Considerations of Gut Microbiome and Cancer—Part 1: Exploring Its Role in Tumorigenesis and Treatment Responses

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ABSTRACT

The gut microbiota is a pivotal determinant of human health, influencing both local and systemic physiological processes. Understanding its composition and function is crucial for exploring its impact on diseases, including cancer. Dysbiosis—or imbalances in the gut microbiota linked to negative health outcomes—is increasingly implicated in the pathogenesis of various cancers through mechanisms such as chronic inflammation, immune modulation, and metabolic interactions. The gut microbiome plays a fundamental role in maintaining host health by influencing gut integrity, metabolism, and immune function, with accumulating evidence suggesting a direct impact on cancer development and also cancer drug metabolism, modulating both treatment efficacy and toxicity. This manuscript explores the interactions between the gut microbiome and cancer, focusing on its role in tumorigenesis and its influence on the efficacy of cancer treatments. We review the underlying mechanisms by which specific bacterial species promote tumour development and discuss the microbiome's role in modulating chemotherapy, immunotherapy and radiotherapy outcomes. The complex interplay between the gut microbiome and cancer therapy continues to reveal new avenues for improving treatment outcomes, and as microbiome science becomes increasingly integrated into oncology, future research should focus on identifying specific microbial signatures predictive of treatment response, developing targeted microbiome-modulating interventions, and incorporating microbiome profiling into clinical trial design.

Key Words Gut microbiota, dysbiosis, microbial metabolites, host-microbiome-drug interactions

INTRODUCTION

Overview of the Human Gut Microbiota and its Microbiome

The term "microbiota" refers to the overall microbial taxa associated with humans[1] and therefore, "gut microbiota" refers to the large range of microorganisms inhabiting the gastrointestinal tract (GIT).[2] Each host shares a unique, generally symbiotic relationship with its microbiota.[3] These microbial communities, which can act as health-promoting microorganisms, innocuous commensals, or opportunistic pathogens,[2] reside within the various epithelial surfaces of the human body (skin, airways, urogenital tract, oral and nasal cavities). It is well established that the majority of human microbiota reside in the GIT, particularly in the large intestine,[4,5] and that both microbial density and diversity within the GIT increase from the proximal to the distal gut.[6] Figure 1 illustrates the microbial density and diversity throughout the human GIT.

Composition of the Gut Microbiota

The human gut microbiota is a complex and diverse community consisting of an estimated 10^{13} to 10^{14} microorganisms.[7,8] Bacteria are the predominant microbes, which also include viruses, fungi, protozoa, and archaea. This dynamic ecosystem is home to more than 1000 distinct bacterial phylotypes dominated by up to 10 bacterial phyla.[9,10] It has been reported that 90% of the total gut microbial population is often constituted by two phyla, Bacteroidetes and Firmicutes.[7,11] The other major phyla are often Actinobacteria, Proteobacteria and Verrucomicrobia.[7,11,12] Facultative anaerobic and anaerobic microorganisms populate the healthy adult gut. Gram-negative rods (belonging to genera *Bacteroides, Fusobacterium* and *Enterococcus*) and anaerobic Gram-positive bacteria (including *Lactobacilli* and *Streptococci*) are present in abundance, while *Bifidobacterium* species may account for up to 25%[13,14] (see Table 1).

The gut microbiota undergoes continuous adaptive remodelling, supporting a bidirectional, mutually beneficial symbiosis with the

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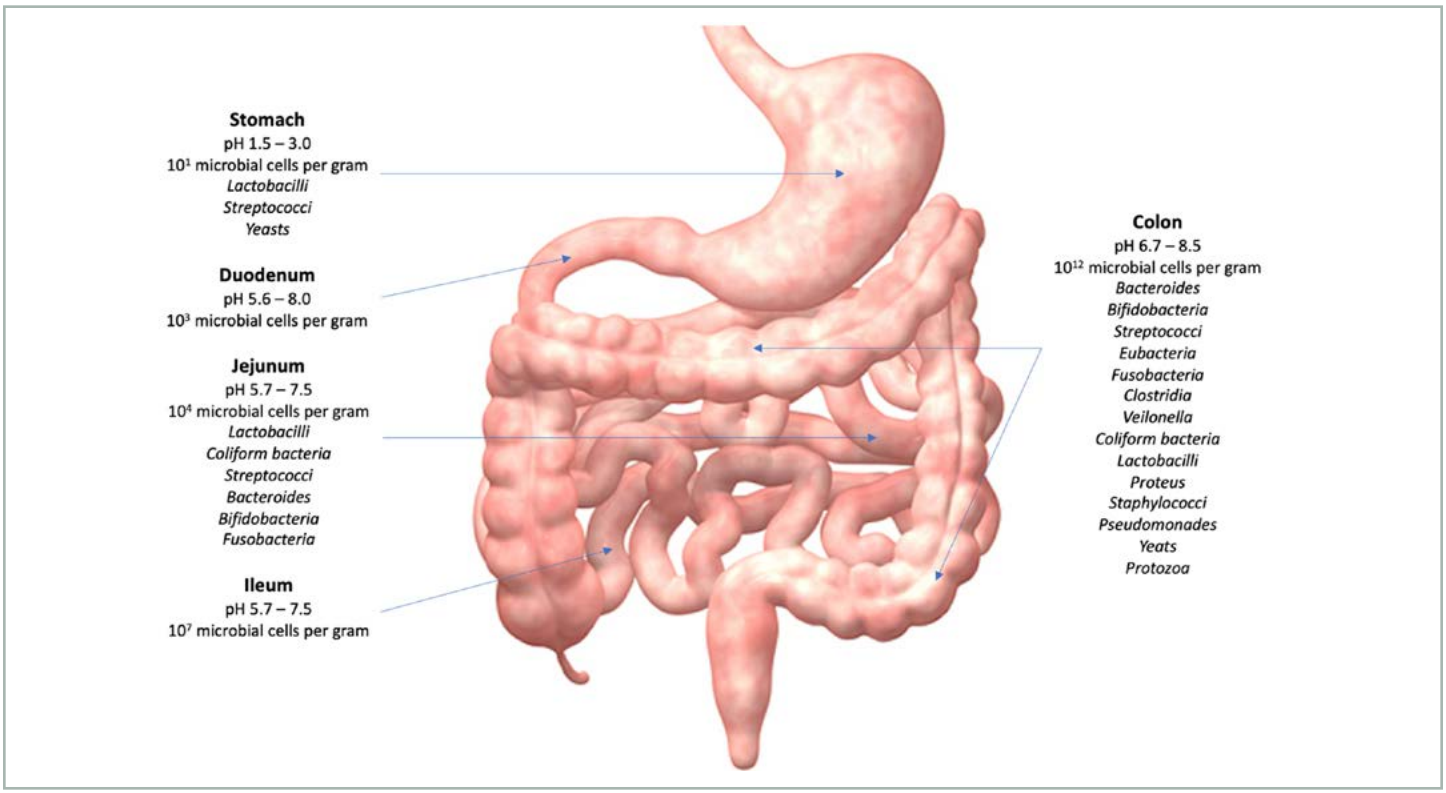

FIGURE 1 Microbial Density and Diversity at Various Sites Within the Gastrointestinal Tract

TABLE 1 Major Bacterial Phyla of the Human Gut Microbiota and Their General Actions

Major phyla	Representative examples	Actions
Bacteroidetes	*Bacteroides* and *Prevotella*	Regulation of immune responses and carbohydrate metabolic pathways.
Firmicutes	*Lactobacillus* and *Faecalibacterium*	Production of short-chain fatty acids and maintenance of epithelial barrier function.
Actinobacteria	*Bifidobacterium*	Facilitation of nutrient digestion and biosynthesis of bioactive metabolites.
Proteobacteria	*Escherichia* and *Helicobacter*	Potential pathobiont activity under dysbiotic or immunocompromised states.
Verrucomicrobia	*Akkermansia*	Support of epithelial homeostasis and host metabolic regulation.

host. There is significant variation in microbial diversity within populations,[15,16] and composition is influenced by factors such as genetics, age, medication use, nutritional status, and physical activity.[17] A balanced gut microbiota supports various physiological processes, including regulating metabolism and maintaining intestinal homeostasis. The GIT also acts as a major immune organ, containing up to 80% of the body's immune cells and helping to maintain systemic immune balance despite constant exposure to exogenous antigens.[1]

However, altered microbial balance can disturb communications between host and microbiota. The term "dysbiosis" refers to a perturbation [of the microbiota], marking a detrimental shift in its composition and/or function. Some researchers use the term "pathobiosis" to describe this disturbed microbial state. Petersen and Round define dysbiosis as "any change to the composition of resident commensal communities relative to the community found in healthy individuals."[19] However, such definitions tend to be broad and non-specific, which can create ambiguity about the role of dysbiosis in disease or may lead to inappropriate correlations between illness and microbial profiles. At present, our understanding of the mechanisms underlying these associations remains limited, making it difficult to determine whether dysbiosis is a cause or consequence of disease.[20]

Dysbiosis has been linked to inflammatory bowel disease, irritable bowel syndrome, and colorectal cancer (CRC).[21,22] Growing evidence illustrates that the influence of GIT microbiota extends beyond the gastrointestinal system, affecting neurological, musculoskeletal and cardiovascular disorders. Microbiome imbalances have been implicated in obesity, diabetes, Alzheimer's and Parkinson's diseases, depression, rheumatoid arthritis and sarcopenia.[23-26] An overgrowth of pathogenic populations can disrupt various metabolic and nutrient signalling pathways and promote chronic inflammation and DNA damage, processes that have been linked to carcinogenesis.[27]

Functions of the Gut Microbiome

Often incorrectly used interchangeably with "microbiota," the term "microbiome" refers to the collective genomes of the microorganisms residing in a specific habitat[28] and the metabolic capabilities they provide.[29] Collectively, the genes in the microbiome outnumber those in the human genome by at least 150-fold. The

gut microbiome alone is estimated to contain 3.3 million non-redundant genes[11] compared with the approximately 22,000 in the human genome.[30] This vast genetic reservoir supports a wide array of metabolic and biochemical functions, significantly contributing to host physiology, with a metabolic capacity comparable to that of the liver.[15]

The gut microbiome performs a range of essential functions that impact overall health and disease susceptibility. It is involved in immune system conditioning, drug metabolism and protection against epithelial cell injury.[31,32]

Metabolic Functions

Gut bacteria assist in the digestion of complex carbohydrates, producing short-chain fatty acids (SCFAs) such as butyrate, acetate, and propionate from fermentation of dietary fibres, which provide energy to colonocytes and exert anti-inflammatory effects. Microbial metabolism influences the biosynthesis and absorption of essential nutrients, including vitamin K and B vitamins (e.g., pyridoxine, cobalamin, folate, biotin). Gut microbial enzymes modify bile acids, impacting lipid digestion, cholesterol homeostasis and systemic metabolic pathways.

Immune System Modulation

The microbiome plays a critical role in the establishment and maintenance of immune tolerance, modulating the equilibrium between pro-inflammatory and anti-inflammatory responses. Intestinal microbiota are instrumental in educating the immune system to discriminate between pathogenic organisms and commensal microbes. Gut microbes influence adaptive immune responses, promoting the differentiation of CD4+ and CD8+ T cells.[33] Commensal bacteria, including *Lactobacillus*, support immune homeostasis by inducing and activating regulatory T cells, while *Clostridium* species increase production of interleukin (IL)-17 through proliferation of intestinal T helper (TH)17 cells.[34] Specific bacterial taxa, including *Bacteroides fragilis* and *Faecalibacterium prausnitzii*, produce immunomodulatory metabolites, such as SCFAs, indoles, and polysaccharides, that modulate immune signalling cascades and attenuate inflammatory processes, while *Bifidobacterium* species stimulate B cells to release secretory immunoglobulin A (IgA).[35]

Epithelial Barrier Integrity

The gut microbiome reinforces intestinal barrier function by promoting mucus secretion and enhancing the integrity of tight junctions between epithelial cells. Specific commensal bacteria, such as *Akkermansia muciniphila*, stimulate goblet cell activity and mucus layer production, thereby fortifying the mucosal barrier.[36] Additionally, beneficial microbes confer protection against pathogenic invasion by excluding harmful organisms through nutrient competition and occupation of epithelial binding sites.[37] Microbiota-derived metabolites—including SCFAs and antimicrobial peptides such as P-glycoprotein (P-gp)—further enhance epithelial cohesion and barrier integrity. SCFAs modulate the expression and function of tight junction proteins, including claudins and zonula occludens, which enhance barrier function, while P-gp modulates the movement of xenobiotics and bacterial toxins across the intestinal mucosa.[38,39] Compromised intestinal barrier integrity can facilitate the translocation of microbial components and metabolites, such as lipopolysaccharide (LPS) and trimethylamine (TMA), into the systemic circulation. LPS, a glycolipid endotoxin derived from the outer membrane of many gram-negative pathogenic bacteria, exerts potent proinflammatory effects and further disrupts epithelial barrier function.[40] TMA, a metabolite generated by gut microbiota from dietary choline, is subsequently oxidized in the liver to form trimethylamine-N-oxide (TMAO), a compound strongly implicated in the pathogenesis of cardiometabolic disorders and CRC.[6,41]

RATIONALE FOR INVESTIGATING THE GUT MICROBIOME'S INFLUENCE ON CANCER TREATMENT

The microbiome is increasingly recognized as a key modulator in the pathophysiology of numerous human diseases, including cancer. Emerging evidence highlights its significant influence on the efficacy of cancer therapies, with studies indicating that modulation of the gut microbiome can alter therapeutic responses across various treatment modalities.[42] Microbial-derived metabolites have been shown to influence tumour microenvironments, affecting gene expression, cell cycle regulation and apoptosis.[43] By altering drug metabolism, the gut microbiome can modulate the bioavailability and efficacy of chemotherapeutic and immunotherapeutic agents, leading to enhanced immune responses and mitigation of treatment toxicities.[44] A better understanding of an individual's microbiome could lead to more tailored and effective cancer treatments, which are increasingly explored in the emerging fields of personalized medicine and pharmacomicrobiomics.[45,46]

Several recent papers have described relationships between altered gut microbial composition and various malignancies, including gastrointestinal and hematological cancers.[47,48] Accumulating evidence indicates that the gut microbiome can modulate host immune responses, influencing outcomes across a spectrum of oncologic treatments, including chemotherapy, immunotherapy, and radiotherapy,[49] and the gut microbiome has been proposed as a potential biomarker in cancer therapy.[50,51] This narrative review summarizes current literature examining the relationship between the gut microbiome and its role in cancer development and therapeutic response. Relevant studies were identified through non-systematic searches of PubMed, Scopus, and Google Scholar using keywords such as "gut microbiome," "cancer," "gut microbial metabolites," and "host-microbiome drug interactions." Priority was given to peer-reviewed review articles and original research published in the past 5 to 10 years, although earlier foundational studies were included where appropriate. Articles were selected based on relevance and contribution to key themes, without formal inclusion or exclusion criteria or a systematic protocol. This manuscript aims to examine how the human gut microbiome contributes to cancer pathogenesis and explores how various microbial-derived metabolites interact with cancer treatments, influencing drug metabolism, therapeutic response, and resistance.

DYSBIOSIS AND ITS ROLE IN CANCER DEVELOPMENT AND PROGRESSION

Dysbiosis has been increasingly recognized as a contributing factor in cancer development and progression, either through direct cellular interactions or the secretion of bioactive metabolites.[43] This disruption in gut microbial homeostasis can result in an inflammatory environment, immune dysfunction and metabolic alterations, which may contribute to tumorigenesis. A reduction in beneficial bacteria (*Lactobacillus, Bifidobacterium*) and increased levels of pathogenic bacteria (*Fusobacterium nucleatum, Escherichia coli*) have been associated with immune evasion and tumour growth.[52] Dysbiosis can promote chronic, systemic, low-grade inflammation by increasing the production of pro-inflammatory cytokines IL-6, IL-1β, and tumour necrosis factor (TNF)-α.[35] *Helicobacter pylori* infection is a well-documented cause of gastric cancer, promoting tumorigenesis through chronic inflammation and activation of oncogenic pathways like β-catenin signalling.[53] An overabundance of *Enterococcus faecalis, E. coli, B. fragilis* and *Campylobacter* has been implicated in developing CRC.[54,55] These bacteria drive tumorigenesis by inducing inflammation[56] and through the production of genotoxins—toxic compounds that cause DNA damage and disrupt DNA repair mechanisms—including colibactin and cytolethal distending toxin (CDT).[52] Further, *F. nucleatum* enhances colorectal carcinogenesis progression through the actions of FadA and Fap2, adhesins that promote proliferation and immune evasion.[57]

MICROBIAL METABOLITES AND THEIR IMPACT ON TUMORIGENESIS

Bioactive metabolites, generated from dietary components and microbial metabolic pathways, can influence cancer development and progression by affecting inflammation, immune response, and cellular signalling. Several important classes of microbial metabolites have been identified as key players in tumorigenesis, acting either as tumour-promoting or tumour-suppressing agents.

Short-Chain Fatty Acids

SCFAs are produced by microbial fermentation of non-digestible dietary fibre by gut bacteria and exert significant effects on cancer biology. The most abundant SCFAs, butyrate, acetate and propionate, constitute approximately 90% of the SCFAs produced by the microbiome.[58] Butyrate, produced by bacteria such as *F. prausnitzii, Roseburia intestinalis,* and *Agathobacter rectale*, serves as a primary energy source for colonic epithelial cells.[59] Butyrate supports mucosal integrity, preventing microbial translocation and systemic inflammation.[60] At low concentrations, butyrate has been shown to inhibit histone deacetylases (HDACs), leading to increased apoptosis and reduced proliferation of cancer cells, particularly in CRC.[61,62] Animal models have demonstrated that SCFAs enhance regulatory T-cell (Treg) differentiation and promote an anti-inflammatory microenvironment, which can attenuate tumour progression.[63] In clinical trials, patients with advanced colorectal adenoma were found to have reductions of the main butyrate-generating taxa (*Clostridia, Firmicutes, Eubacterium*) and reduced fecal butyrate.[64] A 2015 systematic review by Borges-Canha et al. reported that decreased butyrate and a microbial profile with reduced representation of butyrate producers were associated with colorectal carcinogenesis.[65] Table 2 provides a summary of the mechanisms of gut microbiota-derived metabolites.

Bile Acid Metabolites

The gut microbiome modifies primary bile acids into secondary bile acids, which can have pro-carcinogenic effects.[92] Colonic bacteria within the phylum Firmicutes have demonstrated 7-dehydroxylation activity, capable of metabolizing cholic and chenodeoxycholic acids into deoxycholic acid (DCA) and lithocholic acid (LCA).[93] DCA and LCA have been linked to oxidative stress and DNA damage in colon epithelial cells, contributing to colorectal carcinogenesis.[94] These metabolites activate nuclear receptors like the farnesoid X receptor (FXR) and pregnane X receptor (PXR), influencing bile acid homeostasis and inflammation pathways associated with cancer.[95] Elevated DCA levels have been associated with the progression of CRC.[94]

Polyamines

Polyamines, such as putrescine, spermidine, and spermine, are synthesized through the decarboxylation of the amino acids, ornithine, arginine, and lysine. Depending on their circulating levels, polyamines can either promote normal cellular differentiation and intestinal mucosal integrity or contribute to tumorigenesis.[96] Elevated polyamine levels, which are linked with dysbiosis, have been associated with increased proliferation of cancer cells, reduced apoptosis and disruption of epithelial barrier integrity. Polyamines have induced oxidative stress, resulting in DNA damage and CRC in animal models.[97] Spermidine reduces the concentration of IL-18 in the colon and has been implicated in modulating chromatin structure and gene expression, affecting pathways involved in cancer progression.[96] Spermine has been associated with increased expression of catenin, involved in tumour cell proliferation.[98]

Indoles and Tryptophan Metabolites

Ingested tryptophan (TRP) that is not absorbed in the small intestine is metabolized by colonic bacteria into several bioactive indole derivatives, which have dual roles in tumorigenesis (tumour-suppressing and pro-carcinogenic effects). *Clostridium* and *Ruminococcus* have been shown to degrade TRP to tryptamine by the action of tryptophan dehydrogenase, and indole-3-acetic acid (IAA) is synthesized by species within *Bifidobacteria, Bacteroides* and *Eubacteria*.[99] Tryptophanase, expressed by certain *Bacteroides* and *Lactobacillus* species, generates indole-3-propionic acid (IPA), which has been shown to enhance gut epithelial integrity.[100] IAA, IPA, indole-3-aldehyde (I3A), indole-3-lactic acid (ILA) and indoxyl-3-sulfate serve as ligands for the activation of aryl hydrocarbon receptor (AhR), expressed on the surface of neutrophils, macrophages, dendritic cells and TH17 cells.[101] These metabolites mediate anti-inflammatory actions through

TABLE 2 Cancer-related mechanisms, actions and effects of gut microbiota-derived metabolites

Metabolite			Mechanism	Action	Effect	Reference
PAs	Spermine		Protect DNA, scavenge free radicals	↓ oxidative damage	Prevention of carcinogenesis	Ha et al, 1998[66]
PPDs	PAA		↑ cytotoxicity in tumour cells	↓ cell proliferation	Enhances apoptosis	Gao et al, 2019[67]
	4-hydroxyPAA		↑ cytotoxicity in tumour cells	↓ cell proliferation	↑ Anti-proliferative effect	Rupasinghe et al, 2019[68]
	DAT		↑ activated T cells and NK cells	↑ immune checkpoint inhibition	Delays tumour growth	Joachim et al, 2023[69]
SBAs			Inhibits NLRP3 inflammasome activation	↓ inflammation	Prevention of carcinogenesis	Guo et al, 2016[70]
	DCA		Activates c-Myc pathway	↑ β-catenin cell signalling pathway	Stimulates cancer cell proliferation	Cheng and Raufman, 2005[71]
	LCA		Activates TGR5 (Gpbar1), ↓ VEGF	↓ cell proliferation, impairs angiogenesis	Inhibits proliferation	Miko et al, 2018[72]
SCFAs			Activates cytotoxic CD8+ T cells	↓ anti-tumour immunity	T cell immunosuppression	Behary et al, 2021[73]
	Butyrate		Modulates CD8+ T cells	↑ anti-tumour immunity	Enhances adaptive immunotherapy	Luu et al, 2021[74]
	Butyrate		Modulates CD8+ T cells	↑ anti-tumour therapeutic effectiveness	Enhances anticancer effectiveness	He et al, 2021[75]
	Butyrate		Modulates CD8+ T cells	↑ anti-tumour therapeutic effectiveness	Enhances anticancer effectiveness	Kang et al, 2023[76]
	Butyrate		Modulates CD8+ T cells	↑ anti-tumour therapeutic effectiveness	Enhances anticancer effectiveness	Zhu et al, 2023[77]
	Butyrate		Inhibits T cell response	↓ anti-tumour immunity	↓ effectiveness of anticancer therapy	Coutzac et al, 2020[78]
	Formate		Activates AhR signaling	↓ anti-tumour immunity	Accelerates tumour expansion	Ternes et al, 2022[79]
	Butyric acid		↑ CTLs, ↓ Treg function	↑ anti-tumour immunity	Enhances anticancer effectiveness	Gao et al, 2023[80]
	Succinic acid		↓ cGAS-interferon-β pathway	↓ anti-tumour immunity	↓ tumour response to immunotherapy	Jiang et al, 2023[81]
TCs	TRP		Modulates CD8+ T cells	Activates AhR signaling	↓ anti-tumour immunity	Hezaveh et al, 2022[82]
	TRP		Modulates CD8+ T cells	↑ immune checkpoint inhibition	AhR agonist within TME	Bender et al, 2023[83]
	5-HT		↓ lipid peroxidation	↓ oxidative damage	Inhibits ferroptosis	Liu et al, 2023[84]
	IND derivatives	I3A	Modulates CD8+ T cells	↑ inflammation	↓ anti-tumour immunity	Mohseni et al, 2023[85]
		I3C	Activates AhR signaling	↑ anti-tumour therapeutic effectiveness	Enhances apoptosis	Megna et al, 2016[86]
		IAA	↑ ROS	↓ inflammation,	Enhances anticancer effectiveness	Tintelnot et al, 2023[87]
		ICA	Inhibits regulatory T cell activity	↑ anti-tumour immunity	Enhances anticancer effectiveness	Fong et al, 2023[88]
		ILA	Modulates CD8+ T cells	↓ inflammation, ↓ tumorigenesis	↑ anti-tumour immunity	Zhang et al, 2023[89]
		ILA	Activates apoptotic pathways	↓ cell proliferation	↓ tumorigenesis	Sugimura et al, 2022[90]
		ILA	↓ IL-17 pathway	↓ tumour burden	↓ tumorigenesis	Han et al, 2023[91]

↓ = suppress; ↑ = promote; 5-HT = serotonin (5-hydroxytryptamine); AhR = aryl hydrocarbon receptor; CTLs = cytotoxic T-lymphocytes; DAT = desaminotyrosine; DCA = deoxycholic acid; Gpbar = G-protein bile acid receptor; I3A = indole-3-aldehyde; I3C = indole-3-carbinol; IAA = indole-3-acetic acid; ICA = indole-3-carboxylic acid; IFN = interferon; ILA = indole-3-lactic acid; IND = indole; LCA = lithocholic acid; NK = natural killer; NLRP = NOD (nucleotide-binding oligomerization domain)-like receptor; PA = polyamine; PAA = phenylacetic acid; PPD = phenylpropanoid derivative; ROS = reactive oxygen species; SBA = secondary bile acid; SCFA = short-chain fatty acid; TC = tryptophan catabolite; TME = tumour microenvironment; TRP = tryptophan; VEGF = vascular endothelial growth factor.

AhR signalling, resulting in increased production of IL-22 and inhibition of LPS-induced IL-6 expression.[102,103] The tumour-suppressing actions of indole-3-carbinol (I3C) through accelerated apoptosis are well characterized.[104] Conversely, kynurenine, a tryptophan metabolite produced through the indoleamine 2,3-dioxygenase (IDO) pathway, has been linked to T-cell inhibition in the tumour microenvironment (TME), promoting cancer cell evasion from immune surveillance.[101] High expression of IDO and tryptophan 2,3-dioxygenase (TDO) in the TME can result in local tryptophan deficiency, immune suppression and tumour expansion and is associated with poor prognosis in patients with gastric adenoma.[105,106] Indeed, the use of IDO and TDO inhibitors to block tryptophan metabolism is currently being investigated in clinical trials.[107]

GUT MICROBIOME INFLUENCE ON CANCER TREATMENT

The gut microbiome shapes the metabolic fate of exogenous compounds. Gut microbes can modify therapeutic compounds directly as they pass through the GIT or influence their processing within the enterohepatic circulation,[108] influencing the pharmacokinetics of various cancer therapies. These modifications may lead to bioactivation or inactivation depending on the activity of enzymes expressed by resident microbes.[109] Further, the microbiome regulates host gene expression in both the liver and intestine, including those involved in detoxification pathways such as cytochrome P450 enzymes and multidrug resistance proteins.[110] The gut microbiome also affects drug absorption, distribution and elimination. It exerts these effects by modulating intestinal permeability, altering the expression of drug transporters and directly binding to the compounds.[111] Bacterial-derived metabolites, including SCFAs, bile acids, and polyamines, influence the expression of P-gp and other efflux transporters in the gut epithelium, affecting drug bioavailability.[112]

Inter-individual differences in drug response pose a significant challenge in cancer treatment. Accumulating evidence suggests that variability in gut microbiome characteristics influences drug response profiles.[113] Recent research on gut microbial co-metabolism indicates substantial within-species variation in bacterial capacity to metabolize drugs,[114] potentially explaining the wide variability in drug–microbiome interactions observed between individuals during treatment. Pharmacomicrobiomics is an emerging field that attempts to clarify the complex host–microbiome–drug interactions (HMDIs). It explores the molecular mechanisms that drive individual differences in clinical outcomes resulting from microbiota-mediated drug metabolism, while also examining how pharmaceutical agents, in turn, affect the composition and function of the microbiome.[45,115] It is well established that the microbiome exerts regulatory control over the biotransformation, bioavailability, absorption and distribution of a wide range of pharmaceuticals.[116,117]

Interactions of Gut Microbiome with Chemotherapy and Immunotherapy

Substantial pre-clinical and human evidence confirms the GIT microbial environment can influence the bioavailability, efficacy, and toxicity of cancer therapeutic agents. Enteric bacterial metabolism can either inactivate these drugs or alter their absorption, resulting in lower plasma concentrations and reduced therapeutic efficacy. Several well-characterized HMDIs provide insight into how the gut microbiome can influence cancer treatment outcomes.

Irinotecan (CPT-11) is a widely used prodrug chemotherapeutic for CRC. Hepatic carboxylation converts CPT-11 into its active form, SN-38, which is later inactivated by glucuronidation in the liver.[118] However, gut bacteria such as *E. coli* and *Clostridium* species express β-glucuronidases, which can deconjugate SN-38, leading to its reactivation in the intestine.[119] This process results in severe gastrointestinal toxicity, including diarrhea, which can limit treatment efficacy.[118] It is widely accepted that administration of cytotoxic agents results in changes to the gut microbiome.[120] However, chemotherapy can disrupt niche-specific competitive inhibition, permitting pathobionts to flourish, which in turn may contribute to drug-induced toxicity. For example, a 2017 study of tumour-bearing rats reported that increased abundances of pathobiont species *Fusobacteria* and *Proteobacteria* were detected following irinotecan administration.[121]

Gemcitabine (2',2'-difluorodeoxycytidine) is an antimetabolite used in the treatment of various solid tumours, including breast, lung, and ovarian cancers, which interferes with DNA replication, thereby halting the growth of rapidly dividing cancer cells.[122] *Gammaproteobacteria* were shown to metabolize gemcitabine into an inactive form (2',2'-difluorodeoxyuridine) through expression of cytidine deaminase, leading to treatment resistance.[122,123]

Methotrexate (MTX), an antimetabolite chemotherapy agent, is subject to microbial metabolism in the gut. MTX inhibits mammalian dihydrofolate reductase (DHFR) and has been shown to modify human GIT microbiota, which may elucidate differences in treatment responders and non-responders.[124] Genes expressed by *Firmicutes* and *Bacteroidetes* metabolize MTX, reducing its bioavailability, and may contribute to drug resistance.[125] Therefore, differences in GIT microbiome profiles may impact host therapeutic response outcomes.[126]

Cyclophosphamide (CTX), an alkylating agent used in various cancer therapies, is influenced by the immunomodulatory effects of gut microbiota. Gram-positive bacteria, including *Lactobacillus* and *Enterococcus* species, stimulate CTX-induced immune responses in the TME, indirectly promoting the activation of Th1 and Th17 cells and enhancing anti-tumour immunity.[127] *Barnesiella intestinihominis*, a gram-negative bacterium, stimulates the accumulation of tumour-specific cytotoxic CD8+ and CD4+ T cells and enhances the infiltration of interferon (IFN)–γ–producing T cells into the TME following CTX treatment.[128]

The gut microbiome shapes innate and adaptive immune responses, influencing immune homeostasis, regulating chronic inflammation and suppressing tumour growth. The interaction between the microbiota and the host immune system is complex, involving immune cell modulation, cytokine signalling pathways and various receptors, including pattern recognition receptors such as the Toll-like receptor (TLR) superfamily.

Bacterial taxa, including *A. muciniphila, B. fragilis, E. coli,* and *Lachnospiraceae* and *Bifidobacterium* species, exhibit anti-inflammatory properties and are associated with immune cell activation.[129] The gut microbiome modulates T-cell differentiation, influencing the balance between pro-inflammatory Th1/Th17 responses and anti-inflammatory Treg cells. *B. fragilis* produces polysaccharide A, which induces Treg differentiation and suppresses excessive inflammation. Segmented filamentous bacteria (SFB) promote Th17 responses, which can be beneficial for mucosal defense. Commensal bacteria, including *E. coli, Bifidobacteria* and SFB, stimulate B cell activation, leading to the production of IgA, which reinforces mucosal immunity by neutralizing pathogens and maintaining epithelial integrity.[130] Commensal bacteria interact with host immune cells through TLRs,

which helps maintain immune surveillance and inflammatory balance. *Bifidobacteria* and *Lactobacilli* promote the maturation of dendritic cells, enhancing antigen presentation and immune tolerance.[131] *Akkermansia* and *Bifidobacteria* stimulate dendritic cells, leading to improved antigen presentation and activation of cytotoxic T cells.[132]

Other microbes, including *F. nucleatum* and *Bacteroides vulgatus*, are associated with cancer progression, in part, by driving chronic inflammation and facilitating immune evasion.[57] While some *Bacteroides* species are beneficial, *B. fragilis* has been linked to immunotherapy resistance due to its role in suppressing immune responses and inducing regulatory T cells.[133] Further, *B. fragilis* augments phagocytosis, polarizing macrophages to an M1 state.[134] *Enterococcus faecalis* drives nuclear factor (NF)-κB pro-inflammatory pathways,[135] while *Peptostreptococcus anaerobius* has been shown to induce reactive oxygen species (ROS) formation and stimulate cell proliferation through activation of the PI3K-Akt pathway.[136,137]

Microbial metabolites such as SCFAs influence macrophage polarization, shifting them from a pro-inflammatory (M1) to an anti-inflammatory (M2) phenotype through histone acetylation, which promotes tissue repair and reduces inflammation.[138] SCFAs, particularly butyrate, produced by *F. prausnitzii* and *Ruminococcus,* reinforce Treg activity while simultaneously enhancing cytotoxic T lymphocyte infiltration into tumours.[139] Butyrate has been shown to inhibit the release of IL-6 and IL-12, modulate immune tolerance of colonic macrophages to commensal organisms,[62] and induce apoptosis in cancer cells, enhancing the efficacy of gemcitabine.[14]

The gut microbiome also significantly influences the response to immune checkpoint inhibitors (ICIs), which target lymphocyte-associated antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1) and its ligand (PD-L1). Perhaps unsurprisingly, an inverse correlation has been reported between antibiotic treatment and positive ICI outcomes in observational studies.[141-143] The abundance levels of specific bacterial species have been associated with enhanced efficacy of ICIs by promoting immune activation and improving therapy response rates.[144-146] Higher microbial diversity has been linked to improved responses to anti-PD-1 therapy in patients with lung and renal carcinoma; in particular, non-responders to PD-1 blockade were found to have low levels of *A. muciniphila.*[143] *A. muciniphila* enhances gut epithelial integrity, promotes immune system activation and inhibits inflammation.[147] Higher abundances of *Bifidobacteria* have been reported in patients responding to ICIs, which appear to promote dendritic cell activation and augment anti-tumour immune responses, although the specific mechanisms underlying these immunomodulating effects are still unknown.[148-150] Profiling of gut microbiota in melanoma patients receiving combined immune checkpoint blockade targeting PD-1 and CTLA-4 demonstrated a significantly higher abundance of *Bacteroides intestinalis* in patients with adverse events.[151]

Interactions of Gut Microbiome with Radiotherapy

Various factors, particularly immunological modulation, critically influence tumour progression and therapeutic response to ionizing radiation. Radiotherapy has been shown to induce immunogenic cell death, facilitating antigen release and enhancing the recruitment and infiltration of effector lymphocytes into the TME. Radiation therapy is a cornerstone of cancer treatment; however, its efficacy and side effects can be influenced by the gut microbiome. Radiation therapy, particularly for abdominal and pelvic cancers, can cause significant gastrointestinal side effects, including mucositis, diarrhea, and dysbiosis.[152] Radiation exposure often leads to dysbiosis, characterized by a relative decrease in the richness of favourable microorganisms, e.g., *Lactobacilli* and *Bifidobacteria*, and an increase in the richness of opportunistic pathogens, e.g., *Fusobacteria* and *Clostridium difficile*. Dysbiosis following radiation exposure may exacerbate radiation enteropathy, resulting from impaired epithelial integrity, bacterial translocation and systemic inflammation.[153] Mounting evidence suggests microbiome-mediated interactions impact both radiation sensitivity and toxicity, impacting treatment outcomes. Certain bacterial species can enhance tumour response to radiation therapy by modulating immune activity, oxidative stress and antioxidant responses, and augmenting DNA repair pathways.

A. muciniphila has been linked with improved responses to radiation due to its role in promoting anti-tumour immunity. Previous studies have demonstrated a positive correlation between relative abundances of *A. muciniphila* and clinical responses to radiotherapy.[128] SCFAs and other bacterial metabolites promote the expansion of regulatory Tregs, reducing the effectiveness of radiation-induced immune responses.[155] Chronic inflammation induced by pathogenic bacteria may activate NF-κB and signal transducer and activator of transcription (STAT)3 pathways, which promote tumour survival and resistance to radiation.[156]

Some bacterial metabolites can impact DNA repair pathways, making tumour cells more susceptible to radiation-induced damage. SCFAs, particularly acetate and butyrate, influence epigenetic modifications that upregulate DNA repair genes.[157] Conversely, certain bacteria can enhance the DNA repair capabilities of tumour cells, leading to increased radiation resistance.[158] *B fragilis,* for example, has been demonstrated to stimulate host cellular stress responses,[159] which may enhance the ability of cancer cells to repair radiation-induced DNA damage.

ROS generated during radiotherapy serve as key mediators of oxidative stress, inducing extensive molecular and cellular damage within tumour cells. The gut microbiome can modulate cellular antioxidant defenses, enhancing radiation-induced tumour cell death and reducing radiation sensitivity. The antioxidant capacity of several *Lactobacilli* strains has been described, which includes producing ROS-scavenging metabolites and regulating antioxidant enzyme activity and signalling pathways.[160,161] In murine models, *L. casei* increased superoxide dismutase (SOD) and glutathione peroxidase (GPx) activity, while *L. plantarum* could attenuate oxidative stress induced by D-galactose.[162,163] Early in-vitro studies demonstrated *L. acidophilus* is capable of protecting against lipid peroxidation, and *L. fermentum* species were shown to have SOD activity.[164,165] Further, some bacteria affect host iron regulation, impacting the Fenton reaction and decreasing the generation of cytotoxic free radicals.[16] Interestingly, most

pathogenic GIT bacteria possess enhanced systems for acquiring free iron, enabling them to outcompete commensal microbiota. Iron deficiency anemia is a common clinical manifestation of CRC patients, necessitating iron supplementation. However, the route of iron administration may contribute to a pro-carcinogenic microbial profile.[167] Oral supplementation can increase the amount of iron directly available to gut microbes, leading to the proliferation of oncogenic species.[168] This microbial shift is less likely following intravenous administration, which doesn't increase luminal iron.[169]

Future Directions for Integrating Microbiome Science into Oncology

The gut microbiome is central in regulating metabolic, immune, and inflammatory processes. Gaining deeper insight into host–microbiome–drug relationships may lead to innovative microbiome-targeted strategies that enhance oncologic treatment efficacy. Emerging evidence supports the utility of microbial signatures as predictive biomarkers for treatment response, representing a promising frontier in precision oncology. As the field advances, the integration of microbiome-informed diagnostics and therapeutics into clinical workflows may enable more effective, personalized treatment paradigms tailored to individual microbiota profiles. By leveraging microbiome insights, clinicians can refine therapeutic approaches, enhance patient outcomes, and minimize treatment-related complications, moving toward a more precise and individualized approach to oncology care.

CONCLUSION

The gut microbiome is a critical modulator of host physiology, exerting both local and systemic effects by preserving intestinal epithelial barrier integrity, regulating host metabolic homeostasis, and modulating innate and adaptive immune responses. Dysregulation of the gut microbiome is increasingly implicated in the initiation and progression of various malignancies, mediated through mechanisms including chronic inflammation, disruption of immune homeostasis, and alterations in microbial metabolic activity. The human microbiome may directly contribute to oncogenesis by modulating anti-tumour immune surveillance and shaping host responses to treatment. Microbial-mediated drug resistance is an ongoing concern in cancer therapy. The current review described several bidirectional interactions between the gut microbiome and cancer, highlighting the microbiota's capacity to influence the pharmacokinetics of anticancer therapies, thereby affecting treatment efficacy and toxicity profiles. Gut microbial enzymes may directly modify drugs as they pass through the intestinal tract before they reach their target or indirectly by affecting detoxification pathways within the enterohepatic circulation, impacting drug clearance mechanisms. A better understanding of HMDIs could lead to enhanced treatment outcomes by enabling the development of personalized microbiome-targeted therapies, such as identifying microbial biomarkers that predict drug efficacy or toxicity, engineering probiotics to modulate specific immune pathways, and tailoring antibiotic or dietary interventions to preserve beneficial microbial communities during treatment.

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CONFLICTS OF INTEREST DISCLOSURE

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