SCIENTIFIC CULTURE
www.sci-cult.com

SCIENTIFIC CULTURE, Vol. 12, No. 4, (2026), pp. 11635-11638
Open Access. Online & Print

DOI: 10.5281/zenodo.124261103

GUT MICROBIOTA AND CHEMOTHERAPY RESPONSE: IMMUNE MODIFICATION AS A DETERMINANT OF THERAPEUTIC EFFICACY

Dr. K.G. Padmanabhan[1], Dr. Vinayak Munirathnam[2]

[1]Medical advisor and Researcher Khoday Centre for Integrative Medicine & Research, Bangalore
[2]Senior medical oncologist Sri Shankara Cancer Hospital and Research Center: Bengaluru, Karnataka

Received: **18/12/2025**
Accepted: **24/03/2026**

Corresponding Author: Vinayak Munirathnam (email)

ABSTRACT

The gut microbiota has emerged as a critical determinant of host response to chemotherapy, influencing treatment efficacy, toxicity, and resistance through systemic and local immune modulation. Beyond direct pharmacokinetic interactions, intestinal microbes regulate antitumor immunity by shaping innate and adaptive immune responses, altering cytokine tone, remodeling the tumor microenvironment (TME), and generating immunologically active metabolites. Evidence from preclinical and clinical studies indicates that microbiota composition can influence the therapeutic outcomes of major chemotherapeutic classes, including platinum agents, cyclophosphamide, anthracyclines, taxanes, irinotecan, and fluoropyrimidines. Specific bacterial taxa such as Akkermansia muciniphila, Bifidobacterium spp., Faecalibacterium prausnitzii, and Enterococcus hirae are associated with improved immune priming and treatment responsiveness, whereas dysbiosis and pathobiont expansion may promote chemoresistance and toxicity. Mechanistically, gut microbiota modulates chemotherapy response through dendritic cell activation, T-cell priming, macrophage polarization, myeloid-derived suppressor cell regulation, epithelial barrier integrity, and metabolite-mediated immune signaling. This review synthesizes current evidence on the microbiota–immune–chemotherapy axis, highlighting mechanistic pathways, clinically relevant microbial signatures, and translational strategies including probiotics, prebiotics, fecal microbiota transplantation (FMT), and postbiotic therapeutics. Understanding and therapeutically targeting the gut microbiota may enable personalized microbiome-guided strategies to improve chemotherapy response and reduce adverse outcomes in cancer patients.

KEYWORDS: gut microbiota; chemotherapy; cancer; immune modulation; tumor microenvironment; microbiome; immunometabolism; fecal microbiota transplantation

1. INTRODUCTION

Cancer chemotherapy remains a central pillar of oncologic treatment despite advances in targeted therapy and immunotherapy. However, substantial interindividual variability in chemotherapy response remains a major clinical challenge, driven by tumor heterogeneity, host genetics, immune status, and increasingly recognized microbial determinants. Among these, the gut microbiota has emerged as a pivotal regulator of therapeutic outcomes.

The human gut harbors trillions of microorganisms whose collective genomic and metabolic capacity profoundly influences host immunity and systemic physiology. These microbes act as an "immunological organ," calibrating immune tone, maintaining mucosal integrity, and producing metabolites that shape both local and distal antitumor responses. Recent evidence demonstrates that gut microbiota can modulate chemotherapy response not only through direct biotransformation of drugs but also through immune modification, thereby influencing efficacy, toxicity, and resistance.

Chemotherapy has traditionally been viewed as directly cytotoxic to proliferating tumor cells. However, many chemotherapeutic agents also exert immunomodulatory effects, including induction of immunogenic cell death (ICD), activation of dendritic cells (DCs), antigen cross-presentation, and T-cell priming. The gut microbiota can amplify or suppress these immune-mediated anticancer effects, thereby acting as a critical determinant of chemotherapy success.

This review examines the role of gut microbiota in modifying chemotherapy response through immune regulation, with emphasis on mechanistic pathways, clinically relevant microbial signatures, and therapeutic implications.

2. GUT MICROBIOTA AS A REGULATOR OF HOST ANTITUMOR IMMUNITY

2.1 Microbiota and Immune Homeostasis

The gut microbiota is essential for immune system development and homeostasis. Commensal microorganisms shape mucosal and systemic immunity by regulating:

* differentiation of T helper (Th1, Th17) and regulatory T (Treg) cells,
* maturation of antigen-presenting cells,
* macrophage polarization,
* cytokine production,
* natural killer (NK) cell activation,
* intestinal epithelial barrier integrity.

Microbial-associated molecular patterns (MAMPs), including lipopolysaccharide (LPS), peptidoglycan, and flagellin, activate pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs), thereby tuning basal immune responsiveness.

These signals influence systemic immune tone and can alter the host's capacity to mount effective antitumor responses during chemotherapy.

2.2 Microbial Metabolites as Immune Modulators

Gut microbial metabolites act as key mediators linking microbiota composition to immune function. Important immunoregulatory metabolites include:

* Short-chain fatty acids (SCFAs) (butyrate, propionate, acetate): promote Treg differentiation, enhance epithelial barrier integrity, and modulate CD8+ T-cell metabolism.
* Secondary bile acids: regulate macrophage polarization and inflammatory signaling.
* Tryptophan metabolites (indoles): signal through aryl hydrocarbon receptor (AhR), influencing mucosal immunity and dendritic cell function.
* Polyamines and inosine: modulate T-cell activation and effector differentiation.

These metabolites can either enhance immune surveillance or promote immune suppression depending on context, concentration, and tumor type.

3. MECHANISMS BY WHICH GUT MICROBIOTA MODULATES CHEMOTHERAPY RESPONSE

3.1 Enhancement of Immunogenic Cell Death

Several chemotherapeutic agents, including anthracyclines and oxaliplatin, induce immunogenic cell death (ICD), characterized by release of danger-associated molecular patterns (DAMPs) such as ATP, calreticulin, and HMGB1. These signals activate dendritic cells and promote tumor antigen presentation to T cells.

Gut microbiota enhances ICD by:

* promoting dendritic cell maturation,
* amplifying type I interferon signaling,
* improving antigen cross-presentation,
* enhancing cytotoxic CD8+ T-cell priming.

In germ-free or antibiotic-treated mice, oxaliplatin and cyclophosphamide lose substantial antitumor efficacy, underscoring the requirement for intact microbial-immune crosstalk.

3.2 Modulation of Myeloid Cells

Myeloid cells are major mediators of chemotherapy response. Gut microbiota influences:

* tumor-associated macrophage (TAM) polarization,
* dendritic cell maturation,

* neutrophil recruitment,
* myeloid-derived suppressor cell (MDSC) expansion.

Beneficial microbiota tends to promote M1-like macrophage polarization and antigen-presenting phenotypes, while dysbiosis often favors M2-like immunosuppressive macrophages and MDSC accumulation, leading to reduced chemotherapy sensitivity.

3.3 T-cell Priming and Effector Function

Certain commensals promote systemic Th1 and CD8+ T-cell responses required for durable chemotherapy efficacy. Enterococcus hirae and Barnesiella intestinihominis have been shown to enhance cyclophosphamide efficacy by promoting Th1 memory responses and intratumoral CD8+ T-cell infiltration.

Conversely, microbiota depletion impairs:
* tumor antigen presentation,
* IFN-γ production,
* CD8+ T-cell cytotoxicity,
* memory T-cell persistence.

These effects reduce chemotherapy responsiveness and promote relapse.

3.4 Barrier Integrity and Systemic Inflammation

Chemotherapy frequently damages intestinal epithelium, disrupting barrier integrity and promoting microbial translocation. This can produce divergent outcomes:
* controlled translocation may enhance immune priming,
* excessive barrier disruption can drive endotoxemia, inflammation, and toxicity.

This balance is microbiota-dependent and influences both treatment efficacy and tolerability.

3.5 Microbial Drug Metabolism and Immune Consequences

Gut microbes can directly metabolize chemotherapeutic agents, altering efficacy and immune consequences.

Examples include:
* Irinotecan: microbial β-glucuronidases reactivate SN-38 in the gut, increasing mucosal toxicity and inflammatory injury.
* Cyclophosphamide: translocation of gram-positive bacteria enhances immune priming.
* 5-FU: efficacy and toxicity vary with microbial composition and mucosal inflammatory tone.
* Platinum agents: require microbiota-dependent ROS and myeloid activation for maximal efficacy.

4. MICROBIAL SIGNATURES ASSOCIATED WITH CHEMOTHERAPY RESPONSE

Beneficial taxa associated with improved response
* Akkermansia muciniphila
* Bifidobacterium longum
* Faecalibacterium prausnitzii
* Enterococcus hirae
* Barnesiella intestinihominis

These taxa are linked to:
* enhanced dendritic cell function,
* improved CD8+ T-cell priming,
* increased Th1 polarization,
* reduced systemic inflammation,
* improved progression-free survival.

Detrimental taxa associated with poor response or toxicity
* Fusobacterium nucleatum
* Escherichia coli (pathobiont strains)
* Clostridium spp. (context-dependent)
* β-glucuronidase–producing taxa

These organisms are associated with:
* immune suppression,
* chemoresistance,
* inflammatory toxicity,
* epithelial injury,
* impaired T-cell function.

5. CLINICAL EVIDENCE LINKING GUT MICROBIOTA TO CHEMOTHERAPY OUTCOMES

Clinical studies increasingly support associations between gut microbiota composition and chemotherapy response across gastrointestinal, breast, lung, ovarian, and hematologic malignancies. A recent systematic review of 22 studies found consistent links between gut microbial composition and chemotherapy response, progression-free survival, and treatment-related toxicity.

Patients with microbiota enriched in SCFA-producing and immunostimulatory taxa generally demonstrate:
* improved response rates,
* longer progression-free survival,
* lower inflammatory toxicity.

In contrast, dysbiosis and reduced microbial diversity correlate with:
* poor response,
* higher toxicity burden,
* increased mucositis and diarrhea,
* inferior survival outcomes.

Although causality in humans remains under active investigation, converging clinical and preclinical data strongly support microbiota-mediated immune modification as a determinant of chemotherapy

outcomes.

6. THERAPEUTIC STRATEGIES TO MODULATE THE GUT MICROBIOTA

6.1 Probiotics and Prebiotics

Probiotics and prebiotics may enhance chemotherapy tolerance and immune responsiveness by restoring beneficial microbial communities and increasing SCFA production. However, strain specificity, timing, and host context remain critical.

6.2 Fecal Microbiota Transplantation (FMT)

FMT is an emerging strategy to restore microbial diversity and transfer beneficial immune-modulating functions. Although most advanced in immunotherapy, FMT holds potential as an adjunct to chemotherapy to improve immune responsiveness and reduce dysbiosis-associated toxicity.

6.3 Postbiotics and Microbial Metabolites

Postbiotics (microbial metabolites or components) offer a safer and more controllable alternative to live microbial therapeutics. SCFAs, indoles, and engineered microbial metabolites may be leveraged to modulate immune tone during chemotherapy.

6.4 Precision Microbiome Oncology

Future strategies may integrate:

* microbiome profiling,
* metabolomics,
* immune phenotyping,
* AI-driven microbial response prediction

to personalize chemotherapy and improve outcomes through microbiome-guided interventions.

7. CHALLENGES AND FUTURE DIRECTIONS

Despite compelling evidence, several challenges remain:

* lack of standardized microbiome sampling and analysis,
* interindividual and geographic microbial variability,
* difficulty establishing causality in human studies,
* limited prospective interventional trials,
* safety concerns with live microbial therapeutics.

Future research should prioritize:

* prospective biomarker-driven trials,
* standardized microbiome diagnostics,
* mechanistic validation in humans,
* microbiome-informed chemotherapy stratification.

8. CONCLUSION

The gut microbiota is a major regulator of chemotherapy response through immune modification. By shaping systemic immunity, modulating the tumor microenvironment, regulating inflammatory tone, and producing immunologically active metabolites, the gut microbiota influences chemotherapy efficacy, toxicity, and resistance. Integrating microbiome science into oncology may enable a new generation of precision cancer therapeutics in which microbial composition becomes both a biomarker and a therapeutic target for optimizing chemotherapy outcomes.

REFERENCES:

1. Blake SJ, Wolf Y, Boursi B, et al. Role of the microbiota in response to and recovery from cancer therapy. Nat Rev Immunol. 2024;24:308–325.
2. Böhm D, Russ E, Guchelaar HJ, et al. The role of the gut microbiota in chemotherapy response, efficacy and toxicity: a systematic review. npj Precis Oncol. 2025;9:265.
3. Li Z, Xiong W, Liang Z, et al. Critical role of the gut microbiota in immune responses and cancer immunotherapy. J Hematol Oncol. 2024;17:33.
4. Wang L, Jiang W, Yang M, et al. Combination strategies of gut microbiota in cancer therapy through metabolic reprogramming and immune remodeling. Cell Commun Signal. 2025;23:270.
5. Elkrief A, Pidgeon R, Vareki SM, et al. The gut microbiome as a target in cancer immunotherapy: opportunities and challenges for drug development. Nat Rev Drug Discov. 2025;24:685–704.
6. Arnone AA, Ansley K, Heeke AL, et al. Gut microbiota interact with breast cancer therapeutics to modulate efficacy. EMBO Mol Med. 2025;17:219–234.
7. The gut microbiome and cancer: from tumorigenesis to therapy. Nat Metab. 2025.