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Review Article

Gut Microbiome and Cancer: Identifying Microbial Signatures, Tumorigenesis Pathways, and Therapeutic Opportunities Across Cancer Development, Progression, and Treatment Response

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Abstract

Background: The gut microbiome has emerged as a pivotal modulator of human health, exerting profound effects on host physiology, immunity, and disease susceptibility. Mounting evidence from translational and clinical studies implicates the gut microbiota in both the initiation and progression of various malignancies, as well as in modifying responses to cancer therapies.

Objective: This review aims to critically synthesize recent advances (2019–2026) in understanding the gut microbiome's role in cancer biology, with emphasis on microbial signatures, mechanistic pathways of tumorigenesis, and translational opportunities for diagnosis and therapy across major cancer types.

Methods: We systematically reviewed high-quality original and review literature published between 2019–2026, prioritizing mechanistic, clinical, and translational studies. Select pre-2019 landmark studies were included for essential context. Major focus areas include microbial diversity, cancer-specific signatures, mechanistic pathways (inflammation, metabolites, immune modulation), and the microbiome's influence on cancer treatment response.

Key Findings: Distinct gut microbial signatures are consistently associated with colorectal, breast, lung, hepatocellular, and pancreatic cancers. Mechanistic studies elucidate how microbiota-driven inflammation, microbial metabolites (SCFAs, bile acids, tryptophan catabolites), and immune modulation contribute to tumorigenesis. The microbiome influences chemotherapy, immunotherapy, and radiotherapy outcomes, offering new therapeutic avenues. However, conflicting evidence and unresolved questions persist regarding causality, inter-individual variation, and clinical translation.

Conclusion: The gut microbiome is a key player in cancer development, progression, and therapeutic response. Integration of multi-omic, mechanistic, and clinical research will be vital for translating microbiome science into precision oncology.

Keywords: Gut microbiome, Cancer, Microbial signatures, Tumorigenesis, Inflammation, Microbial metabolites, Immune modulation, Chemotherapy, Immunotherapy, Radiotherapy, Precision oncology, Translational research.

Introduction

Global Cancer Burden

Cancer remains a leading cause of morbidity and mortality worldwide, with an estimated 19.3 million new cases and nearly 10 million deaths reported globally in 2020, according to GLOBOCAN data [1]. Despite advances in detection and treatment, the global cancer burden is projected to rise, driven by demographic shifts, environmental exposures, and lifestyle factors. The heterogeneity of cancer, both within and across tumor types, continues to challenge efforts in prevention, diagnosis, and therapy.

Role of Gut Microbiome in Cancer Biology

In parallel with advances in cancer biology, the field of microbiome science has undergone unprecedented growth. The human gut harbors trillions of microorganisms, collectively referred to as the gut microbiome. These microbes interact dynamically with host cells, influencing immune surveillance, metabolic homeostasis, and barrier integrity. Recent research has illuminated the gut microbiome as a critical modulator of carcinogenesis affecting tumor initiation, progression, and response to therapy [2-4]. These effects are mediated through a complex interplay of microbial metabolites, immune modulation, inflammation, and direct genotoxicity (Figure 1).

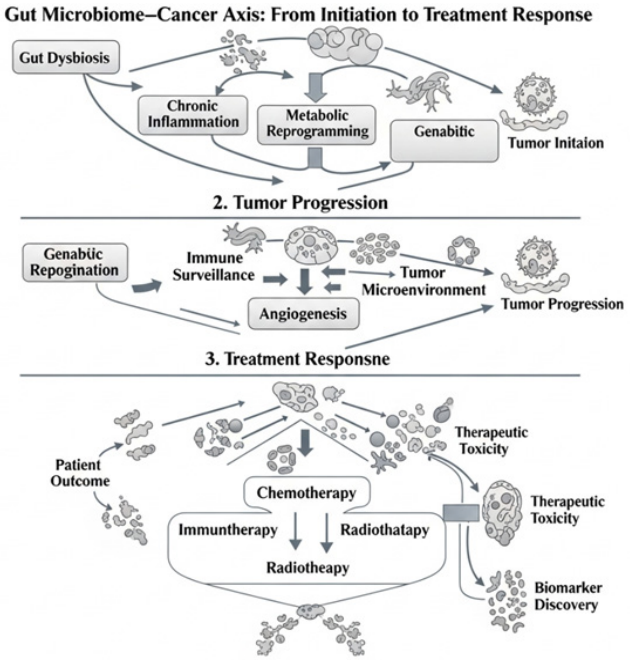

Figure 1: Overview of the Gut Microbiome–Cancer Axis (Initiation, Progression, and Treatment Response).

Clinical and Therapeutic Relevance

The clinical relevance of the gut microbiome in oncology is underscored by studies linking specific microbial taxa and dysbiosis to cancer risk and prognosis. Notably, the gut microbiome modulates responses to chemotherapy, immunotherapy, and radiotherapy, with translational implications for biomarker discovery and therapeutic intervention [5–7]. Microbiota-targeted strategies—ranging from probiotics and dietary modulation to fecal microbiota transplantation (FMT) and engineered bacterial therapeutics—are being explored as adjuncts to conventional cancer treatments.

Limitations of Existing Reviews and Novelty of this Review

While several reviews have summarized the microbiome–cancer nexus, most are limited by outdated literature coverage, narrow cancer type focus, or insufficient mechanistic insight. This narrative review provides a critical synthesis of high-impact studies from 2019–2026, emphasizing cancer-specific microbial signatures, mechanistic underpinnings, and translational potential across the cancer continuum. Unlike prior reviews, we integrate multi-omic, clinical, and experimental data, address conflicting evidence, and highlight gaps and opportunities for future research.

Gut Microbiome: Composition and Function

Microbial Diversity

The gut microbiome is a highly diverse ecosystem, composed of bacteria, archaea, viruses, and fungi. Bacterial phyla such as Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria dominate healthy adult microbiomes [8]. Microbial diversity is a marker of gut homeostasis, with higher alpha diversity generally reflecting resilience and health. Dysbiosis—characterized by reduced diversity and altered community composition—has been linked to multiple diseases, including cancer [9].

Dysbiosis

Cancer-associated dysbiosis is typified by the expansion of pro-inflammatory or pathogenic taxa and the depletion of commensal or beneficial microbes. For instance, colorectal cancer (CRC) is associated with increased *Fusobacterium nucleatum*, *Escherichia coli*, and *Peptostreptococcus anaerobius*, alongside reduced butyrate-producing bacteria such as *Faecalibacterium prausnitzii* [10,11]. Dysbiosis may result from or contribute to oncogenesis via inflammation, metabolic reprogramming, and immune evasion.

Host–Microbiome Interactions

Bidirectional interactions between host and microbiota shape gut homeostasis and cancer risk. The gut epithelium, mucosal immune system, and microbial communities form a dynamic interface. Microbial metabolites—short-chain fatty acids (SCFAs), secondary bile acids, and indole derivatives—modulate epithelial integrity, immune cell function, and signaling pathways implicated in cancer. Host genetics, diet, antibiotics, and xenobiotics further influence microbial composition and function [12]. Deciphering these interactions is key to understanding the microbiome's role in cancer biology.

Cancer-Specific Microbial Signatures

Recent high-throughput sequencing and functional studies have revealed that the gut microbiome harbors distinct alterations in composition—referred to as microbial signatures—across multiple cancer types. These signatures not only reflect disease status but may also drive or modulate oncogenic processes. Below, we critically examine cancer-specific gut microbiome signatures, emphasizing mechanistic and translational implications (Figure 2, Table 1).

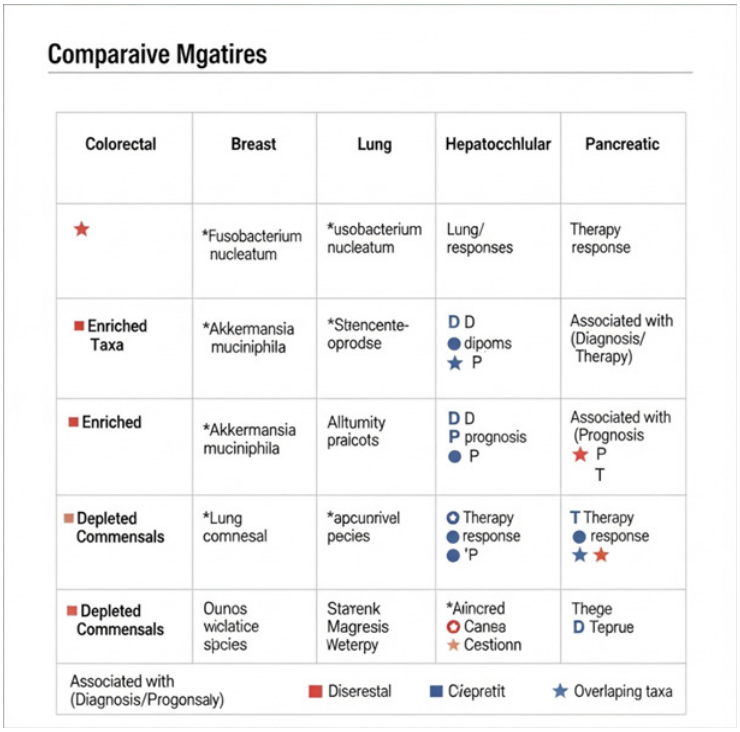

Figure 2: Cancer-Specific Gut Microbial Signatures Across Major Cancer Types.

Table 1: Key Gut Microbial Taxa Associated with Different Cancers

Cancer Type	Enriched Taxa	Depleted Taxa	Proposed Mechanisms	Clinical Relevance
Colorectal	*Fusobacterium nucleatum, Bacteroides fragilis, pks+ Escherichia coli, Peptostreptococcus*	*Faecalibacterium prausnitzii, Roseburia*	Inflammation (NF-κB, Th17), genotoxicity (colibactin), immune modulation	Diagnosis, prognosis, therapy response
Breast	*Clostridium spp., Bacteroides, Escherichia/ Shigella*	*Lachnospiraceae, Ruminococcaceae*	Estrogen metabolism (estrobolome), inflammation	Risk prediction, prognosis
Lung	*Streptococcus, Veillonella, Prevotella*	*Bifidobacterium, Faecalibacterium*	Immune modulation (gut–lung axis)	Prognosis, immunotherapy response
Hepatocellular	*Enterobacteriaceae, Streptococcus, Escherichia coli*	*Akkermansia muciniphila, Ruminococcaceae*	Inflammation, endotoxemia, liver fibrosis	Diagnosis, progression
Pancreatic	*Proteobacteria (e.g., Escherichia, Klebsiella), Fusobacterium, Porphyromonas*	Commensal diversity	Immune suppression, metabolic reprogramming	Prognosis, therapy response

1. Colorectal Cancer

Colorectal cancer (CRC) remains the most extensively studied malignancy in the context of the gut microbiome. Landmark metagenomic and metatranscriptomic studies have consistently identified a CRC-associated dysbiotic signature characterized by:

Enrichment of pro-oncogenic taxa:

- *Fusobacterium nucleatum*: Promotes tumorigenesis via invasion, E-cadherin/β-catenin signaling, and immune modulation [13,14].
- *Bacteroides fragilis*: Enterotoxigenic strains (ETBF) induce colitis and drive CRC through toxin-mediated DNA damage and Th17 responses [15].
- *Escherichia coli*: Certain strains harbor the polyketide synthase (pks) island, producing colibactin, a genotoxin linked to DNA damage [16].

Depletion of beneficial commensals:

- Butyrate producers such as *Faecalibacterium prausnitzii* and *Roseburia* spp., vital for maintaining epithelial integrity, are frequently reduced [17].

Mechanistically, these microbial shifts contribute to chronic inflammation, DNA damage, and immune evasion (see Section 6). Several meta-analyses and prospective cohort studies have validated the diagnostic utility of CRC-specific microbial signatures, supporting their integration into non-invasive screening strategies [18].

2. Breast Cancer

The gut microbiome's influence on breast cancer has gained attention through studies demonstrating altered microbial profiles in patients versus healthy controls:

Microbial shifts:

- Increased abundance of Clostridium spp., Bacteroides, and Escherichia/Shigella in patients [19].
- Reduced diversity and depletion of SCFA-producing bacteria, such as *Lachnospiraceae* and *Ruminococcaceae*.

Estrogen metabolism:

- The "estrobolome," a collection of microbial genes involved in estrogen metabolism, modulates systemic estrogen levels and may influence hormone-driven carcinogenesis [20].

Translational studies suggest that gut dysbiosis may alter systemic inflammation, estrogen recycling, and metabolic profiles, ultimately impacting breast cancer risk and progression. However, findings remain heterogeneous across populations and require further validation.

3. Lung Cancer

Emerging evidence links gut microbiome alterations to lung cancer incidence, prognosis, and therapeutic response (the so-called "gut–lung axis"):

Signature taxa:

- Elevated *Streptococcus*, *Veillonella*, and *Prevotella* spp. in lung cancer patients [21].
- Decreased *Bifidobacterium* and *Faecalibacterium*.

Mechanistic links:

- Microbial-derived metabolites and immune modulators can influence lung immune microenvironments, impacting tumorigenesis and resistance to immunotherapy [22].

Longitudinal clinical studies have begun to reveal that specific gut microbial compositions correlate with response rates to immune checkpoint inhibitors in lung cancer [23].

4. Hepatocellular Carcinoma

Chronic liver diseases, including cirrhosis and hepatitis, are established risk factors for hepatocellular carcinoma (HCC), with gut microbial dysbiosis implicated in this pathogenic continuum:

Dysbiosis features:

- Increased *Enterobacteriaceae*, *Streptococcus*, and *Escherichia coli* in HCC [24].
- Depletion of *Akkermansia muciniphila* and *Ruminococcaceae*.

Gut–liver axis:

- Microbial products (e.g., lipopolysaccharide) translocate due to increased intestinal permeability, activating hepatic inflammation and fibrogenesis [25].

Recent research highlights the predictive value of microbial signatures in distinguishing HCC from cirrhosis and in foreseeing disease progression [26].

5. Pancreatic Cancer

Pancreatic ductal adenocarcinoma (PDAC) exhibits a unique gut and intratumoral microbiome profile:

Microbial enrichment:

- Increased Proteobacteria (e.g., Escherichia, Klebsiella), and oral-origin taxa such as *Fusobacterium* and *Porphyromonas* [27].
- Reduced commensal diversity.

Clinical implications:

- Gut microbiota composition correlates with tumor immune infiltration and overall survival [28].

Notably, transplantation of "protective" microbiota from long-term survivors into murine models has demonstrated reduced tumor growth, underscoring the translational potential of microbiome-based interventions.

Mechanisms of Microbiome-Driven Tumorigenesis

The gut microbiome influences carcinogenesis through a network of interdependent pathways, involving modulation of inflammation, production of microbial metabolites, induction of DNA damage, and alteration of host immune responses (Figure 3, Table 2). This section critically synthesizes recent mechanistic insights, highlighting advances since 2019 and unresolved questions in the field.

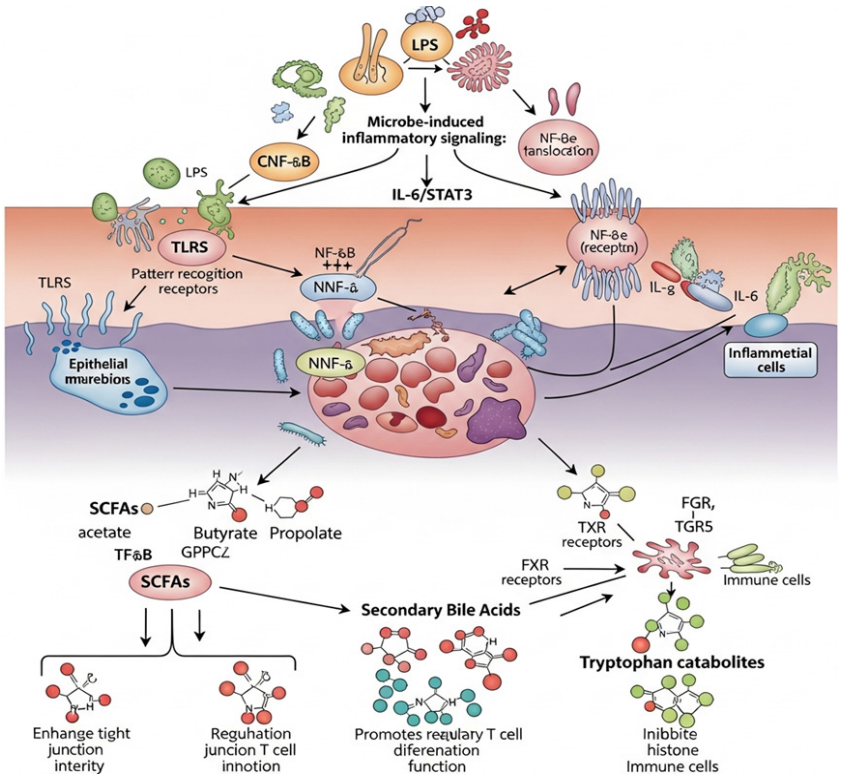

Figure 3: Molecular and Immune Pathways Linking Gut Microbiome to Tumorigenesis and Therapy Response.

Table 2: Major Microbial Metabolites and Cancer-Related Signaling Pathways.

Metabolite Class	Source Microbes	Major Metabolites	Host Signaling Pathway(s)	Net Impact on Tumorigenesis
Short-chain fatty acids (SCFAs)	*Faecalibacterium, Roseburia, Lachnospiraceae*	Butyrate, propionate, acetate	HDAC inhibition, GPR43/41 signalling, Treg induction	Anti-inflammatory, tumor suppression (context-dependent)
Secondary bile acids	*Clostridium spp., Bacteroides*	Deoxycholic acid, lithocholic acid	FXR, TGR5, DNA damage, oxidative stress	Pro-carcinogenic, DNA damage
Tryptophan metabolites	*Bacteroides, Clostridium, Lactobacillus*	Indole, indole-3-propionic acid, kynurenine	AhR activation, immune modulation	Tumor suppressive or promoting (context-dependent)
Polyamines	*Escherichia, Streptococcus*	Putrescine, spermidine	Cell proliferation, DNA stability	Tumorigenic (overproduction)
Hydrogen sulfide	*Desulfovibrio, Bilophila*	H2S	Mitochondrial function, DNA damage	Genotoxic, pro-carcinogenic

1. Inflammation

Chronic inflammation is a recognized hallmark of cancer, and the gut microbiome is a potent regulator of mucosal and systemic inflammatory signaling. Several mechanistic studies have elucidated the role of microbiota in activating key oncogenic pathways:

NF-κB Pathway:

Microbial dysbiosis can activate nuclear factor kappa B (NF-κB) signaling in epithelial and immune cells, promoting transcription of pro-inflammatory cytokines (e.g., TNF-α, IL-1β). *Fusobacterium nucleatum* and *Escherichia coli* have been shown to upregulate NF-κB in colorectal cancer models, driving tumorigenesis [29,30].

IL-6/STAT3 Axis:

Certain bacteria, such as enterotoxigenic *Bacteroides fragilis* (ETBF), induce IL-6 production, leading to activation of the signal transducer and activator of transcription 3 (STAT3). Persistent STAT3 signaling promotes proliferation, angiogenesis, and immune evasion [31].

Immune Cell Recruitment and Polarization:

Microbiota-driven chemokine and cytokine gradients recruit and polarize tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), and T helper (Th17) cells, creating a pro-tumorigenic microenvironment [32].

2. Microbial Metabolites

Gut microbes generate a diverse array of metabolites that exert profound effects on host signaling and tumorigenesis:

Short-Chain Fatty Acids (SCFAs):

SCFAs such as butyrate and propionate are produced by fermentation of dietary fibers by commensal bacteria (e.g., *Faecalibacterium, Roseburia*). Butyrate exhibits anti-inflammatory and anti-cancer properties by inhibiting histone deacetylases (HDACs) and supporting epithelial barrier integrity [33]. However, in the context of dysbiosis and cancer, reduced SCFA production may facilitate tumor progression.

Bile Acids:

The microbiota converts primary bile acids into secondary bile acids, some of which (e.g., deoxycholic acid) have been implicated in DNA damage, oxidative stress, and promotion of hepatocellular and colorectal carcinogenesis [34].

Tryptophan Metabolites:

Indole derivatives produced by microbial tryptophan metabolism can modulate aryl hydrocarbon receptor (AhR) signaling, influencing immune cell differentiation and cancer risk. Recent studies have highlighted the dual role of these metabolites in both tumor suppression and promotion depending on context [35].

3. DNA Damage and Immune Modulation

Genotoxic Bacteria:

Certain gut bacteria harbor virulence factors that directly induce DNA damage. Notably, E. coli strains with the pks genomic island produce colibactin, a genotoxin causing double-stranded DNA breaks, mutagenesis, and chromosomal instability in colonocytes [16,36]. Enterococcus faecalis produces reactive oxygen species (ROS) that contribute to genomic instability in colonic epithelium.

Immune Modulation:

The microbiome modulates both innate and adaptive immunity. Commensal-derived signals are essential for the development and function of mucosal immune cells. Conversely, dysbiosis can promote immune evasion by expanding regulatory T cells (Tregs) and suppressive myeloid populations, weakening anti-tumor immunity [37].

Tumor Microenvironment Reprogramming:

Microbial metabolites and inflammatory mediators reprogram the tumor microenvironment (TME), influencing immune infiltration, angiogenesis, and response to therapy. For instance, SCFA depletion and secondary bile acid accumulation are linked to reduced cytotoxic T cell activity and increased tumor-promoting inflammation [38].

4. Integrative Mechanistic Models

Recent multi-omic studies have integrated microbial profiling with host transcriptomics, metabolomics, and immune phenotyping to construct comprehensive models of microbiome-driven tumorigenesis. These integrative approaches have identified synergistic effects wherein dysbiosis, metabolite imbalance, and immune suppression converge to drive malignant transformation and progression (Figure 3).

Conflicting Evidence and Unresolved Questions:

Despite advances, important questions remain regarding causality versus correlation, context-dependent effects of specific metabolites (e.g., indoles), and the influence of host genetics and environmental factors on microbiome–cancer interactions [39]. Longitudinal and intervention studies are needed to clarify these relationships.

Gut Microbiome and Cancer Treatment Response

The gut microbiome's influence extends beyond cancer initiation and progression, playing a pivotal role in shaping responses to chemotherapy, immunotherapy, and radiotherapy. Recent studies have elucidated underlying mechanisms, identified predictive microbial signatures, and inspired translational strategies to modulate the microbiome for enhancing cancer treatment efficacy (Table 3).

1. Chemotherapy

Chemotherapeutic agents often alter gut microbiota composition, and, conversely, the microbiome can modulate chemotherapy outcomes via several mechanisms:

Microbial Metabolism of Drugs:

Certain gut bacteria can metabolize or inactivate chemotherapeutic agents. For example, *Gammaproteobacteria* have been shown to metabolize and inactivate gemcitabine, a standard-of-care drug for pancreatic cancer, thus conferring chemoresistance [40].

Microbiome-Mediated Toxicity:

Microbial β-glucuronidase activity may reactivate the toxic metabolite of irinotecan, leading to increased gastrointestinal toxicity [41].

Microbiome and Drug Efficacy:

Commensal bacteria can modulate host immune responses required for chemotherapy-induced tumor regression. *Alistipes* and *Akkermansia muciniphila* have been associated with improved efficacy of cyclophosphamide and platinum-based therapies through immune modulation [42].

2. Immunotherapy

The advent of immune checkpoint inhibitors (ICIs) has revolutionized cancer therapy. However, inter-individual variability in response remains a major challenge. The gut microbiome has emerged as a key determinant of ICI efficacy:

Predictive Microbial Signatures:

Multiple studies have shown that the presence of certain taxa (e.g., *Akkermansia muciniphila, Bifidobacterium longum, Faecalibacterium prausnitzii*) is associated with enhanced responses to anti-PD-1/PD-L1 immunotherapy in melanoma, lung, and renal cell carcinoma [43,44].

Mechanistic Insights:

These bacteria promote antigen presentation, T cell recruitment, and activation within the tumor microenvironment. Fecal microbiota transplantation (FMT) from ICI responders into germ-free mice confers increased therapeutic benefit compared to FMT from non-responders [45].

Microbiome-Immune Crosstalk:

Microbial metabolites, including SCFAs and tryptophan catabolites, modulate the differentiation and function of tumor-infiltrating lymphocytes and regulatory T cells (Tregs), influencing immunotherapy outcomes [46].

Adverse Effects:

Certain dysbiotic profiles may predispose patients to immune-related adverse events (irAEs) during ICI therapy, underscoring the dual impact of the microbiome on efficacy and toxicity [47].

3. Radiotherapy

Radiotherapy can disrupt the gut microbiota, leading to mucositis and increased infection risk. Conversely, the baseline microbiome composition influences both the anti-tumor efficacy and toxicity profile of radiotherapy:

Microbiome and Radiotherapy Efficacy:

Commensal bacteria modulate local and systemic immune responses needed for radiotherapy-induced tumor control. Mice with depleted microbiota exhibit worse tumor control after irradiation, highlighting the microbiome's role in mediating radiotherapy efficacy [48].

Radioprotective and Radiosensitizing Effects:

Certain taxa (e.g., *Lactobacillus* spp.) demonstrate radioprotective properties by enhancing barrier integrity and reducing inflammation, whereas dysbiosis may increase susceptibility to radiation-induced injury [49].

Clinical Translation:

Early-phase clinical studies are evaluating probiotics, prebiotics, and FMT as adjuncts to reduce radiotherapy-related gastrointestinal toxicity and improve outcomes [50].

Table 3: Influence of Gut Microbiome on Cancer Treatment Outcomes and Therapeutic Strategies.

Treatment Modality	Key Microbial Influences	Microbiome-Driven Mechanisms	Translational Strategies
Chemotherapy	*Gammaproteobacteria, Akkermansia, Alistipes*	Drug metabolism, immune modulation, toxicity	Microbiome modulation to reduce toxicity, enhance efficacy
Immunotherapy	*Akkermansia, Bifidobacterium, Faecalibacterium*	Antigen presentation, T cell activation, irAEs	FMT, probiotics, targeted antibiotics
Radiotherapy	*Lactobacillus,* diverse commensals	Barrier integrity, immune modulation	Probiotics, prebiotics, FMT

Therapeutic Opportunities and Clinical Translation

The growing understanding of the gut microbiome's role in cancer development and therapy has galvanized interest in microbiota-targeted interventions. Multiple strategies are being explored to modulate the gut microbiota, aiming to prevent oncogenesis, enhance treatment efficacy, and reduce adverse effects. Here, we discuss current and emerging therapeutic avenues, along with translational challenges and opportunities.

1. Microbiome Modulation Strategies

1.1. Probiotics and Prebiotics

Probiotics—live microorganisms that confer health benefits—have been studied for their potential to restore microbial balance, enhance immune responses, and mitigate treatment-related toxicity. Recent randomized controlled trials have demonstrated that specific probiotic strains (e.g., *Lactobacillus rhamnosus GG*) can reduce chemotherapy- and radiotherapy-induced gastrointestinal side effects [51]. Prebiotics, such as inulin and resistant starch, promote the growth of beneficial commensals and increase SCFA production, contributing to anti-inflammatory and anti-cancer effects.

1.2. Dietary Interventions

Diet is a primary determinant of gut microbiome composition and function. Diets rich in fiber, polyphenols, and fermented foods are associated with increased microbial diversity and butyrate-producing bacteria, which may reduce cancer risk and improve therapeutic responses [52]. Ongoing clinical studies are assessing the impact of personalized dietary interventions on microbiome composition and treatment outcomes in cancer patients [53].

1.3. Fecal Microbiota Transplantation (FMT)

FMT involves the transfer of stool from a healthy donor to a patient, with the aim of restoring microbial balance. Several early-phase clinical trials have demonstrated that FMT from immunotherapy responders can confer sensitivity to checkpoint inhibitors in refractory melanoma, non-small cell lung cancer, and renal cell carcinoma [45,54]. FMT is also being explored to mitigate treatment-related toxicities, though optimal protocols and donor selection remain to be standardized.

1.4. Engineered Microbiota and Next-Generation Biotherapeutics

Advances in synthetic biology have enabled the design of engineered bacteria for targeted delivery of therapeutic molecules, immune modulation, and tumor-specific colonization [55]. Preclinical studies of engineered *Escherichia coli* and *Lactococcus lactis* strains show promise for delivering anti-inflammatory cytokines, checkpoint inhibitors, or cytotoxic agents directly to the tumor microenvironment [56]. Clinical translation will require rigorous safety assessment and regulatory oversight.

2. Microbiome-Based Biomarkers

Integrating microbiome-derived biomarkers into clinical practice holds promise for improving cancer screening, risk stratification, and predicting therapeutic response. Non-invasive diagnostic assays leveraging fecal microbial and metabolomic profiles are under development for early detection of colorectal and other gastrointestinal cancers [18,57]. Predictive microbiome signatures are being validated in prospective trials to guide immunotherapy selection and monitor response [44,58].

3. Challenges in Clinical Translation

Despite significant progress, several challenges remain:

Inter-individual Variation:

Microbiome composition is highly personalized, influenced by host genetics, environment, diet, and comorbidities. This complexity complicates the development of universal interventions and biomarkers.

Causality vs. Correlation:

Distinguishing whether observed microbial changes are causal or consequential to cancer remains difficult, necessitating rigorous longitudinal and interventional studies.

Standardization and Safety:

There is a need for standardized protocols for microbiome sampling, sequencing, and analysis. Safety concerns, particularly with FMT and engineered bacteria, warrant ongoing monitoring and regulatory guidance.

4. Clinical Trials and Future Directions

A growing number of interventional trials are underway across cancer types, evaluating dietary, probiotic, prebiotic, and FMT interventions alone or in combination with standard therapy. Multi-omic approaches integrating metagenomics, metabolomics, and host immune profiling are expected to yield actionable insights for precision oncology [59].

Challenges, Knowledge Gaps, and Future Perspectives

Despite substantial advances, the integration of the gut microbiome into precision oncology faces significant obstacles and unresolved questions. Addressing these gaps is critical for translating research findings into impactful clinical interventions.

1. Major Challenges

1.1. Inter-individual and Population-Level Microbiome Variation

Inter-individual variability in microbiome composition, driven by genetics, diet, geography, antibiotic exposure, and comorbidities, presents a formidable challenge for developing universally applicable microbial biomarkers and interventions [60]. Population-specific microbial signatures may limit the generalizability of findings across diverse cohorts, underscoring the need for large, multi-ethnic, and longitudinal studies.

1.2. Causality versus Correlation

A central unresolved question is the causal role of specific microbes or community structures in carcinogenesis and therapy response. While numerous associations have been described, definitive demonstration of causality in humans remains rare, largely due to ethical and methodological constraints. The use of advanced gnotobiotic models, longitudinal human cohorts, and interventional trials will be key for disentangling cause-effect relationships [61].

1.3. Conflicting and Heterogeneous Evidence

Heterogeneity in study design, sequencing technologies, bioinformatic pipelines, and statistical analyses contributes to variable and sometimes conflicting results. Standardization of methodologies, rigorous validation in independent cohorts, and transparent data sharing are urgently needed to resolve discrepancies and strengthen the evidence base [62].

1.4. Safety and Regulation of Therapeutic Interventions

Microbiome-targeted therapies, especially FMT and engineered bacterial therapeutics, raise concerns regarding safety, long-term consequences, and regulatory oversight. Adverse events, including the transmission of drug-resistant organisms via FMT, have been reported, prompting the development of stricter screening protocols and regulatory guidance [63].

2. Knowledge Gaps

2.1. Mechanistic Insights

While significant mechanistic advances have been made, the specific pathways through which individual microbes or metabolites modulate tumorigenesis and therapy response remain incompletely understood. The context-dependent effects of microbial metabolites, such as indole derivatives and bile acids, pose particular challenges for therapeutic targeting [35,64].

2.2. Microbiome–Drug–Host Interactions

The complex interplay between microbiome, pharmacology, and host immunity is only beginning to be unraveled.

How microbiome-mediated drug metabolism, immune modulation, and host genetics interact to shape cancer outcomes warrants further investigation, ideally using integrated multi-omics and systems biology approaches [65,66].

2.3. Microbiome Beyond Bacteria

Most studies to date have focused on bacterial communities, but the roles of fungi (mycobiome), viruses (virome), and archaea in cancer biology remain underexplored. These non-bacterial components may play critical roles in modulating host immunity, inflammation, and therapeutic response [67].

3. Future Perspectives

3.1. Multi-Omic and Personalized Approaches

Future research will benefit from integrating metagenomics, metabolomics, transcriptomics, and host genetic/immune profiling to develop personalized microbiome-based interventions and predictive biomarkers. Machine learning and artificial intelligence hold promise for extracting clinically actionable insights from complex, multi-layered datasets [68,69].

3.2. Rational Design of Microbiome-Targeted Therapies

The rational design of next-generation probiotics, synbiotics, and engineered bacteria offers opportunities for precise modulation of tumorigenic pathways and immune responses. Synthetic biology, combined with targeted delivery platforms, may enable the safe and effective deployment of these interventions in the clinic [55,70].

3.3. Clinical Implementation and Policy

Translating microbiome science into clinical practice will require multidisciplinary collaboration among oncologists, microbiologists, dietitians, and regulatory agencies. Development of evidence-based guidelines, robust clinical trials, and regulatory frameworks will be essential to ensure safety and efficacy [71].

3.4. Education and Patient Engagement

Educating healthcare providers and patients about the potential and limitations of microbiome-based interventions is crucial to avoid misinformation and ensure informed decision-making. Shared decision-making and patient-centered approaches will enhance the acceptance and effectiveness of microbiome-targeted strategies.

Conclusion

The gut microbiome has emerged as a dynamic and integral player in cancer biology, influencing tumor initiation, progression, and patient responses to therapy. The identification of cancer-specific microbial signatures and elucidation of mechanistic pathways ranging from inflammation and metabolite production to immune modulation have transformed our understanding of oncogenesis and provided new avenues for diagnosis and intervention. Recent advances underscore the microbiome's potential to predict and improve responses to chemotherapy, immunotherapy, and radiotherapy, while also revealing promising strategies for therapeutic modulation.

However, significant challenges remain, including inter-individual variability, lack of causality in most human studies, safety concerns, and the need for standardized methodologies. Addressing these issues will require robust, multi-center, longitudinal studies, integration of multi-omic approaches, and interdisciplinary collaboration. Ultimately, leveraging the gut microbiome for cancer prevention, prognosis, and therapy is a realistic and exciting frontier in precision oncology, with the potential to improve outcomes and quality of life for cancer patients worldwide.

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