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Review

Tumor Microecology: From a Bystander Phenomenon to an Intervenable Therapeutic Niche

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Abstracts

The microbiome has emerged as a fundamental modifier of host immunity, metabolism, tissue homeostasis, therapeutic responsiveness and treatment-related toxicity. In oncology, accumulating evidence indicates that microorganisms are not merely passive bystanders or infectious complications, but active ecological determinants of tumor development, immune surveillance, treatment response and adverse events. The concept of tumor microecology extends beyond the gut microbiome and includes intratumoral microorganisms, microbial metabolites, mucosal barrier integrity and tissue-specific immune niches. This Commentary discusses the evolving role of microbial ecosystems in cancer biology, with particular attention to cancer immunotherapy, intratumoral microbiota and hematologic malignancies. We propose that future cancer microbiome research should move from descriptive association studies toward mechanism-defined, clinically actionable ecological interventions. Rather than searching for universal “beneficial bacteria,” the field should focus on microbial functions, host context, longitudinal dynamics, methodological rigor and safety-controlled translational strategies.

Keywords: tumor microecology; microbiome; cancer immunotherapy; intratumoral microbiota; bone marrow niche; multiple myeloma; microbial metabolites

1. Introduction

Cancer has traditionally been understood through the lens of malignant genetic alterations, dysregulated signaling pathways and cell-autonomous survival advantages. This view has been substantially expanded by the concept of the tumor microenvironment, which emphasizes the contribution of immune cells, stromal cells, endothelial cells, extracellular matrix and soluble mediators to tumor progression and therapeutic resistance. A further conceptual expansion is now taking place: tumors should be considered not only as cellular and molecular systems, but also as ecological systems influenced by microbial communities and their functional outputs.

The microbiome is increasingly recognized as an essential regulator of host physiology. Microorganisms and their metabolites shape immune maturation, mucosal barrier integrity, systemic inflammatory tone and metabolic homeostasis. In cancer, microbial ecosystems may influence carcinogenesis, metastatic progression, immune escape, treatment sensitivity, drug metabolism and treatment-related toxicity (1-3). Importantly, cancer microbiome research has moved beyond descriptive profiling. Recent translational studies and clinical trials have begun to evaluate microbiome-directed interventions, including fecal microbiota transplantation, diet-based modulation and defined microbial or metabolic strategies, particularly in patients receiving immune checkpoint inhibitors (4-8).

These developments raise a central question: should the microbiome be viewed merely as a biomarker of therapeutic response, or as an actionable component of cancer treatment? This Commentary argues that the next stage of tumor microecology research should shift from cataloging microbial differences to defining microbial functions and therapeutic mechanisms. This transition is particularly important for hematologic malignancies, where the bone marrow niche, systemic immunity, infection risk and microbial metabolites are closely intertwined.

2. Tumor Microecology Is More Than the Gut Microbiome

The term “tumor microecology” should not be reduced to the gut microbiome alone. At least three interconnected layers should be considered.

The first layer is the intestinal microbiome. The gut contains a dense and metabolically active microbial ecosystem that can influence distant tumors through immune, metabolic and endocrine pathways. Gut microorganisms regulate antigen-presenting cells, T cell differentiation, regulatory T cell balance, myeloid cell function and systemic cytokine profiles. These effects provide a mechanistic basis for the observed associations between gut microbiota and responses to immune checkpoint blockade.

The second layer is the intratumoral microbiome. Multiple studies have detected bacteria, fungi or microbial signatures within tumor tissues. Nejman and colleagues reported that human tumors contain tumor type-specific intracellular bacteria, with microbial signals detectable in both cancer cells and immune cells (11). In pancreatic cancer, tumor microbiome diversity and composition have been linked to long-term survival and immune infiltration (12). More recent studies have further emphasized that tumor-associated microbes may differ not only at the species level but also at the strain or clade level. For example, a distinct Fusobacterium nucleatum clade, Fna C2, has been shown to dominate the colorectal cancer niche and exhibit features of gastrointestinal pathoadaptation (13). These observations suggest that local microbial communities may participate directly in shaping the tumor immune microenvironment and therapeutic response.

The third layer is the tissue-specific ecological niche. In many cancers, microbial effects are mediated not by direct bacterial colonization of tumor tissue, but by systemic ecological remodeling. The gut microbiome can alter circulating metabolites, inflammatory mediators and immune cell trafficking, thereby changing the permissiveness of distant tissue

niches. This concept is especially relevant for hematologic malignancies, where tumor cells reside in immune-rich and metabolically active environments such as bone marrow, lymph nodes and peripheral blood.

Therefore, tumor microecology should be defined broadly as the dynamic interaction among microorganisms, microbial products, host immunity, metabolism and tissue niches that collectively influence tumor behavior.

3. Microbial Regulation of Cancer Immunotherapy

Immune checkpoint inhibitors have transformed the treatment landscape of multiple cancers, yet only a subset of patients achieve durable benefit. The microbiome has emerged as one contributor to this interpatient heterogeneity. Cross-cohort metagenomic analyses in advanced melanoma confirmed that gut microbial features are associated with immune checkpoint inhibitor response, but also demonstrated that species-level signatures are not universally reproducible across cohorts (4). This finding challenges the oversimplified idea that a single “good bacterium” or “bad bacterium” can predict immunotherapy outcome across populations.

Mechanistically, microbiota may influence immunotherapy through several pathways. First, microbial antigens and pattern-recognition signals can promote dendritic cell maturation and T cell priming. Second, microbial metabolites such as short-chain fatty acids, bile acid derivatives and tryptophan metabolites can regulate T cell differentiation and effector function. Third, microbiota may alter the balance between antitumor immunity and immune-related toxicity. Fourth, antibiotic exposure may disrupt beneficial microbial communities and weaken immunotherapy efficacy.

Recent clinical studies have strengthened the translational relevance of microbiome modulation. In previously untreated advanced melanoma, fecal microbiota transplantation combined with anti-PD-1 therapy was feasible and showed encouraging antitumor activity in a phase I study (6). More recently, the phase 2 FMT-LUMINate trial extended this approach to first-line treatment settings in non-small cell lung cancer and melanoma (7). A 2025 meta-analysis also provided preliminary evidence supporting the combination of fecal microbiota transplantation and immune checkpoint inhibitors, while emphasizing the need for larger randomized trials and better patient stratification (8).

Together, these studies suggest that microbiome modulation is no longer merely a theoretical concept. However, they also highlight the complexity of translating microbial ecology into oncology practice. The next challenge is to determine which patients should receive microbiome modulation, which microbial functions should be targeted, and which intervention is safest and most reproducible.

4. Microbial Metabolites as Functional Bridges

A major limitation of taxonomic microbiome studies is that bacterial names do not necessarily explain biological function. The same species may behave differently across hosts, diets, anatomical sites and treatment contexts. Therefore, microbial metabolites may provide a more stable mechanistic bridge between microbial ecology and antitumor immunity.

Short-chain fatty acids, tryptophan metabolites, bile acid derivatives, polyamines and other microbial products can influence immune cell differentiation, epigenetic regulation and inflammatory tone. In 2024, Jia and colleagues reported that the microbial tryptophan metabolite indole-3-propionic acid enhanced immune checkpoint blockade efficacy by modulating CD8+ T cell stemness in pan-cancer models (9). In 2025, Bachem and colleagues further showed that microbiota-derived butyrate promotes a FOXO1-dependent stemness program and preserves CD8+ T cell immunity against melanoma (10). These findings suggest that the therapeutic value of the microbiome may depend less on the presence of a particular bacterial species and more on conserved metabolic functions that shape antitumor immunity.

This concept is especially important for clinical

translation. It may be easier to standardize and monitor a defined metabolic output than to reproduce an entire microbial ecosystem across individuals. Metabolite-centered strategies may also offer better safety control than live microbial products in immunocompromised patients. However, microbial metabolites are not universally beneficial. Their biological effects depend on concentration, anatomical context, immune status and tumor type. Thus, metabolite-based interventions require the same mechanistic rigor as microbial interventions.

5. Intratumoral Microbiota: Biological Signal or Technical Noise?

Intratumoral microbiome research is one of the most exciting yet technically challenging areas in tumor microecology. Tumor tissues often contain low microbial biomass, making them highly vulnerable to contamination from reagents, instruments, sampling procedures and sequencing pipelines. Therefore, rigorous negative controls, spatial validation and orthogonal detection methods are essential.

Despite these challenges, several studies support the biological relevance of intratumoral microorganisms. In pancreatic ductal adenocarcinoma, microbial diversity within tumors has been associated with long-term survival and immune activation (12). In colorectal cancer, strain-level analysis has revealed that Fna C2, a distinct clade of Fusobacterium nucleatum subspecies animalis, is enriched in the colorectal cancer niche and carries genetic features consistent with gastrointestinal adaptation (13). Interestingly, another recent study suggested that F. nucleatum may, under specific contexts, facilitate anti-PD-1 efficacy in microsatellite-stable colorectal cancer through butyrate-associated modulation of CD8+ T cell exhaustion (14). These apparently paradoxical findings reinforce a key point: microbial effects in cancer are context-dependent and may vary according to strain, tumor type, immune state and metabolic output.

At the same time, intratumoral microbiome studies require exceptional methodological rigor. A recent Perspective in Nature Cancer called for higher standards in reports of microbial species in human cancers, including improved contamination control, negative controls, spatial validation, careful interpretation of sequencing reads and awareness of reference genome contamination (19). This is a critical message for the field. Without rigorous validation, tumor microbiome research risks overinterpreting computational signals. With rigorous methodology, however, intratumoral microbiota may become a new dimension of precision oncology.

The key question is no longer simply whether microbes are present in tumors, but whether they are functionally active and clinically meaningful. Future studies should address several issues: Are intratumoral microbes alive or residual microbial DNA? Are they located within cancer cells, immune cells, stromal compartments or necrotic regions? Do they drive tumor progression or merely reflect local tissue conditions? Can they be targeted safely without disrupting beneficial systemic microbiota?

Answering these questions requires integration of spatial transcriptomics, imaging-based microbial detection, microbial culture, single-cell profiling, metabolomics and functional animal models.

6. Hematologic Malignancies and the Bone Marrow Ecological Niche

Most microbiome-oncology studies have focused on solid tumors, but hematologic malignancies may be particularly sensitive to microbial regulation. These diseases arise within immune and hematopoietic organs, where systemic inflammation, microbial metabolites, mucosal barrier damage and infection risk can profoundly influence disease behavior.

Multiple myeloma provides a useful example. Myeloma cells depend on the bone marrow microenvironment for survival, proliferation and drug resistance. Bone marrow stromal cells, osteoclasts, osteoblasts, endothelial cells, T cells,

myeloid cells and cytokines collectively form a protective niche. The gut microbiome may influence this niche through metabolites and immune cell trafficking. Microbiota-driven interleukin-17-producing cells have been implicated in accelerating myeloma progression in experimental models (16). More recently, microbiome modulation with Prevotella melaninogenica or butyrate was shown to delay myeloma progression and improve the balance between immune checkpoint blockade efficacy and toxicity in mouse models (17).

These findings are especially relevant because immune-based therapies are rapidly changing the management of plasma cell dyscrasias. CAR-T cells, bispecific antibodies, monoclonal antibodies and immunomodulatory agents all depend on a functional immune system, yet patients with myeloma frequently experience immune suppression, recurrent infections and treatment-related immune exhaustion. The microbiome may therefore influence both antitumor immunity and treatment safety.

The bone marrow niche should be studied as an ecological system rather than a passive anatomical site. In this system, microbial metabolites such as short-chain fatty acids may alter dendritic cell function, T cell polarization, myeloid inflammation and stromal cell behavior. Such effects may be particularly important in premalignant stages such as monoclonal gammopathy of undetermined significance and smoldering myeloma, where ecological intervention might delay disease progression before irreversible immune dysfunction occurs.

Microbiome research is also relevant to hematopoietic stem cell transplantation. Gut microbiota composition has been associated with infection risk, graft-versus-host disease and mortality after allogeneic transplantation (18). This further supports the idea that microbial ecosystems are clinically meaningful determinants of hematologic outcomes.

7. From Empirical Supplementation to Mechanism-Defined Intervention

A major risk in the current enthusiasm for microbiome-based therapy is premature clinical simplification. The idea that cancer patients can benefit from nonspecific probiotics or empirical “microbiome improvement” is scientifically inadequate and potentially unsafe. This is particularly true for immunocompromised patients, including those with hematologic malignancies, intensive chemotherapy, transplantation or mucosal barrier injury.

Microbiome intervention should be developed according to several principles.

First, the target population must be defined. Not all patients require microbiome modulation. Baseline microbiome composition, dietary pattern, antibiotic exposure, immune status, cancer type and treatment modality may all influence whether intervention is beneficial.

Second, the therapeutic objective must be clear. Microbiome modulation may aim to enhance immunotherapy efficacy, reduce immune-related adverse events, prevent infection, support immune reconstitution or delay disease progression. These endpoints require different designs and biomarkers.

Third, the intervention should target function rather than taxonomy alone. A bacterial species may be beneficial in one ecological context and neutral or harmful in another. Functional outputs such as short-chain fatty acid production, bile acid metabolism, antigenic mimicry, mucosal barrier repair or dendritic cell modulation may be more relevant than species abundance.

Fourth, safety must be central. Fecal microbiota transplantation, live biotherapeutic products, engineered bacteria and defined microbial consortia all carry potential risks, including pathogen transmission, bacteremia, horizontal transfer of antimicrobial resistance genes and unpredictable immune activation. These risks are magnified in cancer patients with neutropenia or impaired mucosal integrity.

Finally, microbiome trials should include

mechanistic endpoints. Clinical response alone is insufficient. Trials should measure microbial engraftment, strain-level persistence, metabolomic changes, immune cell states, tumor microenvironment alterations and treatment-related toxicity. Only mechanism-rich trials can distinguish true ecological causality from correlation.

8. Methodological Priorities for the Next Stage

To mature as a translational field, tumor microecology must overcome several methodological limitations.

Longitudinal sampling is essential. The microbiome is dynamic and can be altered by diet, antibiotics, chemotherapy, immunotherapy, hospitalization and infection. A single baseline stool sample cannot capture the full ecological trajectory of treatment.

Multi-omics integration is also necessary. 16S rRNA sequencing provides limited functional resolution. Shotgun metagenomics, metatranscriptomics, metabolomics, immune profiling, single-cell sequencing and spatial analysis should be integrated to identify microbial functions linked to host biology.

Cohort diversity must be improved. Diet, geography, ethnicity, medication exposure and healthcare systems strongly influence the microbiome. Biomarkers discovered in one population may not generalize to another.

Causality must be tested experimentally. Germ-free animals, antibiotic-treated models, defined bacterial consortia, metabolite supplementation and humanized microbiome models remain important tools. However, animal models should be interpreted cautiously because murine microbiota and immune systems do not fully recapitulate human disease.

Standardization is critical. Sample collection, storage, DNA extraction, sequencing depth, contamination control, bioinformatic pipelines and statistical adjustment should be harmonized. Without standardization, cross-study comparison will remain difficult. This is particularly important for low-biomass tumor microbiome studies, where false-positive microbial signals may arise from sampling, processing, sequencing or database contamination (19).

9. Conclusion

Tumor microecology reframes cancer as an ecological disease shaped by malignant cells, host immunity, stromal niches, metabolism and microbial ecosystems. This perspective does not replace genetic and immunological models of cancer; rather, it extends them. The microbiome can influence cancer therapy through immune education, metabolic signaling, barrier regulation, local tumor colonization and tissue niche remodeling.

The field should now move beyond descriptive associations. The most important future advances will come from identifying microbial functions that are mechanistically linked to tumor behavior and therapeutically actionable. In solid tumors, this may involve improving immunotherapy responsiveness or overcoming resistance. In hematologic malignancies, it may involve reshaping the bone marrow immune niche, reducing infection risk and improving immune-based therapies.

Ultimately, microbiome-based oncology should not be built on the notion of adding “beneficial bacteria” indiscriminately. It should be developed as a precise ecological medicine: mechanism-defined, patient-stratified, dynamically monitored and safety-controlled. If achieved, tumor microecology may become an important pillar of next-generation precision cancer therapy.

Declaration

Consent to publication

Not applicable.

Ethical approval and consent to participants

Not applicable.

Disclosure of conflict of interests

The author declare that no competing interest exists.

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5) ***Availability of data and material***

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