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Intratumoural Microbiota: Roles in Cancer Development, Prognosis, and Therapy

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ABSTRACT

Breakthroughs in sequencing technologies have overturned the notion that tumors are sterile. Recent studies reveal that bacteria, fungi, and viruses—collectively termed the intratumoral microbiota—are present across diverse cancer types. These microorganisms may colonize tumors through mucosal barrier disruption, local tissue spread, or circulation in the blood. Once established, they act as key modulators of the tumor microenvironment.

Mechanistic evidence shows that intratumoral microbiota can induce genomic instability, alter epigenetic states, promote chronic inflammation, evade immune surveillance, and reshape tumor metabolism. The composition and diversity of these microbial communities differ by tumor type and stage. Distinct microbial signatures are associated with patient prognosis and therapeutic response. The intratumoral microbiota are increasingly recognized not only as biomarkers for early detection and prognosis but also as potential therapeutic targets, especially in immunotherapy. However, significant challenges remain in understanding their origins, biological functions, and the safe manipulation of these microbes. Overall, advances in this field hold promise to transform cancer diagnosis, prognosis, and treatment through microbiota-targeted strategies. This review highlights the characteristics and origins of intratumoral microbiota, their prognostic significance, and their emerging role in cancer therapy.

Keywords:Cancer Progression; Immunotherapy; Intratumoral Microbiota; Microbiome-Based Therapy; Microbial Biomarkers; Tumor Microenvironment

INTRODUCTION:

The human microbiome, consisting of around 38 trillion microorganisms, including bacteria, viruses, fungi, protozoa, and archaea, inhabits not only external sites like the gut, skin, oral cavity, and vagina but also internal organs once thought sterile, such as the lungs, liver, and pancreas (1). Advances in sequencing have revealed microbial presence within both healthy and tumor tissues, leading to growing research on their roles in cancer. A breakthrough is the discovery of intratumoural microbiota—microbes living inside tumor tissues found in over 33 cancer types, where they influence tumor initiation, progression, immune responses, and metastasis (2, 3). Historically, microbes have been linked to cancer since the 19th century, with key discoveries like Micrococcus neoformans and the Rous sarcoma virus (3). The International Agency for Research on Cancer recognizes several microbes, including Helicobacter pylori, oncogenic viruses, and parasites, as definite carcinogens responsible for millions of cancer cases worldwide (4). Beyond directly causing cancer, microbes can indirectly promote cancer risk via chronic inflammation, immune modulation, and producing genotoxic compounds—such as Escherichia coli strains that generate colibactin, leading to DNA damage in colorectal cancer (5).

While much focus has been on gut microbiota, recent attention has shifted to the tumor microbiome itself, which impacts cancer cell survival, immune evasion, and treatment outcomes. Additionally, microbes are being harnessed therapeutically—from early bacterial cancer therapies to modern vaccines and engineered bacteria and viruses—highlighting the tumor microbiome as a promising frontier for novel cancer diagnostics and treatments (6).

This review will first summarize the origins and characteristics of intratumoural microbiota across different cancer types. We will then explore how these microbial communities vary with tumor type and stage, and discuss their prognostic significance. Next, we will examine the mechanisms by which intratumoural microbiota influence cancer biology, including immune modulation, inflammation, and metabolic reprogramming. Finally, we will highlight emerging therapeutic strategies that target the tumor microbiome and outline the current challenges and future directions in this rapidly evolving field.

Characteristics of Intratumoural Microbiota

Intratumoural microbiota colonize tumors through multiple pathways, including mucosal barrier invasion, adjacent tissue spread, and hematogenous (bloodstream) transport. In mucosal organs like the esophagus, lungs, colon, and cervix, “driver” bacteria such as Bacteroides and Enterobacteriaceae initially establish themselves by penetrating damaged mucosal barriers and promote tumor development, later giving way to “passenger” microbes that further affect tumor growth. In non-mucosal organs like the pancreas, microbes may translocate from the gut through ducts when barrier integrity is compromised, altering the tumor microenvironment (7). Tumor-associated microbial communities often resemble those of neighboring tissues, influenced by chronic inflammation or infections like Helicobacter pylori, though the exact origins of these microbes require further study (2). Additionally, microbes such as Fusobacterium nucleatum can spread to tumors via the bloodstream from distant sites like the oral cavity or intestines, especially through damaged blood vessels (8) (Figure 1).

The diversity and density of intratumoural microbiota vary significantly across cancer types, subtypes, and stages. This heterogeneity highlights the importance of understanding tumor-specific microbial profiles to unravel their role in cancer progression and to develop targeted diagnostic and therapeutic strategies (see Table 1).

Lung Cancer and the Microbiome

The lung microbiome, shaped by environmental exposure and nearby body regions, plays a key role in lung cancer development. Patients with lung cancer typically show reduced microbial diversity, but certain bacteria Modestobacter, and fungi are more abundant, especially in smokers (9).

Microbiome composition varies with tumor type and smoking status. Squamous cell carcinoma (SCC), linked to smoking, has greater diversity and includes genera like Acidovorax, while lung adenocarcinoma (LUAD) is associated with different bacteria like Acinetobacter. Some microbes Veillonella, Prevotella are linked to advanced cancer stages (10).

Animal studies confirm increased microbial load and show that microbiome disruption can worsen cancer outcomes. Tumor tissue samples are the most reliable for studying these microbial patterns. Overall, the

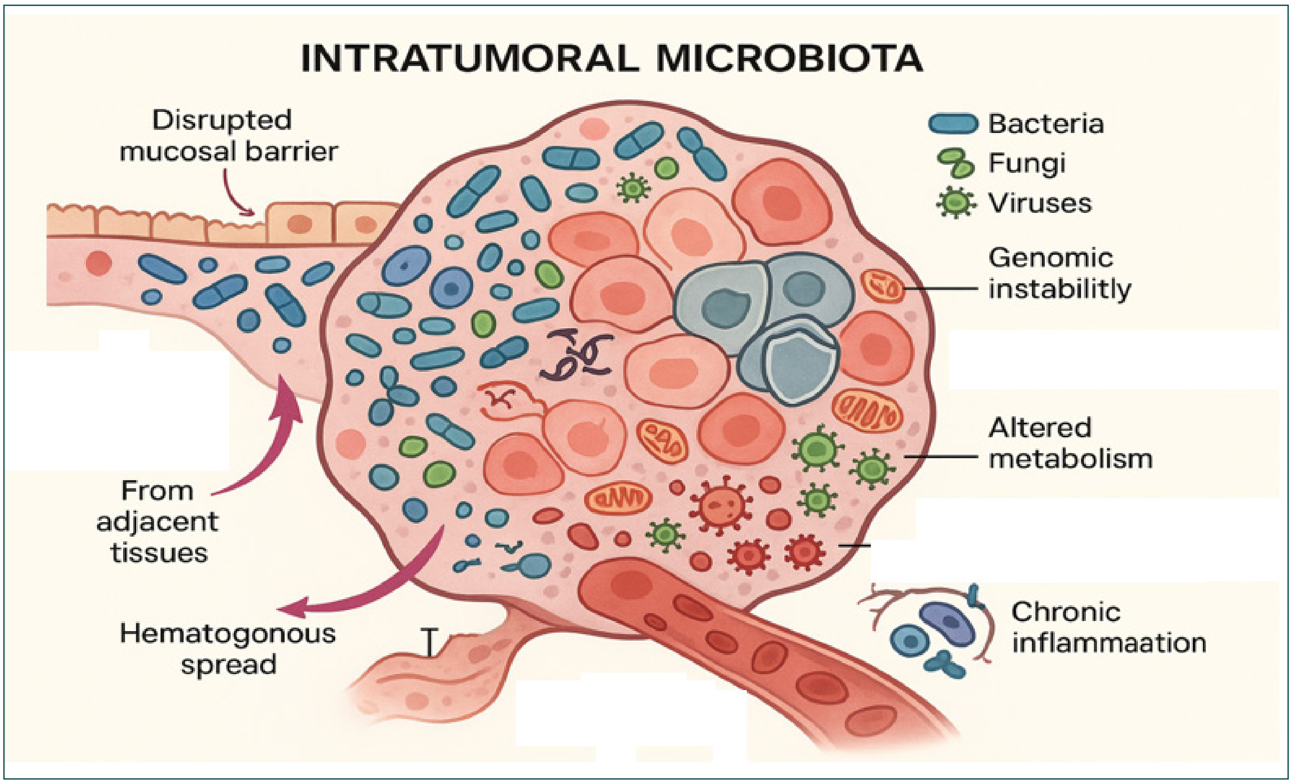

Figure 1: Intratumoral microbiota: microbial entry routes and interactions within the tumor microenvironment.
This illustration presents a conceptual cross-section of a solid tumor colonized by diverse intratumoral microorganisms, including bacteria (depicted as blue rods and cocci), fungi (green yeast-like cells), and viruses (green viral particles). Microbial colonization is visualized via three principal routes: (1) disruption of the mucosal barrier, enabling translocation of microbes from external or luminal surfaces; (2) local extension from adjacent infected or inflamed tissues; and (3) hematogenous dissemination, with microbes entering the tumor through blood vessels.
Within the tumor microenvironment, these microorganisms interact dynamically with both cancer cells and immune cells, influencing tumor progression through multiple mechanisms. Schematic indicators highlight key biological processes modulated by the microbiota, such as genomic instability (broken DNA strands), chronic inflammation (inflammatory cell infiltration), immune evasion (shielded cancer cells), and metabolic reprogramming (altered mitochondria or metabolic icons).
Color-coded labels clearly distinguish microbial types and entry pathways. This figure underscores the multifaceted roles of intratumoral microorganisms in shaping the immune landscape, genomic architecture, and metabolic state of tumors, emphasizing their potential as diagnostic biomarkers and therapeutic targets in cancer biology.

lung microbiome influences cancer progression and could support new diagnostic and treatment strategies, though more research is needed to understand its full impact (11).

Liver Cancer and the Microbiome

The gut–liver axis enables gut microbes to influence liver health and has become central to liver cancer research. Primary liver cancer (PLC), especially hepatocellular carcinoma (HCC), often arises in the context of chronic liver disease caused by HBV or HCV. While direct studies of microbes within liver tumors are limited, Helicobacter pylori and related species have been detected in HCC tissues, though their causal role in humans remains uncertain (12).

Microbial profiles differ by liver cancer type and condition. Gammaproteobacteria are more abundant in HCC than in normal liver, and in cirrhotic HCC, Streptococcaceae and Lactococcus levels are elevated. Other studies report increased Enterobacteriaceae in HCC and decreased Caulobacteraceae and Rickettsiaceae in combined HCC-ICC. In ICC, Paraburkholderia fungorum is more common in surrounding tissues and may have antitumor effects (13).

Although early findings suggest microbial involvement in liver cancer, more research is needed to understand how specific microbes influence tumor development and progression.

Colorectal Cancer and the Microbiome

Colorectal cancer (CRC) is closely linked to microbial dysbiosis, with both bacteria and fungi playing key roles

Table 1. Characterization of the Intratumoural Microbiota in Various Cancers

Cancer Type	Key Microbial Compositions	Quantitative Dynamics	Notable Functions / Associations
Lung Cancer	Modestobacter (↑), Propionibacterium (↓), Enterobacteriaceae (↓), Blastomyces (↑), Agaricomycetes (↑), Aspergillus (↑), Acidovorax (↑), Klebsiella (↑), Anaerococcus (↑), Acinetobacter (↑), Brevundimonas (↑), Cyanobacteria (↑), Veillonella (↑), Megasphaera (↑), Coriobacteriaceae, Pasteurella, Nontypeable Haemophilus influenzae (↑)	Increase or decrease depending on taxa and subtype	Acidovorax: linked to TP53 mutation; Veillonella & Megasphaera: diagnostic biomarkers; NTHi: IL-17C release, neutrophil recruitment; Coriobacteriaceae & Pasteurella: related to CD8+ T cells & M2 macrophages
Liver Cancer	Hepatitis B virus (↑), Hepatitis C virus (↑), Helicobacter pylori (↑), Gammaproteobacteria (↑), Streptococcaceae (↑), Lactococcus (↑), Enterobacteriaceae (↑), Caulobacteraceae (↓), Rickettsiaceae (↓), Paraburkholderia fungorum (↓)	Several taxa increased, some decreased	HBV/HCV: genome integration, m6A RNA modification, Treg recruitment; Streptococcaceae & Lactococcus: cirrhosis-HCC markers; Paraburkholderia fungorum: antitumor activity
Colorectal Cancer	Enterotoxigenic Bacteroides fragilis (↑), Fusobacterium (↑), Lactococcus (↑), Bacteroides (↑), Prevotella (↑), Streptococcus (↑), Pseudomonas (↓), Escherichia-Shigella (↓), Fusobacterium nucleatum (↑)	Several taxa increased, some decreased	B. fragilis: carcinogenic toxins, pro-inflammatory signaling; F. nucleatum: M2 macrophage polarization, advanced stage, histone modification, autophagy inhibition, β-catenin activation
Pancreatic Cancer	Enterobacteriaceae (↑), Bacteroides(↑), Fusobacterium (↑), Proteobacteria(↑)	Increased in tumor tissue	Microbial translocation via pancreatic duct, reshaping TME, promoting inflammation and tumorigenesis
Breast Cancer	Methylobacterium(↑), Sphingomonas(↑), Enterobacteriaceae (↑), Staphylococcus (↑)	Increased in tumor tissue	May influence estrogen metabolism, immune modulation, and tumor progression
Prostate Cancer	Propionibacterium (Cutibacterium) (↑) , Escherichia(↑) , Streptococcus species(↑) , Enterobacteriaceae(↑)	Increased in tumor tissue	Potential roles in inflammation and local immune response

Legend:
↑ = Increased abundance in tumor tissue
↓ = Decreased abundance in tumor tissue

in its initiation and progression. Genotoxic substances like colibactin, produced by certain Escherichia coli strains, and pro-inflammatory or toxin-producing microbes like Fusobacterium nucleatum and enterotoxigenic Bacteroides fragilis (ETBF), contribute to tumor development (14).

CRC tumors have distinct microbial profiles, showing enrichment of Fusobacterium, Bacteroides, and Streptococcus, while adjacent normal tissues harbor more Pseudomonas and Escherichia-Shigella. In familial adenomatous polyposis (FAP), bacterial biofilms containing E. coli and B. fragilis further increase cancer risk through toxin production. Some microbes, like B. fragilis, can either promote or suppress cancer depending on the strain (15)Microbial differences exist between left-sided and right-sided colon cancers, reflecting underlying molecular subtypes. A large meta-analysis identified 94 microbial species distinguishing CRC from healthy individuals, with virulence genes like fadA and colibactin enriched in CRC (16). Fungal shifts are also observed, with Candida and Malasseziomycetes elevated in advanced CRC, while beneficial fungi like Saccharomyces decline. Changes in the virome, especially bacteriophages, are linked to CRC severity and survival outcomes (17). Chronic inflammation, such as in IBD, increases CRC risk, with microbes like Helicobacter hepaticus, E. coli NC101, and Candida albicans promoting tumorigenesis. While some bacteria, like Lactobacillus reuteri and Ruminococcus gnavus, may protect against CRC, study inconsistencies hinder definitive microbial signature identification (18).

Overall, the CRC microbiome reflects a complex, context-dependent interplay that influences cancer risk and offers promising targets for diagnostics and therapies.

Breast Cancer and the Microbiome

Breast cancer (BC), the most common cancer in women, is now known to be associated with distinct microbial populations in breast tissue. Tumor tissues generally have lower bacterial DNA levels than adjacent normal tissue, with total bacterial load decreasing as cancer progresses (19). BC tissues exhibit high microbial diversity, with bacteria such as Pseudomonas, Proteus, Streptococcus, Staphylococcus, and Lactobacillus commonly found. Methylobacterium radiotolerans is often more abundant in tumors and lymph nodes, while Sphingomonas yanoikuyae is more frequent in healthy tissue (19). Fungal species like Cladosporium and Malassezia are also more prevalent in breast tumors, especially in older patients (20).

Microbial composition varies by tumor subtype; for instance, Streptococcaceae are enriched in triple-negative breast cancer (TNBC). Experimental models show that disrupting tumor bacteria can reduce metastasis, while some microbes (Staphylococcus, Lactobacillus) may promote tumor spread (21). The gut microbiome also influences breast cancer, with microbes like Helicobacter hepaticus enhancing tumor formation in mice (22). Overall, both local and systemic microbiomes appear to affect breast cancer development and progression, with potential implications for diagnostics and therapy.

Pancreatic Cancer and the Microbiome

Pancreatic cancer (PC), especially pancreatic ductal adenocarcinoma (PDAC), is a highly lethal disease with limited treatment options. Contrary to earlier beliefs, the pancreas hosts diverse microbial communities, with tumor tissues showing higher bacterial loads than normal pancreas. PDAC microbiota are dominated by Proteobacteria, Firmicutes, and Bacteroidetes, resembling duodenal profiles. Specific microbes are linked to PDAC development. Fusobacterium nucleatum, known from colorectal cancer, is enriched in PDAC and may promote tumor progression, while beneficial Lactobacillus species are reduced. Other common bacteria include Pseudomonas, Elizabethkingia, and Helicobacter pylori, the latter potentially activating cancer-promoting pathways through unique pancreatic strains (23, 24).

Basal-like PDAC tumors, associated with poor outcomes, are enriched in Acinetobacter, Pseudomonas, and Sphingopyxis. Tumor microbial diversity correlates with prognosis: long-term survivors have higher levels of Pseudoxanthomonas, Saccharopolyspora, and Streptomyces, while short-term survivors show more Clostridia and Bacteroides. Microbial biomarkers like Bacillus clausii have strong prognostic value, likely linked to immune activation (2, 25).

The pancreatic mycobiome is also altered, with increased Malassezia species possibly contributing to tumor growth through immune and metabolic effects (26). These findings reveal complex microbe–tumor interactions in PDAC, offering potential for novel diagnostic and therapeutic strategies.

Oral Cancer and the Microbiome

The oral cavity hosts a diverse microbiota, which shifts notably during oral squamous cell carcinoma (OSCC) development. As cancer progresses, the microbiome transitions from predominantly aerobic to more anaerobic species. Viral pathogens like HPV (particularly type 16), EBV, and HSV-1 are key contributors to OSCC, with HPV linked to up to 35% of cases. Bacterial changes are also central: Fusobacterium nucleatum and Porphyromonas gingivalis are enriched in OSCC and associated with worse outcomes. Other elevated bacteria include Prevotella intermedia, Treponema denticola, Pseudomonas aeruginosa, and Campylobacter, while some aerobic species like Streptococcus anginosus show variable patterns (27, 28).

Sequencing data reveal increased levels of Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria in OSCC, with Capnocytophaga more prominent in advanced tumors. Animal models confirm that F. nucleatum and P. gingivalis promote tumor growth. In contrast, beneficial bacteria like Streptococcus, Corynebacterium, and Lactobacillales are reduced (29). Fungal diversity remains relatively stable, but richness declines in cancer. Candida albicans, Candida etchellsii, and Hannaella-like species are more common in OSCC. As the disease advances, Fusobacterium levels increase, while Streptococcus, Haemophilus, and Actinomyces decrease (30). These microbial shifts highlight the role of the oral microbiome in OSCC progression and suggest potential biomarkers and therapeutic targets.

Urogenital Microbiome and Cancer

The urinary and reproductive tracts, once thought sterile, harbor unique microbial communities that may influence cancer development. In mice, Helicobacter hepaticus can trigger prostate cancer, with immune cell transfer spreading disease, which is reduced by anti-inflammatory treatment. In humans, prostate cancer urine microbiota are dominated by Corynebacterium, Staphylococcus, and Streptococcus, with species like Streptococcus anginosus and Ureaplasma more common in cancer cases. These bacteria, linked to urogenital infections, suggest chronic inflammation or genotoxicity may promote prostate carcinogenesis. Bladder cancer shows altered microbiomes, with increases in Fusobacterium, Streptococcus, and others, though findings vary due to sampling and patient differences (31-33).

In female reproductive cancers, dysbiosis is frequent. Healthy cervicovaginal microbiota, usually dominated by Lactobacillus, is often depleted in ovarian cancer, replaced by diverse bacteria, fungi, viruses, and parasites, some serving as potential biomarkers. Endometrial cancer is associated with elevated Firmicutes, Actinobacteria, and other phyla, with Atopobium vaginae and Porphyromonas somerae linked to disease. Cervical cancer shows overrepresentation of A. vaginae and Sneathia spp., especially in HPV-positive and bacterial vaginosis cases, where loss of Lactobacillus supports tumor growth. Distinct microbial patterns correlate with tumor grade and may predict cervical cancer outcomes more accurately than traditional clinical markers, highlighting the urogenital microbiome's role in cancer biology and its diagnostic potential (34-36).

Microbiota in Other Tumor Types

Microbial alterations have been observed across various cancers. In head and neck squamous cell carcinomas (HNSCC), Actinomyces decreases while Parvimonas increases, with HPV16 commonly present and often excluding mutations in key genes like TP53 (30). Nasopharyngeal carcinoma (NPC) features Corynebacterium and Staphylococcus, with higher bacterial loads linked to worse outcomes (37). Ovarian cancer tissues show increased Aquificae and Planctomycetes but decreased Crenarchaeota, along with a higher prevalence of high-risk HPV types. Endometrial cancer is associated with Bacteroides and Faecalibacterium, while Staphylococcus, Blautia, and Parabacteroides are more common in benign tissue. Cutibacterium acnes persists in prostate tissue (38). Microbes are also found in brain tumors, including glioblastomas and pituitary neuroendocrine tumors, with microbial patterns varying by tumor subtype (39). Epstein–Barr virus (EBV) appears in several hematologic cancers, and human endogenous retroviruses, especially ERV1, are highly expressed in chronic lymphocytic leukemia (40). Despite these observations, the precise roles and impacts of intratumoral microbiota in many cancers remain unclear, underscoring the need for further research.

The role of intratumoral microbiota in cancer development, prognosis, diagnosis, and therapy

Intratumoral microbiota plays a multifaceted role in cancer biology, influencing tumor initiation, progression, diagnosis, therapeutic response, and prognosis. Certain microbes promote tumorigenesis by inducing DNA damage, activating oncogenic signaling pathways, evading immune surveillance, and sustaining chronic inflammation. For example, genotoxins like colibactin from Escherichia coli and toxins from Bacteroides fragilis can trigger DNA damage and oncogenic transformation. Conversely, other microbes exert anti-tumor effects by inducing cancer cell apoptosis or enhancing host immune responses. This duality suggests that the composition of the intratumoral microbiome directly impacts tumor behavior and patient prognosis (41) (Figure 2).

In the context of therapy, the microbiome significantly modulates responses to chemotherapy, radiotherapy, and immunotherapy. Some microbes metabolize or inactivate anticancer drugs, alter drug bioavailability, or reshape the tumor microenvironment. For instance, Fusobacterium nucleatum has been shown to impair chemotherapy efficacy in colorectal cancer, whereas Bifidobacterium and Akkermansia muciniphila have been associated with improved outcomes in immunotherapy (42, 43). Consequently, microbiome-targeted interventions—such as the use of probiotics, antibiotics, engineered bacteria, and fecal microbiota transplantation (FMT)—are being explored to enhance therapeutic responses and overcome treatment resistance (44).

From a diagnostic standpoint, microbial signatures identified in non-invasive samples (e.g., saliva, stool, and blood) are emerging as valuable biomarkers. Distinct microbial profiles have been detected in

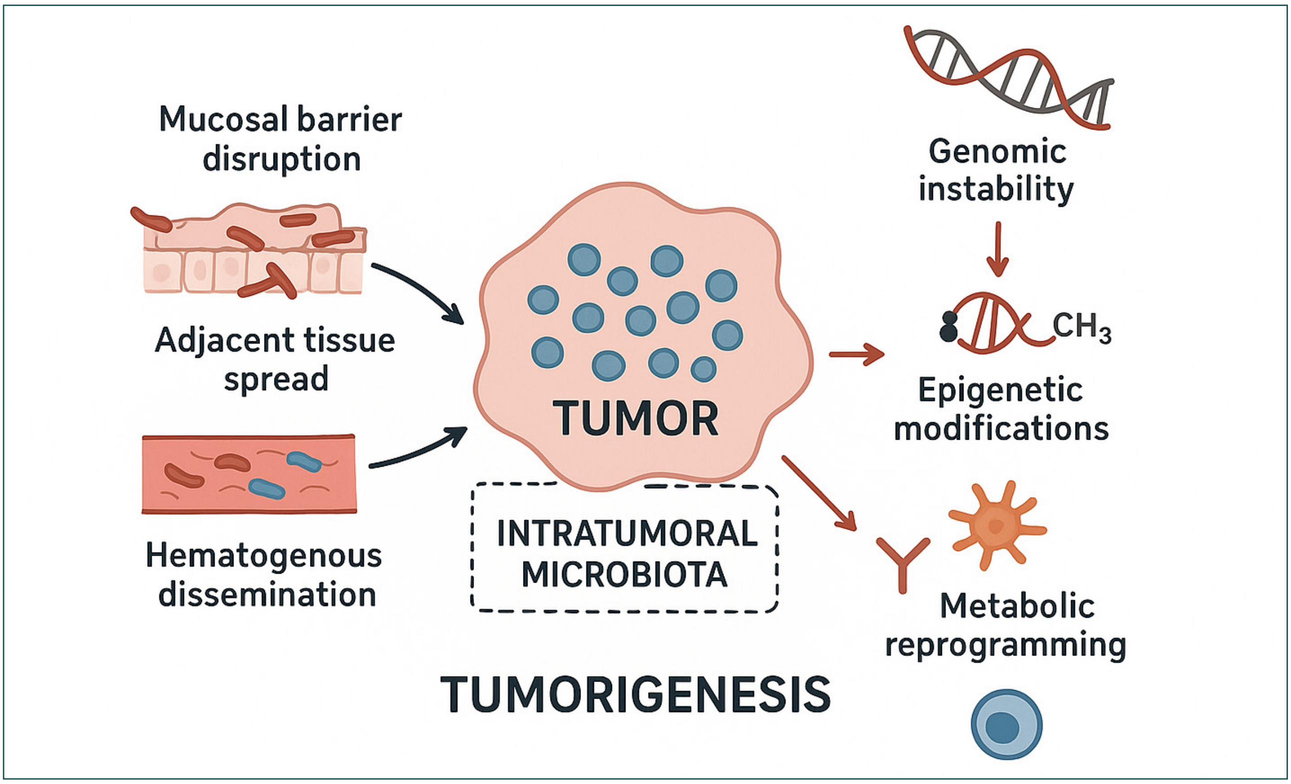

Figure 2: Mechanistic pathways of intratumoral microbiota in tumorigenesis.
This schematic illustrates the primary microbial entry routes into tumor tissues, including (1) mucosal barrier disruption, (2) local spread from adjacent tissues, and (3) hematogenous dissemination. Once established within the tumor microenvironment, intratumoral microbes modulate cancer biology through several mechanisms: induction of genomic instability (e.g., via microbial genotoxins such as colibactin), epigenetic modifications, chronic inflammation, immune evasion through modulation of immune checkpoints, and metabolic reprogramming of tumor cells. Collectively, these microbial influences contribute to tumor initiation, progression, therapeutic resistance, and immune modulation across diverse cancer types, highlighting the microbiota as critical modulators and potential therapeutic targets in oncology.

patients with cancers such as colorectal and pancreatic cancer. Advances in sequencing technologies now enable the precise identification of these microbial shifts, offering promising tools for early detection and accurate tumor classification (45).

Modulating the microbiome presents a promising strategy to enhance therapeutic efficacy and minimize side effects. Techniques include antibiotic regimens, probiotics, FMT, and genetically engineered microbes. However, clinical implementation faces challenges due to inter-individual variability influenced by diet, medications, geography, and the complex nature of host–microbiome interactions. Therefore, standardized protocols and large-scale longitudinal studies are necessary to unlock the full therapeutic potential of microbiome manipulation (46).

As prognostic and therapeutic biomarkers, tumor-resident microbial communities show significant promise. These communities differ by tissue type, cancer stage, genetic mutations, and metastatic status. Their presence and diversity can impact tumor progression, patient survival, and treatment outcomes. For example, high levels of F. nucleatum correlate with poorer survival in colorectal, pancreatic, and vulvar cancers but are paradoxically linked to better outcomes in oral and anal cancers, potentially due to immune modulation (47).

Other microbes also possess prognostic value: in lung cancer, specific bacterial genera associate with survival outcomes; in liver cancer, microbial profiles correlate with disease progression; and in pancreatic cancer, certain microbial signatures are linked to long-term survival. In ovarian cancer, intratumoral fungal communities reflect tumor advancement. Notably, microbial community structures offer more robust prognostic insights than single species, with higher intratumoral microbial diversity potentially improving immunotherapy response rates (48).

Table 2. Microbes Known to Affect Cancer Therapies

Microbe/Group	Cancer Type(s)	Effect on Therapy	Mechanism/Notes
Fusobacterium nucleatum	Colorectal cancer	Reduces chemotherapy efficacy	Promotes chemoresistance by modulating autophagy and immune evasion
Bacteroides fragilis	Colorectal cancer	Modulates immunotherapy response	Produces toxins, influences T cell responses
Gammaproteobacteria	Pancreatic cancer	Reduces gemcitabine efficacy	Inactivates gemcitabine via bacterial cytidine deaminase
Helicobacter pylori	Gastric cancer	Alters therapy response	Chronic inflammation, affects immune microenvironment
Enterococcus hirae	Various (preclinical)	Enhances immunotherapy efficacy	Stimulates anti-tumor immunity, increases T cell infiltration
Bifidobacterium spp.	Melanoma (mouse)	Enhances PD-L1 blockade efficacy	Promotes dendritic cell function and T cell activation
Akkermansia muciniphila	Lung, kidney (mouse)	Improves response to PD-1 blockade	Stimulates IL-12 secretion, improves anti-tumor immune response
Lactobacillus spp.	Various (preclinical)	Enhances anti-tumor immunity	Modulates gut and tumor immune environment
Oncolytic viruses (e.g., T-VEC)	Melanoma	Direct tumor lysis, immune activation	Infects and lyses tumor cells, releases tumor antigens, boosts immune response
Hepatitis B virus (HBV) vaccine	Liver cancer (HCC)	Prevents cancer	Reduces incidence of HCC by preventing chronic HBV infection

Moreover, the intratumoral microbiota can influence therapy resistance and sensitivity. For instance, F. nucleatum is associated with chemotherapy resistance in esophageal cancer, while other microbes modulate responses to immunotherapy. Despite challenges such as the invasiveness of tumor sampling and limitations of surrogate samples, novel technologies like spatial microbiome mapping and AI-powered analytics are improving clinical applicability (49). Overall, incorporating tumor microbiota could advance cancer diagnosis, prognosis, and personalized treatment.

The effect of microbiome on cancer therapies

Microbes play direct roles in some cancers, and targeting them is part of current treatment strategies, such as antibiotic therapy for Helicobacter pylori in gastric cancer, antivirals for hepatitis C, and vaccines for HPV and HBV to prevent cervical, head-and-neck, and liver cancers. Addressing harmful intratumoral microbes holds promise to enhance precision therapy and reduce cancer recurrence. (Table 2).

Microbial Intervention in Immunotherapy

The microbiome significantly influences immunotherapy responses, including checkpoint inhibitors and CAR T-cell therapies (42). Treatments like fecal microbiota transplantation (FMT), probiotics, and antibiotics can alter outcomes (43). Beneficial bacteria such as Bacteroides fragilis and Bifidobacterium improve efficacy, while antibiotic use often correlates with worse results. Microbial metabolites like short-chain fatty acids and inosine help regulate immunity, and fungi and phages may also affect responses (46, 50). However, inconsistent findings and no universal microbial predictors highlight the need for more research.

Current evidence for fecal microbiota transplantation (FMT) in cancer treatment is still limited but promising, especially as an adjunct to immunotherapy for patient's refractory to checkpoint inhibitors, particularly in melanoma. Early-phase I/II clinical trials using responder-derived FMT in ICI-refractory melanoma have reported objective response rates (ORRs) of approximately 20–40 % (51). A 2025 meta-analysis pooling 10 studies (164 patients) found a combined ORR of 43 % (95 % CI: 0.35–0.51) for FMT plus ICIs, with significantly higher response rates when anti-

PD-1 was combined with anti-CTLA-4 (60 % vs 37 % for anti-PD-1 monotherapy; P = 0.01). Safety data showed grade 1–2 adverse event (AE) rates of 42 % (95 % CI: 0.32–0.52) and grade 3–4 AEs in 37 % of patients (95 % CI: 0.28–0.46)(52). Multiple ongoing clinical trials are currently investigating FMT in combination with PD-1/PD-L1 inhibitors across various solid tumors—including melanoma, lung, colorectal, and gastrointestinal cancers—intending to evaluate effects on gut microbiome modulation, immunotherapy efficacy, and toxicity reduction (53). However, while findings to date are encouraging, large-scale randomized controlled trials with long-term follow-up are still needed to establish FMT as a standard adjunct in oncology (54).

Radiotherapy

Gut microbiota affect radiotherapy effectiveness and toxicity. Depleting Gram-positive bacteria enhances radiation's tumor-killing effects, but supplementing with butyrate reverses this. Reducing fungi boosts radiation response, and certain bacteria help reduce gastrointestinal side effects. These insights suggest microbiome modulation could improve radiotherapy outcomes and lessen toxicities (55).

Chemotherapy

The gut microbiome impacts chemotherapy efficacy. Antibiotics that eliminate gut bacteria reduce the effectiveness of drugs like cisplatin and oxaliplatin. Specific microbial profiles correlate with treatment response, and some bacteria can metabolize or inactivate chemotherapy drugs. Modifying microbiomes locally, including in the lung or tumor environment, can enhance chemotherapy success (56).

Antibiotics

Antibiotics have shown potential to improve cancer treatment outcomes by targeting tumor-associated microbes implicated in tumorigenesis and therapy resistance. For example, metronidazole treatment reduces Fusobacterium load and tumor growth in colorectal cancer models. However, systemic or broad-spectrum antibiotic use poses significant risks due to disruption of beneficial commensal microbiota, which play critical roles in immune homeostasis and treatment efficacy. Such microbiome dysbiosis can impair therapeutic responses and increase immune-related adverse effects (57).

To mitigate these issues, emerging strategies focus on selective targeting of tumor-resident microbes while preserving the commensal microbiome. Approaches include cell-penetrating antibiotics and nanoparticle-based delivery systems that enable localized, controlled release of antimicrobials directly within the tumor microenvironment, minimizing off-target effects. These innovative delivery methods aim to reduce collateral damage and maintain gut and systemic microbial balance, thereby enhancing therapeutic safety and efficacy (58).

Bacteriophages

Bacteriophages offer high specificity in targeting harmful tumor-associated bacteria, including those resistant to conventional antibiotics. Phages can be engineered not only to kill pathogenic microbes but also to deliver therapeutic agents or nanoparticles to tumors. Despite their promise, phage therapy requires personalized phage cocktails tailored to individual microbial profiles and is currently best suited as an adjunct to antibiotics or for treating resistant infections (59).

Engineered Bacteria

Genetically modified bacteria represent a novel therapeutic modality capable of selectively colonizing tumors to deliver prodrug-converting enzymes, produce cytotoxic agents, or stimulate local antitumor immunity. Engineered strains such as Salmonella and Bifidobacterium have demonstrated preclinical efficacy. However, clinical translation is limited by safety concerns, including potential systemic infection and unintended effects, necessitating rigorous safety evaluations before widespread adoption (60).

OncolyticViruses

Oncolytic viruses (OVs) selectively infect and destroy tumor cells while stimulating immune responses. They can enhance checkpoint inhibitor therapies, with some already approved clinically. Challenges remain in safety, delivery, and patient selection for biomarkers (61).

Conclusion and Outstanding Questions

Intratumoural microbiota—bacteria, fungi, and viruses—are now recognized as active players in cancer development, progression, and treatment response. They colonize tumors via mucosal barrier invasion, nearby tissue migration, or bloodstream spread, influencing cancer through genomic instability, epigenetic changes, inflammation, immune modulation, metabolism, and metastasis (62)D.

The composition of these microbes varies widely by cancer type, subtype, and stage, making the tumor microbiome a promising source of diagnostic and prognostic biomarkers. Manipulating these microbes with antibiotics, probiotics, oncolytic viruses, or engineered bacteria could improve therapy outcomes, especially immunotherapy (63).

However, several key questions remain. One major challenge is distinguishing pathogenic "driver" microbes—those demonstrated through functional studies to actively promote tumorigenesis via mechanisms such as genotoxin production, immune suppression, or chronic inflammation—from "passenger" microbes, which are identified primarily through correlative sequencing data and appear enriched in tumors without clear causal roles (64). Clarifying the distinction between intratumoral microbiota (microbes residing within tumor tissues or even intracellularly) and tumor-associated microbiota (those present in the surrounding stroma, vasculature, or adjacent mucosa) is also important, as studies often use these terms interchangeably (65). Furthermore, the marked heterogeneity of microbial communities across cancer types, stages, and patients complicates efforts to establish causality, raising the question of whether microbial changes are initiators of tumorigenesis, consequences of tumor progression, or both. Importantly, whether these microbes act as true drivers of tumorigenesis or merely as bystanders remains context-dependent. For example, Fusobacterium nucleatum is recurrently associated with colorectal, pancreatic, and oral cancers, but its oncogenic potential appears to vary with tumor type and microenvironmental conditions(66). Similarly, host genetic background and environmental factors, including diet and antibiotic exposure, strongly influence microbial colonization, immune modulation, and metabolic activity within tumors. These interactions suggest that microbial contributions to cancer are not uniform but shaped by the dynamic interplay between microbes, host, and environment. Additional uncertainties remain regarding the origins of tumor-resident microbes—particularly in non-mucosal cancers—and the host and environmental factors governing their colonization (67). Safety, specificity, and unintended effects of microbiota-targeted therapies also need careful evaluation (68). Methodological challenges further complicate the study of intratumoral microbiota. Bulk sequencing approaches, while widely used, cannot always distinguish viable microbes from background contamination. Addressing this requires meticulous sterile tissue handling, the inclusion of rigorous controls, and the application of advanced techniques such as single-cell sequencing and spatial transcriptomics, which enable precise mapping of microbial presence and activity within tumor tissues (69). Furthermore, although mouse models have provided valuable mechanistic insights, their translational relevance remains limited by differences in microbial composition, immune system architecture, and tumor biology between mice and humans(70). These discrepancies highlight the need for validation in human cohorts and the integration of cross-species approaches to strengthen clinical applicability. In summary, intratumoral microbiota represent a new frontier in cancer biology, with significant potential to advance diagnosis, prognosis, and personalized therapy. Interdisciplinary efforts will be essential to fully elucidate and harness their roles in clinical oncology.

Future Perspectives

The field of intratumoral microbiota research is rapidly evolving, offering exciting opportunities to deepen our understanding of cancer biology and improve patient care. Future studies should aim to standardize microbiome sampling and analytical methodologies to enhance reproducibility and comparability across investigations(71). Advances in multi-omics technologies, combined with spatial microbiome mapping and integrated computational approaches including artificial intelligence, will enable more precise characterization of tumor-associated microbial communities and their functional interactions within the tumor microenvironment (72). Clinically, there is a pressing need for well-designed, large-scale randomized trials to assess microbiome-targeted therapies such as fecal microbiota transplantation, probiotics, and engineered bacteria, focusing on efficacy, safety, and personalization of treatment (73). Additionally, developing innovative delivery systems to selectively modulate tumor-resident microbiota without disrupting beneficial commensals holds promise to maximize therapeutic benefit while minimizing adverse effects(74). Overall, interdisciplinary collaboration bridging microbiology, oncology, immunology, and bioinformatics will be essential to translate these advances into effective diagnostics and therapeutic strategies, ultimately enhancing precision oncology and patient outcomes.

Abbreviation

1- Colorectal Cancer (CRC)
2- Enterotoxigenic Bacteroides fragilis (ETBF)
3- Fecal Microbiota Transplantation (FMT)
4- Hepatocellular Carcinoma (HCC)
5- Human Papillomavirus (HPV)
6- Intrahepatic Cholangiocarcinoma (ICC),
7- Lung Adenocarcinoma (LUAD)
8- Nontypeable Haemophilus influenzae (NTHi)
9- Oral Squamous Cell Carcinoma (OSCC)
10- Pancreatic Ductal Adenocarcinoma (PDAC)
11- Primary Liver Cancer (PLC)
12- Squamous Cell Carcinoma (SCC)
13- Tumor Microenvironment (TME)
14- Triple-Negative Breast Cancer (TNBC)
15- Talimogene Laherparepvec (T-VEC, Oncolytic virus)

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