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Tumor Microenvironment EDITORIAL

New framework for precision clinical translation of gut microbiota in cancer: From individual variation to functional universality

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The gut microbiota has emerged as a critical modulator of tumor biology and antitumor immunity, yet its clinical translation has been persistently frustrated by one fundamental problem: inter-individual compositional variability so profound that biomarkers and therapeutic strategies defined in one cohort frequently fail to generalize to another.[1] Here, we argue that resolving this impasse requires two complementary paradigm shifts, including recognizing that compositional heterogeneity is governed by conserved ecological organization principles embodied in a "core functional microbiota," and redirecting mechanistic inquiry from microbial taxonomy toward the effector molecules through which the microbiota enacts its influence on distant tumors (Figure 1).

THE PARADOX OF VARIABILITY: FUNCTIONAL UNIVERSALITY BENEATH COMPOSITIONAL CHAOS

At the species level, fewer than 20% of gut bacteria are shared across unrelated individuals, and composition fluctuates substantially with diet, antibiotics, and aging. This profound inter-individual variability, coupled with the intrinsic dynamics of the gut microbiota over time within the same individual, has fueled persistent skepticism. If no two people share the same microbial community, and even a single person's community is subject to constant fluctuation, on what basis can the microbiota be considered a reproducible therapeutic target?

The frustration is not merely academic. Multiple landmark studies in checkpoint immunotherapy have identified putative "responder-associated" taxa including *Akkermansia muciniphila*, *Faecalibacterium prausnitzii*, *Bifidobacterium* species, while independent cohort validation has yielded inconsistent, often contradictory results.[2] A species enriched in responders in one population may be virtually absent in another, not because the biology differs, but because the ecological context does. The result is a graveyard of microbiota biomarkers that validated brilliantly in discovery and failed in replication.

We argue that this limitation stems not from the absence of microbiota-cancer relationships, but from an inappropriate unit of analysis. Focusing on species abundance is analogous to predicting ecosystem productivity by counting individual tree species rather than measuring the balance of producers, consumers, and decomposers. Macroecology established long ago that species composition can vary enormously across habitats without undermining functional organization: a boreal forest and a tropical rainforest share virtually no species, yet both maintain recognizable trophic structures because functional guilds reflect thermodynamic constraints more fundamental than species identity.

An analogous principle operates in the gut. Metagenomic surveys across diverse populations reveal that, while species-level composition is highly individualized, the representation of broad functional metabolic guilds such as butyrate-producing fermenters, bile acid-metabolizing bacteria, and proteolytic bacteria putrefies is considerably more conserved and more predictably disrupted in disease. This convergence at the functional level, even amid species-level divergence, suggests that functional guild structure is the evolutionarily conserved variable that the host metabolic and immune system co-evolved to sense and respond to.

We therefore propose expanding the "core microbiota" concept to cancer diagnosis and treatment, to move the focus from a species-level checklist to a functional guild-level equilibrium. This functional core minimizes population-specific limitations that reflect conserved constraints based on certain disease types, beyond diverse ethnic, dietary, and geographic contexts.[3] Two broadly opposing functional consortia define this balance. The first is characterized by dietary fiber fermentation, producing short-chain fatty acids (SCFAs) and immunomodulatory metabolites that sustain intestinal barrier integrity, promote regulatory T cell differentiation, and dampen systemic inflammation. The second is enriched for proteolytic, genotoxin-producing, and pro-inflammatory activities, generating metabolites associated with chronic inflammation, metabolic dysfunction, and epithelial DNA damage. The relative dominance of these two poles, a seesaw equilibrium, may more reliably shape immunological and oncological trajectory than any individual taxon.[3] Critically, because this framework is defined at the functional rather than taxonomic level, it is robust to the inter-individual compositional noise that has confounded species-level approaches. While this concept shares conceptual ground with prior notions of functional redundancy and core microbiome functions, it differs by explicitly operationalizing guild balance as a quantifiable, clinically actionable metric rather than a descriptive ecological property.

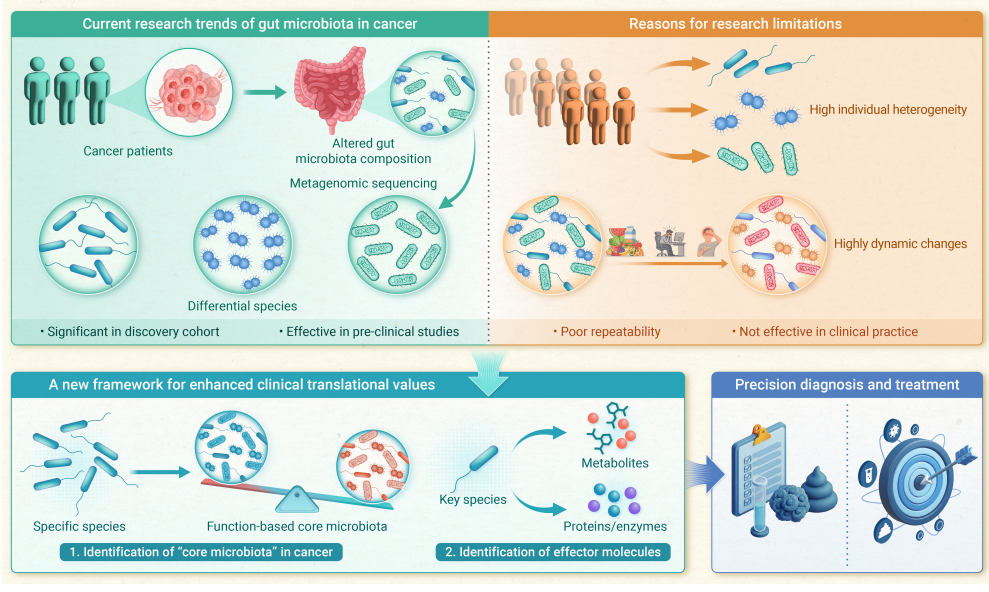

Figure 1. A new framework for precision clinical translation of gut microbiota in cancer Clinical translation of the gut microbiota has been hindered by profound inter-individual compositional variability, which causes biomarkers and therapeutic strategies to fail across populations. This figure illustrates two complementary paradigm shifts to resolve this impasse.

EFFECTOR MOLECULES: THE PROXIMAL MEDIATORS OF MICROBIOTA-TUMOR CROSSTALK

Even accepting the functional guild framework, a mechanistic gap remains: through what physical entities does the gut microbiota influence tumors at distant anatomical sites? Microorganisms themselves rarely translocate beyond the intestinal compartment under homeostatic conditions. Evidence increasingly shows that the microbiota regulates systemic immunity and the tumor microenvironment mainly through the small molecules and secreted proteins it produces. This effector-centered perspective extends beyond the established postbiotics concept by integrating metabolites, microbial enzymes, secreted proteins, and extracellular vesicles (EVs) into a unified mechanistic framework directly linked to tumor biology. These effectors are absorbed into the circulation, that shift from organisms to molecules provides a conceptual bridge between microbiota biology and conventional pharmacology.

Among microbiota-derived effectors, small-molecule metabolites act through distinct but complementary mechanisms. SCFAs suppress inflammatory gene expression, induce peripheral Tregs, and enhance tumor-infiltrating lymphocyte cytotoxicity via G-protein-coupled receptors and histone deacetylase inhibition. Secondary bile acids and tryptophan-derived indole metabolites further modulate antitumor immunity through Farnesoid X Receptor (FXR)/Takeda G-protein coupled receptor 5 (TGR5) and aryl hydrocarbon receptor signaling, respectively. Our previous work additionally demonstrated that microbiota-derived riboflavin (also known as Vitamin B2) suppresses tumor proliferation through host metabolic reprogramming.[4] A key insight is that systemic metabolic and immunological tone is continuously calibrated by the aggregate metabolite output of the gut community. This provides a pharmacological rationale for quantitative, dose-controlled metabolite supplementation strategies that bypass compositional variability entirely.

Beyond small molecules, bacteria produce many active protein effectors and microbial-specific enzymes that directly interact with host cell biology through multiple mechanisms. Secreted enzymes can reshape the extracellular signaling environment and directly modify drug molecules, potentially altering therapeutic responsiveness. Contact-dependent systems including type III and type VI secretion apparatuses deliver effector proteins into the host cytoplasm to control intracellular regulatory networks. Commensal-derived proteins, whether secreted or vesicle-associated, can further regulate immune checkpoint expression on tumor cell surfaces through innate immune signaling. This modulates the visibility of cancer cells to the immune system without requiring direct contact. Other bacterial protein effectors have pore-forming or membrane-remodeling activities that allow them to enter cells and affect epigenetic regulation, shifting the balance between pro-oncogenic and tumor-suppressive gene programs.[3] These findings show that commensal organisms, normally considered harmless background flora, are sources of protein effectors that can influence tumor cell fate. They also establish bacterial proteins emerging as mechanistic targets with translational potential in oncology.

CLINICAL TRANSLATION: FROM PARADIGM TO PIPELINE

Rethinking diagnosis and stratification.

The core functional microbiota model redefines what a clinically useful microbiota measurement looks like. Rather than cataloguing species abundances, the relevant readout becomes the ratio of functional guild activities, which is assessable through metagenomic functional annotation, plasma and stool metabolomics, and targeted microbial proteomics. Integrating large-scale datasets encompassing core microbial composition, key microbiota-derived metabolites, and bacterial protein effectors into AI-driven predictive algorithms could enable the construction of next-generation models for cancer risk stratification, prognostic assessment, and immunotherapy response prediction, which are biologically grounded and cross-population generalizable in ways that species-level biomarkers cannot achieve. While metabolomic profiling is increasingly feasible in clinical research settings, microbial proteomic assays remain largely investigational and will require further standardization and validation before routine clinical deployment.

Rethinking intervention.

Fecal microbiota transplantation (FMT) has demonstrated proof-of-concept efficacy in modulating a range of conditions, including cancer, metabolic disorders, and high-risk factors for malignancy such as obesity, yet faces substantial barriers: donor heterogeneity, regulatory complexity, and uncertain engraftment efficiency.[5] The effector molecule paradigm suggests a more tractable path. If the functional consequences of a favorable microbiome are mediated by specific metabolites and vesicle-associated proteins, then direct delivery of these effectors as defined postbiotic formulations or engineered vesicle products circumvents the compositional lottery of donor transplantation. This approach enables dose-controlled, Good Manufacturing Practice (GMP)-manufacturable products with defined mechanisms of action, which are the attributes that pharmaceutical development and regulatory agencies require. Dietary modulation of functional guild balance using specific dietary fibers to selectively expand SCFA-producing consortia represents a complementary and immediately deployable intervention tier, with plasma metabolite levels serving as pharmacodynamic readouts. Key next steps include validating the function-based predictive models in prospective therapy cohorts, establishing dose-response relationships for priority effector molecules, and addressing confounding factors such as host genetics, concomitant medications, and tumor type in trial design.

CONCLUSION

The gut microbiota would influence cancer not based on any single species, but via the aggregate functional output of an ecological community whose organizing principles were measurable and increasingly manipulable based on their functions. A decade of compositional profiling has yielded limited translational progress, suggesting that the bottleneck lies less in technology than in conceptual framework.

Variability is real, but it is not chaos. Beneath compositional heterogeneity lies a conserved functional architecture, and the effector molecules through which that architecture communicates with the host are defined chemical entities with quantifiable pharmacodynamics. The central opinions of this framework include establishing normative functional core microbiome benchmarks across diverse populations; mapping the therapeutic response consequences of microbial effector molecules; developing targeted postbiotic and microbiota functional-based formulations; and integrating functional microbiome metrics into therapy trial design. The scientific foundations of the gut microbiota in cancers are accumulating rapidly by scientists worldwide, and the conceptual architecture proposed here offers a framework to assemble them purposefully toward truly personalized, microbiome-informed cancer therapy.

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AUTHOR CONTRIBUTIONS

All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.