated adverse events.

Antibiotic regulation

Antibiotic-mediated microbiome modulation represents a critical focus of microbiome-directed tumor intervention

strategies [761–763]. Vancomycin treatment significantly depletes intestinal *Clostridium cluster XIVa* populations in HCC murine models, consequently reducing circulating secondary bile acid concentrations and attenuating hepatocarcinogenesis. This finding elucidates a mechanistic pathway through which antibiotics influence oncogenesis via alterations of microbial metabolite profiles [764]. Notably, combining antimicrobial agents with chemotherapy demonstrates significant synergistic effects. Pre-clinical investigations utilizing colon cancer murine models demonstrate administration of gemcitabine and ciprofloxacin elicits significantly enhanced therapeutic responses compared to gemcitabine monotherapy. That suggests antibiotic-mediated microbiome modulation may enhance chemotherapeutic efficacy [642]. However, antimicrobial interventions necessitate judicious implementation, as perturbations in intestinal microbial ecosystems may significantly influence immunotherapeutic outcomes. A retrospective analysis of clinical trial data of unresectable/metastatic HCC patients treated with ICIs demonstrated that early antimicrobial exposure significantly compromised ICIs' efficacy. The phenomenon is potentially due to disruption of microbiota communities [765]. Administration of anti-anaerobic antimicrobial agents correlates with poor prognosis in HCC patients undergoing chemotherapy, whereas intestinal enrichment with anaerobic *Blaautia* demonstrates a significant association with favorable outcomes. Consequently, rigorous antimicrobial stewardship protocols require implementation for agents targeting anaerobic microbial communities [766].

Dietary regulation

Dietary modification represents a key modifier in microbiome-mediated oncological therapeutic approaches [767–770]. In advanced melanoma patients receiving ICI therapy, adherence to the Mediterranean diet is positively correlated with immunotherapy efficacy [761]. Comprehensive analyses utilizing 3-day, 24-h dietary recall methodologies in lung cancer patients have established significant associations among dietary intake patterns, intestinal microbial diversity indices, and multiple clinical health parameters [772]. Dietary fiber, a critical nutritional component, exerts multiple biological functions in maintaining host homeostasis. It serves as a substrate for intestinal microbial fermentation, subsequently generating bioactive metabolites, including SCFAs and bile acids, and significantly influencing carcinogenesis [773]. Substantial evidence demonstrates dietary fiber has significant chemopreventive and therapeutic effects in preventing and intervening in CRC,

including restoration of microbial community diversity, elevation of SCFA levels, and suppression of EMT [774]. Furthermore, strategic dietary interventions synergize with circadian regulatory mechanisms to maintain physiological homeostasis. Time-restricted feeding (TRF), a chronobiologically aligned nutritional intervention, preserves circadian rhythm synchronization, ameliorates metabolic disorders, and significantly delays lung tumor growth. TRF exerts anti-tumor effects through restructuring intestinal microbial communities, particularly increasing *Lactobacillus* and *Bacillus* abundance, and influencing immune and inflammatory processes [775]. Notably, different dietary components variably affect the gut microbiome. Dietary regimens incorporating sorghum, allium species, and cruciferous vegetables demonstrate inverse associations with risk of BT, which is mediated through circulating extracellular vesicle (EV) associated microbial signatures. However, consumption of specific plant-derived foods, including tumbleweeds and pyrus fruits, potentially enhances oncogenic risk [626]. Furthermore, comparative analysis of dietary lipid models demonstrates that saturated fatty acids and cocoa butter exhibit significantly greater pro-tumorigenic effects compared to monounsaturated (olive oil) or polyunsaturated (corn oil) fatty acid sources [776].

Microbiome-targeted drugs

Within the expanding domain of microbiome-directed therapeutic approaches, the development of agents specifically targeting microbial communities provides new therapeutic ideas and directions for cancer treatment. Studies show 6-HAP secreted by *S. epidermidis* specifically inhibits cancer cells, establishing novel therapeutic strategies for cutaneous malignancies [420]. NPs functionalized with butyrate and co-encapsulating sorafenib and rapamycin demonstrate significantly enhanced therapeutic efficacy in HCC [777]. Researchers increasingly emphasize the critical contributions of intestinal mycobiome components to hepatocarcinogenesis. Specific fungi demonstrate capacity for translocation from intestinal compartments to liver, closely related to HCC development, suggesting fungal genomes represent promising therapeutic targets [723]. Additionally, microbiome-targeted therapies demonstrate significant synergistic interactions with chemotherapeutic agents, potentiating chemotherapeutic efficacy through modulation of drug metabolism [642]. Notably, precision therapeutic strategies against specific microorganisms like *F. nucleatum* show promising results for BC patients, especially when combined with immunotherapy and

autophagy inhibitors [171]. In summary, microbiome-targeted drug development may represent a significant potential to revolutionize contemporary oncological management.

Oncolytic virus therapy

Among microbiome-mediated tumor therapy strategies, OV therapy (OVT) exhibits substantial anti-tumor potential as an emerging therapeutic modality [778–783]. OVs derive predominantly from attenuated human pathogens, vaccine vector platforms, and genetically modified replication-selective viral constructs. RNA virus-derived oncolytic agents include coxsackieviruses, measles viruses, and polioviruses represent typical OVs, while DNA virus-derived therapeutic vectors encompass adenoviruses, vaccinia viruses, and herpes simplex viruses [784]. Each possesses a distinct clinical application. OVs mediate therapeutic effects through the induction of immunogenic cell death and modulation of host anti-tumor immunity, achieving direct oncolysis while preserving non-malignant tissues [785, 786]. Currently, four OV types have received regulatory approval for clinical oncological applications, including talimogene laherparepvec (T-VEC), H101, ECHO-7 (Echovirus), and Teserapaturev [785]. OVT demonstrates promising efficacy across diverse malignancies, yet faces challenges including virus leakage, safety hazards of accidental transmission, strict transportation and storage requirements, and necessity for specialized delivery systems [786, 787]. Therefore, developing safer and more effective OVT strategies represents a critical priority for advancing clinical implementation of its clinical translation.

Engineered bacteria therapy

Within the expanding arsenal of microbiome-directed therapeutic modalities, engineered bacterial platforms represent a transformative approach with exceptional therapeutic potential. Engineered bacteria can be precisely modified to selectively colonize neoplastic tissues and functionalized as delivery vehicles for chemotherapeutic payloads, significantly enhancing chemotherapy efficacy [788]. These engineered microorganisms apply not only independently but also synergistically with other anti-tumor therapies, serving as diagnostic signals and preventive vaccines, demonstrating remarkable multifunctionality [789]. Various bacteria have been engineered as therapeutic agents, with *Listeria monocytogenes* and *Salmonella enterica* representing the most extensively characterized. Currently, multiple engineered

bacteria have progressed to Phase I and II trials, demonstrating favorable results [790]. In a Phase I clinical trial for advanced PC, oral administration of attenuated *Salmonella typhimurium* expressing VEGFR2 increased VEGFR2-reactive CD4⁺ and CD8⁺ T cell responses and promoted production of IFN γ , TNF, and IL-2, while significantly reducing tumor invasion [791]. Simultaneously, *Listeria monocytogenes* attenuated live vaccine (ANZ-100) and *Listeria monocytogenes* attenuated live vaccine expressing tumor differentiation antigen mesothelin (CRS-207) have completed Phase I clinical trials, demonstrating significant efficacy and good tolerability in patients with mesothelioma, lung cancer, PC, and ovarian cancer [792]. Comprehensive analyses of engineered bacterial projects show their capacity to regulate tumor cell and reprogram immune cell metabolism in the TME [793]. Additionally, engineered *S. epidermidis* induces tumor-specific T cell production, resulting in significant inhibition of both primary and metastatic melanoma progression [506]. These studies indicate that engineered bacteria are associated with the TIME [794]. Furthermore, engineered bacteria can assist with immunotherapy for tumors [795–797]. For the specific TME, engineered bacterial therapy functions as a potent immunotherapeutic adjuvant. A recent study shows that engineered *E. coli* precisely expressing anti-TREM2 single-chain antibody fragments (scFv) can regulate macrophages to promote tumor radioimmunotherapy [798]. Bioconjugates of engineered bacteria (facultative anaerobic *Salmonella typhimurium* VNP20009, VNP) with CaCO₃ can precisely target and colonize tumor cells, exerting anti-cancer activity and helping improve immunotherapeutic efficacy [799]. Targeting the unique physiological and immunological characteristics of the TME, engineered microbial therapeutics facilitate precise and multifaceted immunomodulation. In triple-negative BC research, a bacterial-derived outer membrane vesicle (OMV)-coated nanoplateform demonstrates dual-targeting capacity against pathogenic *F. nucleatum* and cancer cells, effectively repurposing intratumoral microbial communities as an immunostimulatory adjuvant, providing an innovative therapeutic approach for triple-negative BC [800]. Engineered bacterial therapies further demonstrate the capacity to maintain oxygen supply, activate chemotherapeutic agents, and enhance tumor radiosensitivity [794].

Fungal treatment strategies

Within the expanding landscape of microbiome-directed oncological interventions, mycobiome-targeted therapeutic approach emerge as an innovative anti-tumor

paradigm. Emerging evidence demonstrates that modulation of mycobiome composition in PC significantly influences treatment response, positioning antifungal interventions as promising therapeutic strategies for specific PC patients [221]. Additionally, targeted modulation of fungal-associated immunological mediators, including MBL and IL-33, provides novel immunotherapeutic strategies in cancer treatment [801]. Pre-clinical studies demonstrate that combination regimens incorporating antifungal agents with radiotherapy enhance tumor cell apoptosis and prolong survival compared to radiotherapy alone. This emphasizes the potential of mycobiome-targeted interventions as radiotherapy-sensitizing strategies [686]. However, the impact of fungal species on oncological outcomes demonstrates significant strain-specific heterogeneity. For example, in BC murine models, *C. albicans* supplementation combined with radiotherapy accelerated tumor progression and decreased survival intervals, illustrating the critical importance of species-specific mycobiome effects on therapeutic response [686]. Furthermore, fungal-derived bioactive metabolites show cancer therapy potential, including impairment of DNA damage repair pathways of malignant cells and direct cytotoxic and genotoxic activities, collectively contributing to their anti-tumor effects [802]. In conclusion, mycobiome-directed therapeutic strategies represent an innovative component of the microbiome-targeted oncological armamentarium, demonstrating notable promise through diverse mechanistic pathways.

FUTURE PERSPECTIVES AND CONCLUSION

The evolving landscape of microbiome science presents unprecedented opportunities coupled with formidable methodological and translational challenges that demand innovative solutions. Microbiome research technologies require continuous refinement and transformative technological innovations. Elucidation of mechanistic pathways mediating microbial influences in oncogenesis, development of precision microbiome-targeted therapeutic interventions, and acceleration of robust clinical translation collectively advance our comprehensive understanding of host-microbe interactions in malignancy while establishing novel paradigms for cancer management. Optimizing microbiome combination therapy strategies will enhance therapeutic efficacy and expand therapeutic paradigms. As scientific understanding advances, microbiome-directed therapeutic agents are progressively entering clinical development pipelines, through necessitating rigorous regulatory frameworks

that address concerns regarding the safety and efficacy. Integration of emerging research directions, exploration of understudied microbial communities, and characterization of their functional interactions promise notable clinical significance. Figure 9 comprehensively illustrates the major challenges and future directions of microbiome and oncology research, including technological innovations, mechanistic explorations, therapeutic strategy development, clinical translation approaches, and multivariate microbiome research frontiers, providing readers with an integrated framework and strategic perspective on the future development of microbiome and tumor research.

Developments and innovations in microbiome research technologies

Recent technological innovations in microbiome research are driving unprecedented analytical depth and expanding investigative breadth across oncology. Single-cell

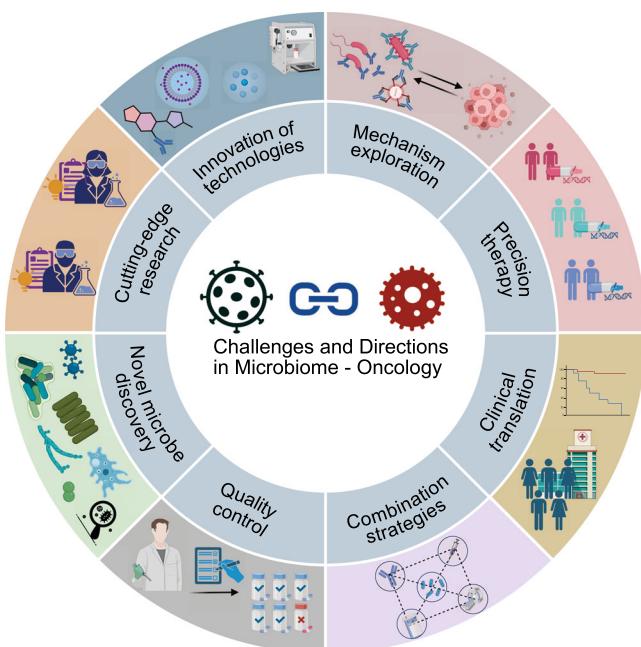


FIGURE 9 Challenges and future directions of microbiome in the field of precision oncology. This circular diagram illustrates eight key aspects defining the frontier of microbiome-oncology research: (1) quality control, (2) clinical translation pathways, (3) combination strategies with microbes-based cancer treatments, (4) personalized therapies based on individual mirobiome profiles, (5) cutting-edge research developments, (6) new microbial species and their potential application, (7) emerging technological platforms and methodological advances of technologies, and (8) mechanistic insights into biological processes governing microbe-tumor microenvironment interactions.

sequencing technology, as a representative emerging methodology, shows unique advantages and broad application prospects in microbiome research. Microbial split-pool ligation transcriptomics (microSPLiT) enables high-throughput transcriptional analysis of Gram-negative and Gram-positive bacteria, revealing gene expression heterogeneity in *Bacillus subtilis* [801]. Additionally, the innovative Barcoding Bacteria for Identification and Quantification (BarBIQ) method significantly improves 16S rRNA identification accuracy through single-bacterial barcode labeling [803]. In the spatial dimension, emerging genomic technologies reveal complex microbe–host relationships within tissue microenvironments, with researchers successfully achieving *in situ* resolution of host–microbe interactions in OSCC and CRC using GeoMx digital spatial profiling (DSP) [804]. At the systemic research level, multi-omics integration strategies establish new paradigms for studying microbial functions within lung cancer and other tumors by simultaneously capturing the microbiome and host transcriptional responses [349]. With the advent of the big-data era, artificial intelligence (AI) and machine-learning applications in microbiome data analysis have become increasingly critical for interpreting complex microbiome data sets. AI demonstrates remarkable potential in predicting host–microbe interactions, resolving uncharacterized metagenomic sequences, and optimizing experimental design [805]. Machine-learning algorithms excel in pattern recognition for cancer risk prediction and therapeutic response forecasting [806]. In summary, multidimensional innovative developments in microbiome research technologies synergistically drive microbiome research in oncology toward greater precision and comprehensive mechanistic understanding.

Despite significant advances in microbiome research technologies, critical challenges remain to be addressed. The low biomass of intratumoral microbiota presents fundamental challenges in detection sensitivity and specificity, with heightened susceptibility to host DNA contamination and background noise that may generate false-positive or false-negative results. Furthermore, existing functional validation methods (such as *in vitro* co-culture or murine models) inadequately recapitulate the complex microbe–host interaction networks in humans, while most studies rely on correlation analyses that provide insufficient evidence for causal relationships. For example, the carcinogenic effects of intratumoral microbes are often indirectly verified through gene knockout or antibiotic intervention approaches, but it remains difficult to exclude the influence of off-target effects or ecological niche disturbances. Future efforts require the development of high-resolution *in situ* detection technologies, particularly single-cell spatial multi-omics, combined with organoid-microbe co-culture

systems to enhance both analytical precision and clinical translational value.

In-depth exploration of microbiome mechanisms of tumors

Intensified mechanistic investigations have progressively elucidated the complex bidirectional interactions between the microbiome and cancer initiation, progression, and therapeutic response. Microbiome-mediated metabolic reprogramming has emerged as a focal area of investigation, with recent research deeply elucidating molecular mechanisms underlying the modulation of tumor proliferation and invasion. The immune–tumor–microbiota (IOM) axis framework, recently conceptualized, illustrates the complex regulatory network among the immune system, cancer cells, and microbiota. Systematic resolution of the gut IOM axis has emerged as a research priority, offering novel perspectives on mechanisms by which microbiota influences the TME through immune regulation. In the realm of epigenetic regulation, significant advances have characterized microbiome-mediated mechanisms, with evidence supporting a bidirectional “epigenome–microbiome axis” [807]. This evidence reveals the critical role of microbiota-mediated epigenetic modifications in tumorigenesis and development. Additionally, SAHMI technology has successfully identified microbes associated with single cells, revealing critical relationships between the intratumoral microbiome and lung cancer progression that may yield novel diagnostic biomarkers and therapeutic targets [808]. In summary, microbiome mechanism studies involve multiple dimensions, including metabolic reprogramming, immune regulation, epigenetic modifications, and cellular interaction networks within the TME. These mechanistic insights substantially advance our understanding of how diverse microbial communities influence tumorigenesis and tumor progression.

Development of precision microbiome therapeutic strategies

The development of precision microbiome-targeted therapeutic strategies has emerged as a significant frontier in addressing diverse malignancies. As an integral component of precision oncology, microbiome analyses in human diseases continue to evolve, providing a reliable scientific foundation for individualized therapeutic strategies [809]. The development of engineered bacterial

platforms represents a pivotal technological approach for modulating microbiome-associated diseases, with therapeutic potential systematically demonstrated in several studies [810, 811]. Evidence indicates that genetically engineered bacteria can function as sophisticated delivery vectors, precisely transporting therapeutic payloads to tumor sites, and significantly enhancing local drug concentrations [812]. Additionally, synthetic biology approaches applied to cancer-associated microbiomes provide innovative strategies for overcoming treatment resistance, with CRISPR-based and genome-engineering technologies demonstrating significant potential for developing novel therapeutic modalities [813]. Therefore, the advancement of precision microbiome-based cancer therapeutics hinges on complementary approaches, including individualized microbiome intervention protocol development, engineered bacterial development and optimization, microbiome-targeted delivery system design, and innovative applications of synthetic biology in microbiome therapy. These integrated approaches collectively advance microbiome-based cancer therapeutics toward improved target specificity and truly personalized interventions.

Among these, bacteriophage-based therapeutic strategies are garnering significant attention in oncology due to their exceptional target selectivity and molecular affinity. Phages interact with immune cell cytokine networks, participating in the regulation of inflammation and immune tolerance [814], while simultaneously modulating the TME and effectively inhibiting tumor cell growth and metastasis. Based on the tumor-suppressive functions of phages, numerous studies have screened highly selective and high-affinity phage vectors combined with bioengineering techniques for cancer treatment. Lei et al. developed a CD40-targeting engineered M13 phage (H-GM-M13CD40) that functions as an *in situ* vaccine by selectively targeting and activating DCs, inducing DC infiltration within tumor tissues to reverse the immunosuppressive TME [815]. Hou et al. developed a phage vector T4-Lox-DNA-Fe (TLDF) that integrates T4 phage and biointelligent plasmids to disrupt redox homeostasis within the TME, achieving remarkable tumor growth inhibition of up to 78% and establishing a novel approach for precise micro-environmental modulation [816]. Additionally, researchers developed a tumor-targeting transforming phage/AAV (RGD4C.TPA) vector engineered to deliver TNF- α genes, which induced selective tumor cell apoptosis and vascular disruption. This approach enhances efficacy when combined with cisplatin, establishing a promising approach against medulloblastoma [817]. M2 macrophage-specific targeting peptides identified through phage display technology have been engineered

to bind with high affinity to both M1 and M2 phenotypes of tumor-associated macrophages. When combined with complementary genetic modifications, these integrative products enable synergistic elimination of malignant cells while providing a dual-targeting, light-controlled therapeutic strategy for precise TME modulation [817]. Phage display technology was recognized with the Nobel Prize in Chemistry in 2018, with increasing research being devoted to phage-based therapeutic exploration. Mechanistic models centered on phage-based interventions will be crucial for future research, as systematic exploration of this direction will significantly advance the translational impact of microbial approaches in precision oncology.

Advancement of clinical translational research

Translational research bridging the microbiome and tumor therapy is rapidly evolving as a critical research direction. Large-scale multicenter clinical trials not only establish solid data foundations for clinical translational research but also provide strong support for the reliability of research outcomes. For example, a multicenter clinical trial revealed microbiota's potential as a novel therapeutic target in urological malignancies, with implications for developing personalized treatment algorithms [818]. Meanwhile, the development of standardized treatment protocols represents a critical prerequisite for advancing rigorous clinical investigation. Currently, tumor treatment modalities are diverse, including chemotherapy, radiotherapy, immunotherapy, targeted therapy, surgery, and microorganism-based combination therapy [712, 819–826]. While this therapeutic diversity expands clinical options, it simultaneously presents substantial methodological challenges for comparative research. In particular, the lack of uniform research standards impedes rigorous cross-study analysis and meta-analytical interpretation. The development of standardized treatment protocols will harmonize translational research methodologies and enhance clinical decision-making efficiency, representing a critical priority for advancing evidence-based oncological practice. Additionally, existing clinical biomarkers demonstrate inherent limitations despite their established utility. Novel biomarker development and validation have significant value in clinical translation of microbiome research. Particularly, microbiome-based assessment protocols may provide precise cancer patient stratification by severity, potentially facilitating optimized intervention strategies and improved survival outcomes. For example, identification of conserved microbial

biomarkers across ethnically heterogeneous patients enables applicability of optimal diagnostic and prognostic models across diverse populations [50]. Establishment of comprehensive systems for monitoring and preventing adverse effects constitutes an essential component of translational research. Despite continuous refinement of therapeutic modalities, adverse events remain key factors affecting the efficacy and quality of life of patients. Consequently, implementing robust pharmacovigilance systems for adverse effect detection and prevention is paramount for optimizing therapeutic outcomes and safeguarding patient well-being. In summary, advancement in microbiome-oncology clinical translational research requires integration of multiple components, including large-scale multicenter clinical trials, standardized treatment protocol development, biomarker development and validation, and adverse events monitoring and prevention systems. These integrated approaches collectively advance oncological therapeutics toward enhanced precision, efficiency, and safety.

Rigorous clinical validation through well-designed prospective multicenter trials represents a critical priority, exemplified by protocols that integrate longitudinal microbiome profiling with treatment response assessment in ICI therapy. Such protocols may randomize eligible patients to receive either monotherapy with ICIs or combination therapy with microbiome-modulating agents, employing standardized techniques for sampling and monitoring changes in microbial marker dynamics. These protocols would incorporate systematic assessment of the TIME parameters, with subsequent analysis of correlations with PFS. Simultaneously, quantitative analysis of microbial metabolites could facilitate the development of integrated diagnostic models incorporating microbial taxa with metabolite signatures, potentially enhancing diagnostic precision and predictive accuracy. In the future, Mendelian randomization methods could further validate causal relationships between the microbiome and clinical outcomes, while elucidating the immunomodulatory mechanisms underlying microbiota-targeted therapeutic interventions.

Optimization of microbiome combination therapy strategies

Optimization of microbiome-targeted combinatorial therapeutic strategies represents a frontier area in contemporary oncological research. In this field, elucidation of synergistic mechanisms between the microbiome and immunotherapy provides a key theoretical foundation for therapeutic development. Numerous studies demonstrate critical associations between the microbiome and

immunotherapy, with in-depth investigation of microbiome-mediated enhancement of anti-tumor immunity providing valuable insights for optimizing clinical protocols and developing precisely targeted combination therapies [827, 828]. Design and evaluation of multimodal therapeutic regimens aim to integrate multiple therapeutic modalities, leveraging mechanism-specific advantages to generate synergistic therapeutic effects. This multimodal treatment strategy integrates various therapeutic approaches, including immunotherapy, chemotherapy, and radiotherapy, while comprehensively accounting for microbiome-mediated influences on treatment efficacy. Through systematic characterization of patient-specific microbiome profiles, precisely tailored multimodal therapeutic regimens can be developed, potentially enhancing treatment efficacy while mitigating adverse events. Additionally, elucidation of microbiome-mediated drug resistance mechanisms represents a critical research priority for overcoming therapeutic resistance and improving treatment efficacy. Studies demonstrate that gut microbes can mediate immunotherapy resistance and accelerate CRC progression [829]. Research has identified intestinal microbe-mediated drug catabolic pathways and key enzymes, providing novel perspectives into microbiome-mediated treatment resistance mechanisms [830]. Notably, the development of patient-specific combinatorial therapeutic approaches constitutes a primary objective in optimizing microbiome-informed treatment strategies. Integrating microbiome profiles with other biomarkers significantly improves diagnostic precision and facilitates prediction of therapeutic responsiveness, enabling the development of precisely tailored interventional approaches. The gut microbiota shows expansive potential applications in precision medicine and individualized therapy, establishing a solid theoretical foundation for developing personalized combinatorial intervention strategies [809, 831–834]. In summary, optimization of microbiome-targeted combinatorial therapeutic strategies requires comprehensive consideration across multiple dimensions, including mechanistic synergies with immunotherapies, multimodal treatment regimen design and evaluation, microbiome-mediated resistance mechanisms, and individualized combination therapy strategy development, collectively advancing oncology toward maximized treatment efficacy.

Quality control in microbiome products

As a cutting-edge biomedical innovation, microbiome-based therapeutic product development and regulation aim to advance microbiome drug research, development,

and clinical application through establishing scientifically standardized processes, stringent quality control standards, comprehensive regulatory frameworks, and systematic ethical guidelines, ultimately facilitating novel precision medicine approaches. Standardization of microbiome-based therapeutic development processes constitutes the foundational infrastructure for successful product advancement. Integrating gut microbiomics into new drug development systems provides new ideas for resolving challenges of drug development while potentially enhancing therapeutic candidate success rates. Throughout therapeutic development pipelines, enhanced interdisciplinary collaboration between the microbiome and complementary research is essential, necessitating a comprehensive evaluation of candidate compounds' effects on microbiome composition and function while maintaining scientifically rigorous development protocols. Establishment of a quality control system critically determines the safety profile and therapeutic efficacy of microbiome-based interventions. Pharmaceutical quality management systems should address all critical parameters influencing product quality to ensure consistent compliance with established quality standards and regulatory requirements. For microbiome-based therapeutic products, quality control strategies must emphasize maintenance of microbial viability, stability, and thorough characterization of interactions with other formulation elements. Robust regulatory frameworks are fundamental to microbiome therapeutic development, encompassing scientifically sound product classification criteria, rigorous approval pathways, and comprehensive post-marketing surveillance requirements to ensure thorough evaluation of safety and efficacy throughout product lifecycles. Meanwhile, ethical guidelines play a critical role in governing microbiome therapeutic advancement, necessitating thorough consideration of potential risks including microbial ecological dysbiosis and drug resistance. In summary, advancement of microbiome-based therapeutic products requires coordinated multidimensional approaches, including R&D process standardization, quality control system construction, regulatory framework improvement, and ethical guideline formulation, to ensure product safety, efficacy, and regulatory compliance while facilitating innovation in precision medicine applications.

Prospects for research direction

Microbiome research represents a frontier area in contemporary biomedical science with profound scientific

implications and extensive applications in oncology. Existing studies have confirmed that the microbiome exerts critical regulatory influences in tumorigenesis and tumor development. Investigators propose that identifying microbial markers with cancer-suppressive properties and developing microbiome-targeted preventive agents will provide a scientific basis for preventive interventions in high-risk populations. Intensive studies show that the microbiome has important indicative roles in tumor progression prediction. Specific microbial signatures and compositional alterations correlate significantly with tumor stage, histological grade, and patient outcomes, providing a theoretical basis for developing more refined microbiome-derived biomarkers. In studies examining microbiome-mediated remodeling of the TIME, researchers focus on optimizing anti-tumor immune responses through targeted modulation of gut microbial communities, thereby enhancing immunotherapeutic efficacy. Strategic manipulation of microbial community composition and function can reshape the TIME to enhance immune cell activation and tumor clearance, offering novel approaches to augment cancer immunotherapy. Additionally, rigorous assessment of the long-term efficacy and durability of microbiome-targeted interventions represents a critical scientific priority. Considering the complexity and dynamic characteristics of microbiome therapy, establishing comprehensive evaluation frameworks and longitudinal monitoring of microbial community dynamics and host responses is essential for ensuring therapeutic safety and efficacy. Microbiome research shows significant research value and application potential across many oncological contexts. By delineating interactions between the microbiome and tumorigenesis, progression, and treatment response, researchers may achieve more precise approaches to cancer prevention, prediction, therapeutic selection, and outcome assessment, ultimately providing novel strategies to improve patient prognosis.

Novel research directions for microbiome

Microbiome research, at the forefront of biomedical investigation particularly within oncology, has illuminated complex host-microbe interaction networks and opened expansive research horizons. In studies examining interactions between viral communities and the TME, researchers have thoroughly investigated viral contributions to tumorigenesis, development, and microenvironmental regulation. Future efforts resolving how viral communities interact with tumor cells, immune components, and other microorganisms to shape the TME may provide novel possibilities for

exploring virus-targeted therapeutic opportunities. Studies investigating fungal communities and tumor immune responses focus on how fungal communities regulate immune responses, affecting tumor therapeutic efficacy and clinical prognosis. Research in this area has elucidated associations between fungal diversity and immune evasion, immune cell functionality, and ICI efficacy, providing a mechanistic foundation for mycobiome-targeted immunotherapeutic approaches. Multidimensional microbiome analyses are emerging as a critical research paradigm that aims to decipher complex ecological networks among diverse microbial communities and host systems by integrating multi-omic data across bacterial, viral, and fungal domains. This comprehensive cross-dimensional analysis enables more sophisticated understanding of microbiome contributions to tumorigenesis, tumor progression, and treatment mechanisms, offering novel insights for precision medicine and personalized therapy approaches. Development of new microbiome-based therapies represents the translational culmination of microbial oncology research. Informed by enhanced mechanistic understanding of microbiome-tumor interactions, interventions targeting specific microbial communities or functions, including probiotics, prebiotics, and bacteriophage therapy, are being developed to regulate anti-tumor immunity, enhance therapeutic efficacy, mitigate adverse effects, and potentially achieve durable tumor control.

In summary, the human microbiome has emerged as a pivotal regulator in cancer pathogenesis, progression, and therapeutic outcomes. This comprehensive review has synthesized substantial evidence demonstrating that diverse microbial communities influence tumorigenesis through multiple mechanisms, including inflammatory pathways, metabolite production, immune regulatory networks, and epigenetic alterations. Beyond their significant diagnostic potential as biomarkers, microorganisms fundamentally influence therapeutic efficacy and modulate treatment-associated toxicities. Innovative therapeutic strategies targeting the microbiome, including probiotics, FMT, engineered bacteria, and precision antimicrobial approaches, have shown considerable promise in enhancing the efficacy of conventional cancer treatments and overcoming resistance. Future advances in this rapidly evolving field will require continued technological innovation, deeper mechanistic insights, standardized methodologies, and rigorous clinical validation to fully harness the microbiome's transformative potential in precision oncology and personalized medicine.

AUTHOR CONTRIBUTIONS

Anqi Lin: Writing—original draft; writing—review and editing. **Minying Xiong:** Writing—original draft;

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

No new data and scripts were used for this review. Supplementary information (graphical abstract, slides, videos, Chinese translated version, and update materials) is available online DOI or <http://www.imeta.science/>.

ETHICS STATEMENT

No animals or humans were involved in this study.

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