ACCSCIENCE PUBLISHING

Eurasian Journal of Medicine and Oncology

REVIEW ARTICLE

The gut microbiome-immune-antioxidant axis: Redox-driven host-microbial crosstalk as a determinant of cancer immunotherapy response

Muhammad Alaa Eldeen[1,2]*, Jinwon Choi[1], Hyo Jeong Kim[1], Sohyun Park[1], Amama Rani[1], Mohamed A. Akl[3,4], Mohamed E. Youssef[5], Gehan A. M. Khodear[6], Kareem M. Abdelraheem[7], and Bonglee Kim[1,8]*

[1]Department of Pathology, College of Korean Medicine, Kyung Hee University, Seoul, Republic of Korea

[2]Division of Computational Genomics and Precision Medicine, EdigenomiX Scientific Ltd., EdigenomiX Research Academy, Zagazig, Sharqia Governorate, Egypt

[3]Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy (Boys), Al-Azhar University, Nasr City, Cairo, Egypt

[4]Department of Pharmaceutics, College of Pharmacy, The Islamic University, Najaf, Iraq

[5]Local Primary Care Federation, Blackburn, United Kingdom

[6]Medical Research Institute Hospital, Alexandria University, Alexandria, Egypt

[7]Department of Biochemistry, Faculty of Pharmacy, Sinai University, Qantara Branch, Ismailia, Egypt

[8]Korean Medicine-Based Drug Repositioning Cancer Research Center, College of Korean Medicine, Kyung Hee University, Seoul, Republic of Korea

***Corresponding authors:**
Muhammad Alaa Eldeen (muhammadalaaeldeen@zu.edu.eg);
Bonglee Kim (bongleekim@khu.ac.kr)

Citation: Eldeen MA, Choi J, Kim HJ, *et al*. The gut microbiome-immune-antioxidant axis: Redox-driven host-microbial crosstalk as a determinant of cancer immunotherapy response. *Eurasian J Med Oncol.* 2026;10(5):026240265. doi: 10.36922/EJMO026240265

Received: June 9, 2026

Revised: August 5, 2026

Accepted: August 10, 2026

Published online: September 15, 2026

Copyright: © 2026 Author(s). This is an Open-Access article distributed under the terms of the Creative Commons Attribution License, permitting distribution, and reproduction in any medium, provided the original work is properly cited.

Publisher's Note: AccScience Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Abstract

Introduction: The gut microbiome, host redox homeostasis, and immune regulation are mechanistically interdependent. However, their integrated role in driving resistance to immune checkpoint inhibitors remains incompletely defined.

Objective: This review introduces the gut microbiome, immune, and antioxidant (GIA) axis as a unifying, systems-level conceptual framework to explain treatment heterogeneity and optimize cancer immunotherapy outcomes.

Scope: We synthesize current mechanistic and translational evidence linking microbiota-derived metabolites, including short-chain fatty acids, bile acids, and tryptophan derivatives, to oxidative stress responses, mitochondrial fitness, and anti-tumor immune competence across colorectal, hepatobiliary, and neuro-oncologic malignancies.

Key findings: Disruption of the GIA network promotes immunotherapy resistance through excessive oxidative burden, pathological Nrf2 signaling, and the expansion of immunosuppressive myeloid populations. Conversely, targeted microbiome interventions, including probiotics, postbiotics, and fecal microbiota transplantation, can successfully restore redox-immune equilibrium, remodel the tumor microenvironment, and enhance the efficacy of checkpoint blockade.

Conclusion: We propose a precision immuno-oncology framework utilizing composite GIA-axis biomarker profiling for patient stratification. Integrating these multidisciplinary insights identifies actionable translational opportunities to overcome therapeutic resistance and transition host-microbiome-immune integration from conceptual promise to clinical reality.

Keywords: Gut microbiome; Redox balance; Cancer immunotherapy; Nrf2 signaling; Oxidative stress; GIA axis; Precision medicine

1. Introduction

Cancer remains one of the leading causes of morbidity and mortality worldwide. According to GLOBOCAN 2020 estimates, there were approximately 19.3 million new cancer cases and nearly 10 million cancer-related deaths globally, with projections suggesting a rise to 28.4 million new cases annually by 2040 due to population growth and aging.[1] The global cancer burden is increasingly shifting toward low- and middle-income countries, where limited screening, late-stage diagnosis, and constrained access to advanced therapies exacerbate mortality disparities.[1,2]

Despite advances in molecular oncology, targeted therapies, and immune checkpoint blockade (ICB), durable responses remain restricted to a subset of patients. Resistance—both primary and acquired—limits the long-term efficacy of chemotherapy, radiotherapy, targeted agents, and immunotherapy.[3,4] Moreover, therapeutic toxicities, tumor heterogeneity, and the immunosuppressive tumor microenvironment (TME) contribute to suboptimal outcomes.[3,5]

These limitations underscore a critical unmet need: the identification of modifiable host-related determinants that influence tumor initiation, progression, and therapeutic responsiveness. Increasing evidence suggests that systemic factors, particularly the gut microbiome, redox homeostasis, and immune regulation, may play pivotal roles in shaping cancer risk and treatment outcomes.[6-9]

The human gut microbiota, comprising trillions of microorganisms, exerts profound effects on host metabolism, immune maturation, and epithelial integrity. Dysbiosis, characterized by reduced microbial diversity and altered taxonomic composition, has been implicated in colorectal, hepatocellular, pancreatic, lung, and breast cancers.[7,10] Mechanistically, microbial metabolites such as short-chain fatty acids (SCFAs), secondary bile acids, and tryptophan derivatives modulate epithelial proliferation, DNA damage responses, and immune signaling pathways.[8,11]

Certain bacterial taxa, such as *Fusobacterium nucleatum* and enterotoxigenic *Bacteroides fragilis*, appear to promote tumorigenesis through inflammatory signaling, the production of genotoxic metabolites, and immune evasion.[10,12] Conversely, commensals such as *Akkermansia muciniphila* and *Bifidobacterium* species have been associated with enhanced anti-tumor immunity and improved responses to immune checkpoint inhibitors.[13,14]

Reactive oxygen species (ROS) are central regulators of oncogenic signaling. While moderate ROS levels promote proliferation and survival by activating pathways such as NF-κB, MAPK, and PI3K/AKT, excessive oxidative stress induces DNA damage, genomic instability, and tumor progression.[15,16] Cancer cells frequently exhibit reprogrammed antioxidant systems, including the upregulation of nuclear factor erythroid 2-related factor 2 (Nrf2)-mediated transcriptional programs, to maintain redox balance and resist therapy-induced oxidative injury.[16,17]

Importantly, the gut microbiota contributes directly to host redox homeostasis. Microbial metabolites influence glutathione metabolism, mitochondrial function, and systemic antioxidant capacity.[9,18] Dysbiosis can exacerbate oxidative stress through increased lipopolysaccharide (LPS) translocation, chronic inflammation, and impaired barrier integrity.[7,9]

The success of immunotherapies, particularly PD-1/PD-L1 and CTLA-4 inhibitors, depends on the effective priming and activation of cytotoxic T lymphocytes within an immunologically permissive microenvironment. Multiple landmark studies have demonstrated that gut microbiome composition correlates with ICB responsiveness across melanoma, lung cancer, and renal cell carcinoma cohorts.[13,14,19] Fecal microbiota transplantation (FMT) from ICB responders into germ-free or antibiotic-treated mice restores anti-tumor immunity, providing causal evidence of microbiota-driven immunomodulation.[13,19]

Redox signaling further intersects with immune function. ROS regulate T-cell activation, differentiation, and exhaustion, while antioxidant pathways influence the function of myeloid-derived suppressor cells (MDSCs) and macrophage polarization.[15,20] Excess oxidative stress within the TME may impair T-cell persistence and responsiveness, thereby contributing to immunotherapy resistance.[20]

Although microbiome research, redox biology, and tumor immunology have traditionally evolved as distinct fields, accumulating evidence suggests they are mechanistically interdependent. The gut microbiota shapes systemic immune tone and redox balance. In turn, oxidative stress modulates immune cell function and microbial ecology, and immune responses reciprocally influence microbial composition and epithelial oxidative

states.

We therefore propose the conceptual framework of the GIA axis, defined as a bidirectional, systems-level network linking intestinal microbial ecology, host redox signaling pathways, and anti-tumor immunity. This integrated perspective provides a unifying model to explain variability in cancer susceptibility, tumor progression, and immunotherapy responsiveness.

This review seeks to establish and mechanistically delineate the GIA axis as an integrative conceptual framework linking microbial ecology, redox homeostasis, and tumor immunobiology. It synthesizes current preclinical and clinical evidence elucidating how alterations in gut microbiota composition influence oxidative stress signaling and immune regulation, thereby shaping cancer initiation, progression, and metastatic potential. Particular emphasis is placed on the translational relevance of the GIA axis in determining responsiveness and resistance to ICB. Furthermore, this review critically examines microbiome-targeted and redox-modulating therapeutic strategies, including probiotic supplementation, dietary interventions, FMT, antioxidant-based approaches, and rational combination immunotherapies designed to restore host-microbial-redox equilibrium. Finally, it identifies key unresolved questions and future research priorities, with particular attention to precision oncology strategies that integrate host, microbial, and oxidative stress-associated determinants of tumor behavior. By consolidating multidisciplinary evidence within this systems-level framework, this review aims to advance the mechanistic understanding of host-tumor interactions and uncover novel opportunities for therapeutic innovation in cancer management (Figure 1).

1.1. Defining the GIA axis and its status as a conceptual framework

The gut microbiome, immune, and antioxidant (GIA) axis is proposed herein as a bidirectional, systems-level network through which intestinal microbial ecology, host redox signaling, and anti-tumor immune competence continuously influence one another to shape cancer risk and immunotherapy outcomes. It is crucial to emphasize that the GIA axis currently functions as an integrative, heuristic framework rather than a definitively validated

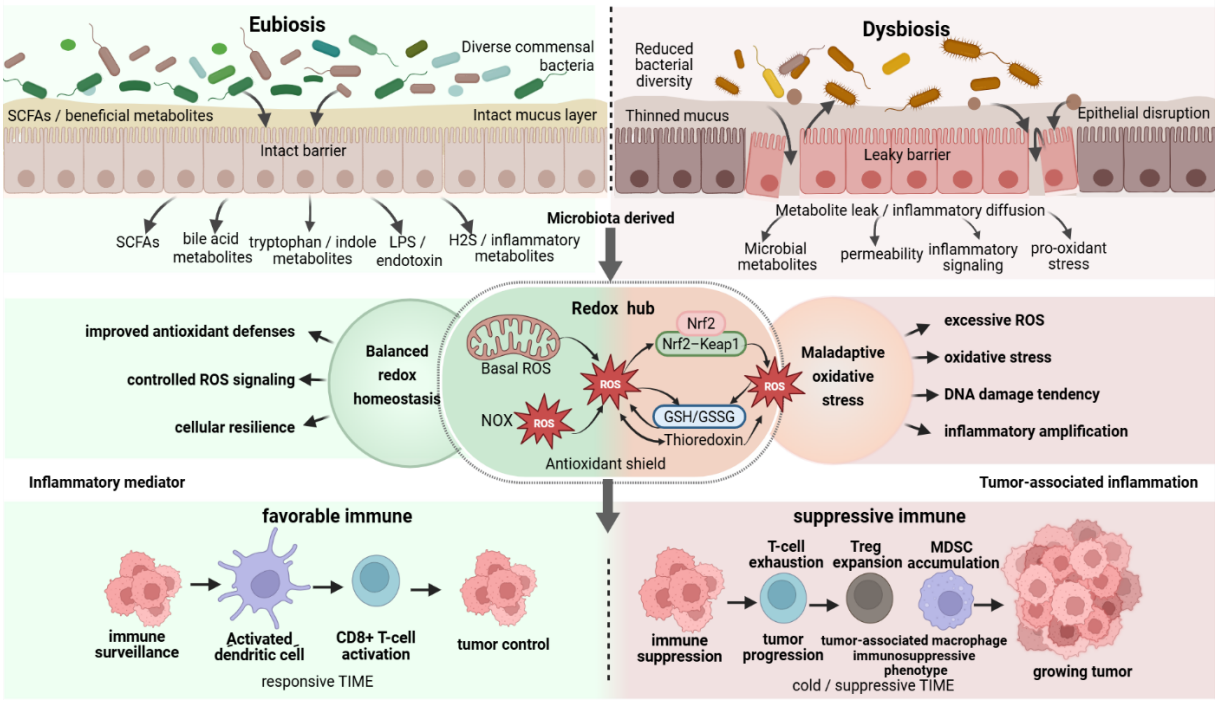


Figure 1. Multiscale mechanistic framework of the gut-immune-antioxidant (GIA) axis in cancer. Intestinal microbial states and microbial metabolites regulate epithelial integrity and systemic redox tone, which converge on antioxidant signaling pathways and redox-sensitive immune circuits in the tumor–immune microenvironment (TIME). Feedback from inflammatory and immune processes further reshapes microbial ecology and barrier function, establishing the GIA axis as a bidirectional network rather than a linear pathway. Schematic created by the authors.
Abbreviations: H_2S: Hydrogen sulfide; LPS: Lipopolysaccharide; MDSC: Myeloid-derived suppressor cells; NOX: NADPH oxidase; Nrf2: Nuclear factor erythroid 2-related factor 2; ROS: Reactive oxygen species; SCFA: Short-chain fatty acid; Treg: Regulatory T cell.

biological model. While substantial mechanistic evidence supports discrete interactions within this network, such as microbiota-derived SCFAs modulating local redox states or specific bacterial taxa correlating with immune checkpoint inhibitor responsiveness, the comprehensive three-way integration remains largely hypothetical. Consequently, this review carefully distinguishes claims supported by direct experimental or clinical evidence from those that represent our integrative hypothesis. As the field advances, rigorous prospective validation will be required to transition the GIA axis from a conceptual scaffold into an established biological paradigm.

1.2. Relationship of the GIA axis to existing microbiome immunity frameworks

The relationship between the gut microbiota, host immunity, and oxidative stress has been the subject of extensive investigation, leading to the development of several conceptual models. Existing literature has robustly described bilateral interactions, including microbiome-immune crosstalk, microbiome-mediated redox regulation, and metabolic-immune integration. We explicitly acknowledge these foundational concepts and do not claim priority over them. Rather than presenting the GIA axis as an entirely unprecedented discovery, we propose it as a necessary evolution of these prior models, designed to synthesize disparate observations into a unified, tripartite network.

The primary novelty of the GIA framework lies in its explicit nomination of redox signaling as the central integrative hub. While previous models have often treated oxidative stress as a downstream consequence of microbial dysbiosis or immune activation, the GIA axis posits that redox homeostasis is the primary mechanistic conduit through which microbial metabolites calibrate anti-tumor immune competence. By positioning redox biology at the center of this network, the framework provides a more cohesive explanation for how specific microbial signatures translate into distinct immunological phenotypes within the TME.

Furthermore, the GIA axis offers enhanced predictive and translational value through two key conceptual extensions. First, it incorporates a route-dependent, multi-organ perspective, as detailed in Section 3.4, which elucidates how gut-derived signals propagate systemically to influence extra-intestinal malignancies. Second, it introduces the concept of composite biomarker profiling, outlined in Section 6.2, which integrates microbial, redox, and immune metrics to stratify patients for immunotherapy.

1.3. Literature search strategy

This narrative review used a structured, non-systematic literature search to identify relevant preclinical, translational, and clinical studies. Comprehensive searches were performed across the PubMed/MEDLINE, Scopus, and Web of Science databases from their inception through July 2026. The primary search strategy utilized Boolean combinations of the following key terms: ("gut microbiome" OR "gut microbiota" OR "intestinal microbiome") AND ("oxidative stress" OR "redox homeostasis" OR "antioxidant" OR "Nrf2") AND ("immunity" OR "immune checkpoint" OR "immunotherapy" OR "tumor microenvironment") AND ("cancer" OR "tumor" OR "oncology"). The search was restricted to English-language articles. Article selection prioritized peer-reviewed original research, comprehensive reviews, and meta-analyses. Priority was given to recent publications (within the last five years) to capture the rapidly evolving translational and clinical landscape, while foundational mechanistic studies were included regardless of publication date. Additional relevant articles were identified through manual screening of the reference lists of included studies.

2. Core components of the GIA axis

2.1. Gut microbiota and redox homeostasis

A eubiotic gut microbiota is characterized by high taxonomic diversity, functional redundancy, and dominance of health-associated commensals such as *Faecalibacterium*, *Akkermansia*, *Bifidobacterium*, and *Lactobacillus* species, which collectively sustain epithelial barrier integrity, immune tolerance, and redox balance.[21,22] In this state, microbial metabolic outputs, including SCFAs, indole derivatives, and other small molecules, support antioxidant defenses, limit endotoxemia, and prevent chronic low-grade inflammation that would otherwise drive oxidative stress and carcinogenesis.[21,23]

By contrast, dysbiosis in cancer and pre-malignant conditions is frequently characterized by reduced microbial diversity, expansion of pathobionts (*e.g.*, *Fusobacterium* and genotoxin-producing *Escherichia coli*), and loss of key butyrate producers, together with altered redox tolerance across the community.[23-25] Experimental profiling of fecal and isolate-level oxidative-stress responses indicates that exposure to ROS reshapes community structure, favoring aerotolerant and pro-inflammatory taxa at the expense of obligate anaerobes.[23] This shift promotes barrier dysfunction, enhances LPS translocation, and perpetuates a feed-forward loop of inflammation and oxidative damage that can modulate cancer risk and therapy responses.[21,23-25]

2.1.1. Taxonomic and functional signatures of the GIA axis

The gut microbiota is a highly complex and heterogeneous community rather than a uniform system, in which individual microbial taxa play distinct, sometimes opposing roles within the GIA axis (Table 1). Beneficial commensals, such as *Akkermansia muciniphila* and *Bifidobacterium* species, help maintain intestinal barrier integrity and enhance systemic anti-tumor immune responses. In contrast, opportunistic pathogens like *Fusobacterium nucleatum* disrupt these protective mechanisms by promoting a pro-tumorigenic environment.[26] These harmful microbes drive the GIA axis toward persistent inflammation through mechanisms that include oxidative stress generation, often mediated by enzymes such as spermine oxidase, and the recruitment of immunosuppressive cell populations.[21] Recognizing these taxonomic and functional distinctions is critical for defining microbial profiles that may serve as biomarkers for cancer susceptibility and response to therapy.[27]

Table 1. Pro- and anti-tumor activities of key gut microbiota: mechanistic insights and immuno-redox interactions

Bacterial taxon	GIA role (pro- or anti-tumor)	Primary mechanism of action	Impact on redox/immune signaling	Ref.
Akkermansia muciniphila (AKK-OMVs, Amuc_1434)	Anti-tumor	The OMVs containing Amuc_1434 contribute to mucosal integrity and acetate production. Furthermore, they exert an antitumor effect by downregulating PD-L1 and activating $CD8^+$ T cells.	Increases $CD8^+$ T cell proliferation and infiltration; elevates IFN-γ and IL-2 levels; enhances antitumor immunity; reduces tumor growth	28
Bifidobacterium spp.	Anti-tumor	Modulates dendritic cell maturation to regulate host immune responses and enhance the efficacy of ICIs, offering potential synergistic effects in immunotherapy.	Improves antitumor immunity; may enhance ICI responsiveness; mechanisms involve immune activation pathways, though precise molecular interactions and redox-related effects remain to be fully elucidated.	29
Fusobacterium nucleatum	Pro-tumor	Induces chronic inflammation via IL-1β, IL-6, and TNF-α; adheres to epithelial cells through FadA, disrupting junctions and promoting EMT; alters gut microbiota and activates Wnt/β-catenin signaling.	Increases ROS production leading to DNA damage; suppresses immune responses; promotes immunosuppressive microenvironment; enhances tumor progression, metastasis, and therapy resistance	30
Faecalibacterium prausnitzii	Anti-inflammatory / Anti-tumor	*F. prausnitzii*: SCFA (butyrate) production, HDAC inhibition, MAM secretion, Treg induction, epithelial barrier enhancement.	Regulates Th17/Treg balance; activates SCFA–GPR signaling; suppresses pro-inflammatory cytokines; enhances barrier integrity; reduces oxidative stress	31
Bacteroides fragilis (ETBF)	Pro-tumor	Produces BFT; modulates tumor-immune microenvironment in liver metastases	Increases $CD68^+$ macrophage infiltration; reduces $FOXP3^+$ regulatory T cells (Tregs); promotes immune evasion without affecting $CD8^+$ T cells or B cells	32

Abbreviations: BFT: *Bacteroides fragilis* toxin; EMT: Epithelial–mesenchymal transition; GPR: G-protein-coupled receptor; ICI: Immune checkpoint inhibitor; IFN: Interferon; IL: Interleukin; OMV: Outer membrane vesicle; ROS: Reactive oxygen species; SCFA: Short-chain fatty acid; TNF-α: Tumor necrosis factor alpha.

Microbial metabolites serve as central mediators linking the microbiota to host redox homeostasis. SCFAs such as butyrate, acetate, and propionate, produced by fermentation of dietary fiber, regulate redox status via multiple mechanisms: inhibition of histone deacetylases (HDACs), activation of G-protein-coupled receptors (*e.g.*, GPR41/43), and upregulation of antioxidant and detoxification genes, partly through Nrf2-dependent transcriptional programs. Butyrate enhances glutathione synthesis, improves mitochondrial efficiency, and reduces ROS production, thereby limiting oxidative DNA damage in the intestinal epithelium and shaping the tumor-immune microenvironment (TIME).[22,33]

Bile acids, extensively modified by gut microbes, also exert strong redox-modulating effects. While activation of FXR and TGR5 by specific bile acid species can dampen inflammation and oxidative stress, accumulation of hydrophobic secondary bile acids (*e.g.*, deoxycholic acid)

promotes mitochondrial dysfunction, ROS generation, and DNA damage in hepatocytes and colonic epithelial cells.[24,25] Tryptophan-derived indole metabolites act through the aryl hydrocarbon receptor (AhR) to maintain barrier integrity, regulate antioxidant gene expression, and modulate mucosal immune tone, whereas dysregulated tryptophan catabolism skews toward immunosuppressive kynurenine pathways that may foster a pro-oxidant, tumor-permissive milieu.[21,25] Hydrogen sulfide (H_2S), produced by both host and bacterial enzymes, further exemplifies this duality: at physiological levels, it acts as a gaseous signaling molecule with cytoprotective and antioxidant effects, but at higher concentrations it becomes cytotoxic, contributing to epithelial damage and genotoxic stress.[22,25]

Collectively, these data support a model in which the functional metabolic wiring of the gut microbiota, rather than taxonomic composition alone, critically determines host redox homeostasis and, by extension, the behavior of the TIME. Within the GIA axis, microbiota-derived metabolites continually calibrate systemic oxidative tone, influencing immune cell programming and responsiveness to anticancer therapies (Figure 2).

2.1.2. The metabolite "highways" of redox signaling

Communication between the gut microbiota and the TME is primarily driven by a wide range of microbial metabolites that function as signaling mediators along the GIA axis (Table 2). Among these, SCFAs, especially butyrate, play a pivotal role as epigenetic regulators by maintaining redox balance through Nrf2 activation and by supporting the differentiation of regulatory T cells, as detailed in Section 2.1. In contrast, other metabolites, such as lipopolysaccharide (LPS) and certain secondary bile acids, can push the system toward a pro-oxidative state, leading to mitochondrial impairment and enhanced systemic inflammation. Overall, this table highlights how these metabolic intermediates serve as signaling pathways that shape the direction and intensity of the host immune response.

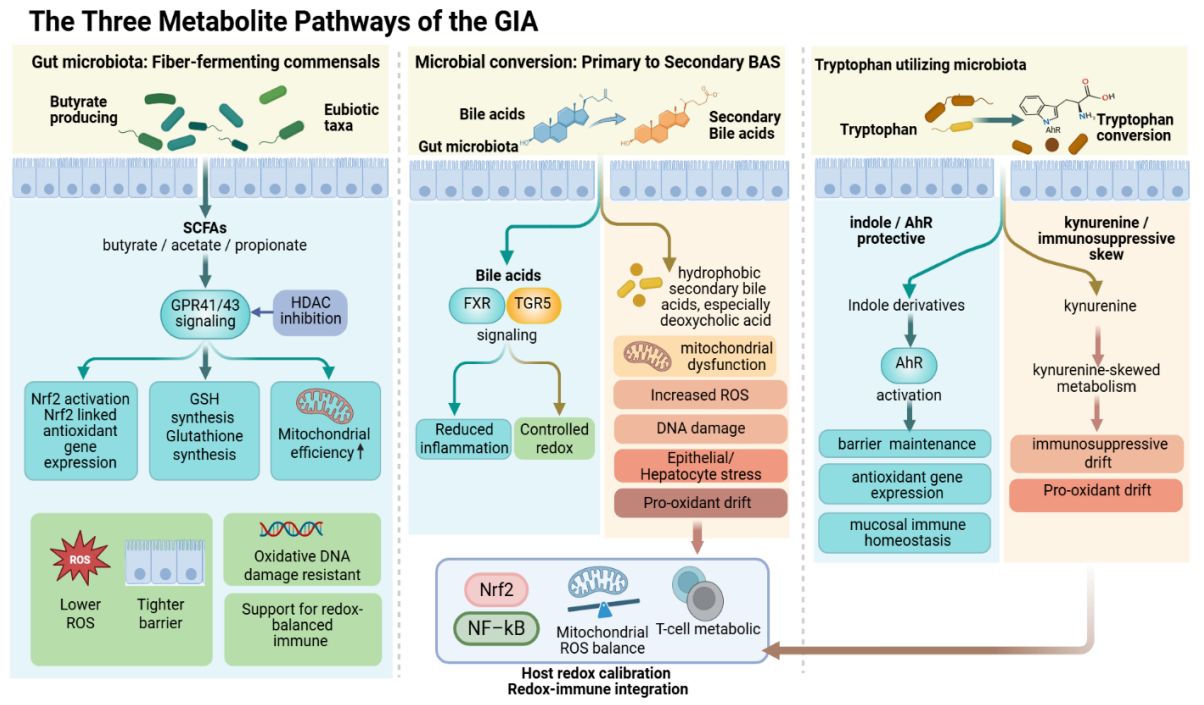


Figure 2. The three metabolite pathways of the gut–immune–antioxidant (GIA) axis. Microbiota-derived metabolites are major functional mediators linking gut ecology to host redox homeostasis. Short-chain fatty acids (SCFA) promote glutathione synthesis, mitochondrial efficiency, and Nrf2-associated antioxidant programs; bile acid derivatives signal through protective FXR/TGR5 pathways or, when skewed toward hydrophobic secondary bile acids, drive mitochondrial dysfunction and reactive oxygen species (ROS) accumulation; and tryptophan-derived indoles support barrier integrity and antioxidant gene expression through AhR, whereas kynurenine-biased routing favors an immunosuppressive, pro-oxidant state. Together, these three metabolite pathways calibrate whether the mucosal environment remains redox-balanced or shifts toward oxidative injury and tumor-permissive drift. Schematic created by the authors.

Abbreviations: AhR: Aryl hydrocarbon receptor; BAS: Bile acids; HDAC: Histone deacetylase; Nrf2: Nuclear factor erythroid 2-related factor 2; ROS: Reactive oxygen species; SCFA: Short-chain fatty acid.

Table 2. Microbial metabolites as redox and immune modulators

Metabolite class	Example	Redox impact	Immunomodulatory effect	Ref.
SCFAs (livestock application)	Butyrate	Enhances antioxidant capacity, activates NRF2, improves mitochondrial efficiency, and reduces oxidative stress.	By inhibiting HDACs, these metabolites promote a healthy Treg/Th1 balance and improve gut barrier integrity. Furthermore, they reduce inflammation, modulate the microbiota, and support mucosal immunity by enhancing IL-22 production.	34
TCM formula–microbiota–bile acid axis	Xiayuxue decoction (XYXD)	Modulates bile acid metabolism via gut microbiota (↑BSH activity → ↑primary bile acids, ↓secondary bile acids); indirectly influences oxidative balance in liver microenvironment.	Activates hepatic natural killer T cells via primary bile acids → ↑IFN-γ production → anti-HCC immune response.	35
Indoles (therapeutic)	Indole-3-carboxaldehyde (IAld)	Activates AhR/AMPK signaling; preserves mitochondrial integrity; promotes autophagy; reduces TNF-α-induced oxidative stress.	Enhances intestinal barrier (↑ tight junctions); maintains mucosal homeostasis; reduces inflammation in colitis.	34
Gasotransmitters	Hydrogen sulfide (H_2S)	Regulates redox homeostasis via the transsulfuration pathway (TSP) and SQR-mediated oxidation; modulates mitochondrial and cytosolic energy metabolism; signals through persulfidation and reactive polysulfides.	Modulates macrophage inflammatory phenotype; reduces proinflammatory activation; influences gene expression, transcription factors, and immune signaling pathways.	36
Pyranocoumarin (natural compound)	Decursinol angelate (DA)	Inhibits NADPH oxidase (NOX) and iNOS → reduces ROS generation; blocks MAPK (Raf–ERK) signaling.	Inhibits NFκB translocation; suppresses IL-1β and IL-6; prevents M1 macrophage polarization and inflammatory activation.	37

Abbreviations: BSH: Bile salt hydrolase; HCC: Hepatocellular carcinoma; HDAC: Histone deacetylase; IFN-γ: Interferon gamma; IL: Interleukin; NFκB: Nuclear factor kappa B; Nrf2: Nuclear factor erythroid 2-related factor 2; SCFA: Short-chain fatty acid; TCM: Traditional Chinese medicine; Th1: T helper cell 1; Treg: Regulatory T cell.

2.1.3. Extracellular vesicles and microbiota-derived signaling particles

Beyond soluble metabolites, membrane-bound extracellular vesicles constitute an additional, less extensively characterized signaling modality within the GIA axis. Outer membrane vesicles (OMVs) released by Gram-negative commensals, exemplified by the *Akkermansia muciniphila* OMVs discussed in Table 1, can carry metabolic enzymes, immunomodulatory proteins, and antigenic cargo capable of engaging host pattern-recognition receptors and modulating anti-tumor T-cell responses at sites distant from their release.[38] Because vesicular cargo is protected from luminal degradation, extracellular vesicles may allow microbiota-derived signals to act with greater spatial and temporal precision than free metabolites. We identify microbiota-derived extracellular vesicles as an emerging axis of GIA signaling meriting dedicated mechanistic and translational investigation.

2.2. Oxidative stress and antioxidant systems in the tumor–immune microenvironment

The tumor–immune microenvironment (TIME) is characterized by highly heterogeneous redox landscapes, shaped by ROS and reactive nitrogen species (RNS) produced by both malignant and immune cells. Mitochondria are major sources of ROS via electron leakage at complexes I and III of the electron transport chain, and elevated metabolic flux in proliferating tumor cells and activated immune cells enhances ROS production.[39,40] Additional enzymatic sources include NADPH oxidases (NOX1-5, DUOX1/2) in tumor, stromal, and immune cells, xanthine oxidoreductase, and peroxisomal oxidases, whereas RNS are generated mainly via inducible nitric oxide synthase (iNOS) in macrophages, dendritic cells, and other myeloid populations.[41,42] In the TIME, hypoxia, nutrient deprivation, and oncogenic signaling converge to amplify ROS and RNS, resulting in oxidative stress that impacts genomic stability, cell death pathways, and immune cell function.[43,44]

To survive in this oxidatively stressed context, both tumor and stromal cells deploy layered antioxidant defense systems. Central to this is the Nrf2-Keap1 pathway: under basal conditions, Keap1 targets Nrf2 for proteasomal degradation, whereas oxidative or electrophilic stress

disrupts this interaction, allowing Nrf2 to accumulate, translocate to the nucleus, and drive transcription of a broad cytoprotective program encompassing glutathione synthesis (GCLC, GCLM), detoxification enzymes, and ROS-scavenging systems.[45,46] Persistent activation of Nrf2 is a common event in human cancers, where it supports metabolic rewiring, ferroptosis resistance, and therapy tolerance, and is increasingly recognized as a key regulator of the TIME and immunotherapy responsiveness.[47,48]

The glutathione (GSH) system constitutes a major redox buffer, with GSH/GSSG cycling controlled by glutamate-cysteine ligase, glutathione synthetase, glutathione peroxidases, and glutathione reductase.[49] In many tumors, increased GSH pools and glutathione peroxidase (GPX) activity mitigate chemotherapy- and radiotherapy-induced ROS, while also shaping redox signals in infiltrating lymphocytes and myeloid cells.[50] In parallel, the thioredoxin (Trx) system (Trx1/Trx2, thioredoxin reductases, and peroxiredoxins) maintains redox-sensitive cysteine residues in metabolic and signaling proteins, influencing antigen processing, cytokine production, and cell survival.[51] Superoxide dismutases (SODs) and catalase further detoxify superoxide and hydrogen peroxide, collectively preventing uncontrolled oxidative damage yet simultaneously constraining ROS-dependent immune activation.

Recent work underscores that antioxidant pathways are not merely protective but immunomodulatory. Nrf2 activation in tumor cells and myeloid cells can dampen inflammatory cytokine production, limit type I interferon (IFN) signatures, and reduce immune-cell infiltration, thereby fostering immune evasion and resistance to ICB.[52,53] Conversely, targeted modulation of Nrf2, glutathione metabolism, or mitochondrial ROS production is emerging as a strategy to recondition the TIME and enhance anti-tumor immunity, placing redox biology at the heart of rational attempts to manipulate the GIA axis.

2.3. Redox-sensitive immune pathways

ROS and RNS act as critical secondary messengers in immune cells, with concentration, localization, and duration of the signal determining whether they support activation or drive dysfunction. In antigen-presenting cells, moderate ROS levels promote efficient antigen processing, cross-presentation, and upregulation of costimulatory molecules. In contrast, excessive oxidative stress impairs proteasomal function, destabilizes MHC-peptide complexes, and can induce dendritic cell apoptosis, reducing the priming of tumor-specific T cells.[54] In T lymphocytes, tightly regulated ROS pulses downstream of T-cell receptor (TCR) engagement, originating from mitochondrial electron transport and NOX2 activity, amplify proximal signaling, sustain calcium influx, and activate redox-sensitive transcription factors such as NFAT, NF-κB, and AP-1.[55] When ROS levels exceed buffering capacity, however, they drive lipid peroxidation, DNA damage, and metabolic exhaustion, leading to T-cell dysfunction and apoptosis within the TIME.[56]

Distinct immune subsets exhibit differential redox vulnerability. Effector $CD8^+$ T cells, which rely heavily on oxidative phosphorylation and glycolysis, are particularly sensitive to mitochondrial ROS-driven exhaustion; strategies that restore mitochondrial fitness and fine-tune ROS levels have been shown to reinvigorate exhausted T cells and improve responses to checkpoint inhibitors.[57] Regulatory T cells (Tregs) and MDSCs often thrive in oxidative, metabolite-depleted niches. MDSCs generate high levels of ROS and peroxynitrite that nitrates TCR and MHC molecules, blunting antigen-specific T-cell recognition, while Tregs harness distinct antioxidant programs that allow them to maintain suppressive function under oxidative stress.[58,59]

These cellular effects are embedded within a broader network of redox-sensitive transcriptional pathways. Nrf2, NF-κB, and type I/II IFN signaling intersect extensively in the TIME. On the one hand, ROS activate NF-κB and IRF family transcription factors, promoting the production of pro-inflammatory cytokines and IFN, which are necessary for effective anti-tumor immunity.[60] On the other hand, sustained oxidative stress and chronic Nrf2 activation in tumor cells, tumor-associated macrophages, and other myeloid populations can skew signaling toward immunosuppressive phenotypes, with reduced IFN signatures, enhanced expression of inhibitory ligands, and metabolic barriers to T-cell infiltration.[61,62] Recent studies show that Nrf2 hyperactivation can directly reduce immune-cell infiltration and polarize tumor-associated macrophages toward cancer-promoting states, thereby undermining checkpoint blockade and other immunotherapies.[63,64]

Within the GIA axis framework, these findings highlight ROS/RNS not simply as byproducts of inflammation or metabolism, but as integrative signals through which the gut microbiota, antioxidant systems, and immune pathways continuously communicate. Modulating redox-sensitive immune circuits through microbiota-derived metabolites, targeted redox therapies, or combined immunomodulatory strategies represents a key opportunity to rewire the TIME toward durable anti-tumor immunity.[21]

2.3.1. Redox–immune interactions and therapeutic resistance

The effectiveness of immunotherapy is strongly shaped by the oxidative balance within the TME, which is significantly modulated by systemic GIA-related signaling (Table 3). Elevated levels of ROS, along with enhanced activation of antioxidant defense mechanisms, such as the Nrf2 pathway, in tumor cells, create conditions unfavorable for cytotoxic T lymphocytes. This oxidative stress contributes to T-cell metabolic dysfunction, reduced survival, and diminished antitumor activity. Understanding the interplay between redox regulation and immune escape mechanisms reveals that resistance to PD-1/PD-L1 blockade frequently reflects an imbalance within the GIA regulatory network. Table 3 summarizes how distinct redox alterations are linked to both intrinsic and acquired resistance mechanisms observed in cancer immunotherapy.[65]

Table 3. Redox signaling crosstalk in immunotherapy resistance

Redox factor	Effect on TME	Impact on immunotherapy response	Ref
Nrf2 overexpression	Enhances antioxidant defense, detoxification pathways, and metabolic adaptation of cancer cells under oxidative stress.	Promotes therapy resistance, immune evasion, and reduced sensitivity to ferroptosis and immune checkpoint blockade.	66
High ROS in TME	Promotes oxidative stress, DNA damage, genomic instability, and activation of proliferative signaling pathways.	Reduces immune cell function and contributes to resistance against immunotherapies.	67
Cadmium-induced HIF-1α stabilization	Enhances K63-linked ubiquitination, promotes ER stress, blocks autophagy, and supports IL-8 and VEGF expression under normoxic conditions.	Favors immune suppression and tumor progression through hypoxia-like signaling, inflammatory cytokine production, and angiogenesis, potentially reducing immunotherapy efficacy.	68
GSH depletion	Weakens intracellular antioxidant defense, increases sensitivity to oxidative stress, disrupts mitochondrial metabolism, and impairs endothelial barrier integrity.	May enhance oxidative-based therapies but can suppress adaptive immune responses through reduced T-cell proliferation and function.	69

Abbreviations: ER: Endoplasmic reticulum; GSH: Glutathione; HIF-1α: Hypoxia-inducible factor 1-alpha; IL: Interleukin; Nrf2: Nuclear factor erythroid 2-related factor 2; ROS: Reactive oxygen species; TME: Tumor microenvironment; VEGF: Vascular endothelial growth factor.

3. Cancer-specific manifestations of the GIA axis

3.1. Colorectal cancer

Colorectal cancer (CRC) is the prototypical malignancy in which the GIA axis is most clearly discernible at the mucosal interface. CRC patients consistently exhibit a CRC-specific dysbiosis characterized by enrichment of pro-inflammatory and genotoxic taxa (*e.g.*, *Fusobacterium nucleatum*, enterotoxigenic *Bacteroides fragilis*, and pks$^+$ *Escherichia coli*) and depletion of butyrate-producing commensals such as *Faecalibacterium prausnitzii*, *Roseburia*, and *Eubacterium rectale*.[70,71] This shift is observed across sporadic, adenoma-bearing, and carcinoma stages, and is accentuated in colitis-associated CRC, suggesting an early and progressive remodeling of the colonic GIA axis. Mechanistically, dysbiosis promotes chronic mucosal inflammation, epithelial barrier disruption, and sustained ROS and RNS generation, creating a mutagenic niche that accelerates genomic instability and clonal evolution.[72,73]

In both sporadic and inflammatory bowel disease (IBD)-associated CRC, oxidative stress is a central mediator linking dysbiosis to carcinogenesis. Dysregulated gut communities increase luminal and mucosal ROS via several routes: induction of inflammatory cascades (NF-κB activation, cytokine release) in epithelial and immune cells; secretion of bacterial toxins (*e.g.*, colibactin, *B. fragilis* toxin) that trigger DNA damage and redox imbalance; and production of metabolites such as secondary bile acids and hydrogen sulfide (H_2S), which impair mitochondrial function and promote lipid peroxidation.[74] In IBD, recurrent cycles of inflammation and injury amplify these redox insults, accelerating the sequence from dysplasia to carcinoma, with elevated oxidative DNA lesions (*e.g.*, 8-oxo-dG) and defective DNA repair frequently reported in colitis-associated neoplasia.[75]

Within this colonic GIA axis, microbial metabolites act as fine-tuners of redox and immune tone. As detailed in Section 2.1, butyrate and other SCFAs support epithelial barrier integrity, fuel colonocytes,

and upregulate antioxidant and detoxification pathways, thereby constraining ROS accumulation and pro-tumor inflammation.[76] Conversely, dysbiosis-associated accumulation of secondary bile acids (*e.g.*, deoxycholic acid) and H_2S enhances mitochondrial ROS, DNA damage, and inflammasome activation, tipping the balance toward a pro-oxidant, tumor-permissive microenvironment.[77] CRC lesions are therefore embedded in a rewired local GIA axis in which pathogenic taxa and their metabolites sustain redox stress, recruit immunosuppressive myeloid and T-cell subsets, and blunt anti-tumor immunity, while loss of eubiotic SCFA-producing consortia removes key antioxidant and immunoregulatory brakes.[78]

3.2. Hepatobiliary and pancreatic malignancies

3.2.1. Gut–liver–pancreas interactions and oxidative injury

The gut-liver-pancreas axis provides a direct anatomical and metabolic route through which the intestinal microbiota modulates hepatobiliary and pancreatic carcinogenesis. Portal venous drainage delivers microbe-associated molecular patterns (MAMPs) such as LPS, peptidoglycan, and bacterial DNA, along with microbially modified bile acids and other metabolites, directly to the liver. In chronic liver disease and metabolic dysfunction–associated steatotic liver disease, dysbiosis and increased intestinal permeability amplify this portal influx, activating TLR4 and related pattern-recognition receptors on Kupffer cells, liver sinusoidal endothelial cells, and hepatic stellate cells.[79] Downstream, NADPH oxidases, mitochondrial respiratory chain enzymes, and inducible nitric oxide synthase (iNOS) generate abundant ROS and RNS, driving lipid peroxidation, stellate-cell activation, and progressive fibrosis that sets the stage for hepatocellular carcinoma (HCC).[80]

Bile acid metabolism forms a second major redox-sensitive conduit within this axis. Gut microbes convert primary bile acids to secondary bile acids, thereby modulating FXR and TGR5 signaling in hepatocytes, cholangiocytes, and immune cells. In HCC, dysbiosis-driven alterations in the bile acid pool foster oxidative stress by inducing mitochondrial dysfunction and NOX-dependent ROS production, while simultaneously reshaping immune cell recruitment and function in the hepatic TME.[81] Recent integrative reviews highlight that gut dysbiosis and bile acid dysregulation collectively damage the gut-vascular barrier, alter intratumoral microbiota composition, and sculpt an immunosuppressive, pro-oxidant hepatic niche that undermines surveillance and promotes HCC progression.[82]

The pancreas is likewise embedded in this GIA circuitry. Translocation of oral and intestinal bacteria into the pancreatic ductal system or parenchyma, together with systemic dissemination of microbial metabolites, contributes to chronic pancreatitis, pancreatic ductal fibrosis, and the initiation of pancreatic ductal adenocarcinoma (PDAC).[83] Pancreas-associated microbiota have been shown to modulate local immune infiltration, stromal activation, and redox balance: certain taxa can shield tumor cells from oxidative damage, whereas others promote smoldering inflammation and ROS and RNS generation that facilitate oncogenic transformation and therapy resistance.[84] Microbiome-focused reviews emphasize that gut, oral, and intrapancreatic communities influence PDAC risk, desmoplastic remodeling, and responses to chemotherapy and immunotherapy, partly via bile acid and SCFA signaling, NOX activation, and modulation of myeloid cell phenotypes within the pancreatic TME.[85]

3.2.2. Fibrosis, carcinogenesis, and therapy response

Across hepatobiliary and pancreatic cancers, the GIA axis shapes both fibrogenesis and therapeutic vulnerabilities. In HCC, gut dysbiosis–driven oxidative stress accelerates stellate-cell activation and extracellular matrix deposition, thereby promoting cirrhosis and providing a fibrotic scaffold for malignant transformation. Intratumoral and portal microbiota also modulate response to locoregional therapies and immunotherapy; HCC cohorts with favorable gut microbial signatures exhibit stronger intrahepatic immune activation and better survival under ICB, whereas dysbiotic profiles correlate with exhausted T-cell phenotypes and impaired IFN signaling.[86]

In PDAC, microbiota-conditioned redox and immune landscapes contribute to the profound therapy resistance that characterizes this disease. Elevated ROS within hypoxic, desmoplastic pancreatic tumors can both promote mutagenesis and select for clones with upregulated antioxidant defenses, reducing susceptibility to ROS-dependent cytotoxic therapies. Microbiome-targeted strategies, including antibiotics, probiotics, engineered consortia, and FMT, are being explored to reconfigure the pancreatic GIA axis, dampen pro-tumor oxidative signaling, relieve immunosuppression, and sensitize tumors to chemotherapy, radiotherapy, and immunotherapy.[87]

Although the mechanistic evidence for hepatobiliary and pancreatic malignancies is currently less mature than that for CRC, emerging multi-omic studies are rapidly elucidating the specific microbial metabolites and redox signatures that drive therapy resistance in these contexts, representing a critical frontier for future GIA axis research.

3.3. Extra-intestinal and CNS tumors

3.3.1. Systemic spillover of inflammatory and redox mediators

The influence of the GIA axis is not confined to the gut and hepatopancreatic systems. Systemic spillover of inflammatory mediators, ROS and RNS, and microbiota-derived metabolites links intestinal dysbiosis to cancers in distant organs, including lung, breast, and hematologic malignancies. Chronic gut-derived endotoxemia and cytokine release promote a state of low-grade metaflammation in which redox-sensitive pathways (*e.g.*, NF-κB, STAT3) are tonically activated in peripheral tissues, biasing toward oncogenic signaling, epithelial-mesenchymal transition, and immune dysfunction.[88] Circulating metabolites such as SCFAs, tryptophan-derived kynurenines, and bile acid derivatives further modulate systemic antioxidant defenses and immune cell differentiation, creating organ-specific niches that can either restrain or favor tumor growth depending on context and metabolite balance.[89]

In this systemic perspective, the GIA axis functions as a body-wide rheostat, in which gut microbial composition and metabolism simultaneously tune redox homeostasis and immune tone across multiple anatomical sites. Tumors arising outside the intestine thus inherit a background of GIA programming shaped by diet, antibiotics, comorbid inflammatory disease, and other host-environment interactions.

3.3.2. The Gut–brain–tumor axis in glioma

Gliomas and glioblastoma provide a clear example of an extra-intestinal malignancy influenced by a gut-brain-tumor branch of the GIA axis. The gut microbiota affects central nervous system (CNS) physiology via immune, neural, endocrine, and metabolic routes, including vagal signaling, modulation of circulating cytokines, and production of BBB-permeable metabolites such as SCFAs, tryptophan derivatives, and microbial neurotransmitter analogs. Recent reviews highlight that dysbiosis in glioma patients is associated with altered inflammatory and metabolic profiles, microglial activation, and changes in BBB integrity, all of which are tightly coupled to redox signaling in the brain TME.[90]

Within gliomas, microglia and tumor-associated macrophages are key executors of redox-dependent immunomodulation. Gut-derived signals can skew these cells toward pro-tumor phenotypes characterized by high NOX activity, ROS production, and secretion of immunosuppressive cytokines, thereby fostering glioma cell proliferation, invasion, and resistance to therapy. Conversely, restoration of eubiotic microbiota or targeted modulation of specific taxa has been shown in pre-clinical models to recalibrate microglial activation states, reduce oxidative stress, and enhance anti-tumor immune responses, including improved efficacy of immune checkpoint inhibitors and radiotherapy.[91]

Clinical and translational studies now describe a glioma-specific GIA signature, wherein gut microbial profiles correlate with systemic oxidative and inflammatory markers, intratumoral immune infiltration, and patient outcomes. Integrative analyses of the gut-brain-immune axis in glioma propose that microbiota-driven modulation of Nrf2, NF-κB, and interferon pathways, both peripherally and within the CNS, critically shapes glioma biology and treatment response. Conceptually, gliomas sit at the distal end of a gut-brain-tumor conduit, where intestinal dysbiosis, redox imbalance, and immune dysregulation converge to regulate tumor growth, progression, and susceptibility to immunotherapeutic and cytotoxic interventions.[92]

3.3.3. Systemic microbiome remodeling beyond the gut

Although the GIA axis is conceptualized primarily around the intestinal microbiota, treatment-associated microbial remodeling is not restricted to the gut. Emerging longitudinal evidence indicates that other mucosal microbial niches, including the oral and salivary microbiomes, undergo significant disease- and chemotherapy-associated compositional shifts during systemic cancer therapy. For instance, longitudinal alterations in the salivary microbiome have been documented in breast cancer patients undergoing neoadjuvant chemotherapy.[93] Such findings suggest that the GIA concept may extend to extra-intestinal mucosal microbial compartments, representing an additional dimension of host-microbe-redox interaction that warrants further investigation beyond the gut-centric framework.

3.4. Comparative GIA manifestations across tumor sites

The behavior of the GIA axis varies according to tumor location and the pathways through which microbial signals spread (Table 4). In CRC, these interactions occur locally through direct contact with the gut environment. In contrast, tumors of the hepatobiliary system and the CNS are influenced through indirect mechanisms, including portal blood flow and gut-brain communication pathways. The accompanying comparison outlines how microbial imbalance, oxidative damage, and immune alterations collectively contribute to disease progression in CRC, HCC, PDAC, and glioma. It emphasizes route-dependent transmission along the GIA axis and highlights the distinct

oxidative stress conditions characteristic of each affected organ.[94]

We selected CRC as the principal model for illustrating the GIA axis in this review because it is the malignancy for which direct mucosal contact with the gut microbiota, the largest volume of mechanistic and clinical evidence linking dysbiosis to redox-driven carcinogenesis, and the most mature microbiome-immunotherapy correlative data currently exist. The comparatively shorter treatment of hepatobiliary, pancreatic, and glioma manifestations presented above reflects the earlier stage of mechanistic and clinical evidence currently available for these tumor types, rather than an assessment of their biological importance within the GIA framework. We acknowledge this asymmetry explicitly as a limitation of the current evidence base, as discussed further in Section 6.3. As longitudinal cohort studies, intratumoral microbiome profiling, and multi-omic integration expand for hepatocellular carcinoma, pancreatic ductal adenocarcinoma, and CNS malignancies, we anticipate that the GIA axis will be elaborated with equivalent mechanistic depth across these tumor types. Until such data mature, the present review necessarily relies on CRC as the most fully characterized exemplar of microbiome-redox-immune integration at the mucosal interface (Figure 3).

Table 4. Manifestations of the GIA axis across different malignancies

Cancer type	Primary GIA route	Dominant redox stressor	Key immune shift	Ref.
GI cancers (general)	Direct local mucosal Interaction; microbial metabolite signaling	Oxidative stress from redox imbalance (ROS, H_2S, NO, SCFAs dysregulation)	Chronic inflammation with immune dysregulation (DNA damage, mutation accumulation)	95
Colorectal (CRC)	Local mucosal (direct bacterial interaction)	Bacterial genotoxins (*e.g.*, colibactin, CDT that lead to DNA damage & ROS-mediated oxidative stress)	• Genomic instability with impaired immune surveillance • loss of SCFA-mediated Treg/Th17 balance	78
Hepatocellular (HCC)	Portal circulation + bile acid accumulation/lymphatic dissemination	Bile acid–induced redox imbalance (cholestasis, oxidative stress from bile acid overload)	Suppressed natural killer T cell recruitment; M2-like TAM polarization that leads to an immunosuppressive microenvironment & enhanced metastasis	96
Pancreatic (PDAC)	Systemic translocation and stromal–tumor interaction	Hypoxia-driven ROS modulation, desmoplastic stroma–mediated redox buffering (CAFs shielding)	Stromal-driven immune modulation with myeloid polarization (TAMs/MDSCs) and inflammatory cell recruitment	97
Glioma (GBM)	Gut–brain axis (microbiota–metabolite signaling)	Metabolite-driven redox modulation (glycine, β-hydroxybutyrate) with altered brain metabolome	Microglia-driven pro-angiogenic TME; astrocyte-mediated pro-inflammatory activation (KD-induced)	98

Abbreviations: CAF: Cancer-associated fibroblast; CDT: Chemodynamic therapy; GIA: Gut microbiome, immune, and antioxidant; H_2S: Hydrogen sulfide; MDSC: Myeloid-derived suppressor cell; NO: Nitric oxide; ROS: Reactive oxygen species; SCFA: Short-chain fatty acid; TAM: Tumor-associated macrophage; TME: Tumor microenvironment; Treg: Regulatory T cell.

4. Modulating the GIA axis: Microbiome-directed strategies

4.1. Probiotics, prebiotics, synbiotics, and postbiotics

Microbiome-directed interventions provide a tractable way to modulate the GIA axis by reshaping microbial composition, metabolite outputs, and host redox-immune signaling. Probiotics, prebiotics, synbiotics, and postbiotics converge on several shared mechanisms. These include ecological remodeling through the displacement of pathobionts and enrichment of SCFA-producing taxa; redox reprogramming via increased antioxidant metabolites and upregulation of Nrf2-dependent cytoprotective genes; and immune recalibration characterized by reinforced barrier integrity, reduced lipopolysaccharide translocation, and attenuation of pro-inflammatory cytokine signaling:[99]

4.2. Therapeutic innovation: Tuning the GIA axis

Harnessing the GIA axis for therapeutic applications calls for a comprehensive, multi-layered strategy that combines modulation of the microbiome with pharmacological approaches targeting redox pathways (Table 5). Existing approaches span from broad interventions, such as

FMT and increased dietary fiber intake, to more refined strategies, such as targeted postbiotics and Nrf2 inhibitors, aimed at enhancing tumor sensitivity to immune responses. Despite this progress, translating these approaches into routine clinical practice remains challenging due to issues related to large-scale production, patient variability, and inconsistent dosing standards. Framing these therapies within the GIA axis enables clinicians to design more individualized treatment plans that focus on the patient's overall systemic environment rather than solely on the tumor.

Table 5. Therapeutic interventions targeting the GIA axis

Strategy	Target component	Proposed mechanism	Status/Challenge	Ref.
Fecal microbiota transplantation	Gut microbiome	Restores microbial equilibrium by re-establishing eubiotic diversity and correcting dysbiosis; also indirectly modulates immune and epithelial responses	Variable donor composition; safety concerns; need for standardized screening and long-term efficacy validation	100
Next-gen probiotics	Microbiome / immune system / gut barrier	Production of bioactive anti-tumor metabolites, competitive inhibition of pathogens, modulation of immune cell activity, and strengthening of gut mucosal barrier; potential use in targeted delivery and combination or engineered therapies	Promising but still under development; challenges include strain identification, targeted delivery optimization, safety validation, and regulatory approval.	101
Dietary fiber	Gut microbiota / intestinal metabolites	Promotes microbiota shift toward increased butyrate (SCFA) production, activates AMPK signaling, improves intestinal epithelial gene expression and barrier integrity, and reduces trimethylamine N-oxide, triglyceride, and glucose levels	Response depends on microbiota composition; variable metabolic and clinical outcomes across individuals; mechanism strongly influenced by diet–microbiome interaction variability.	102
Nrf2 inhibitors	Antioxidant defense system (Nrf2 pathway)	Disrupting redox homeostasis to overcome ROS-driven drug resistance and restore treatment sensitivity	Limited selectivity; risk of systemic toxicity due to interference with normal cellular redox balance	103
Postbiotics	Metabolite / redox pathways	Administration of inactivated microbial products or components (*e.g.*, SCFAs, indole derivatives) to modulate metabolism, reduce inflammation, improve antioxidant status, and enhance gut barrier and immune function.	Promising safety and stability advantages over probiotics, but requires further optimization of efficacy, targeted delivery, and standardized clinical validation.	104

Abbreviations: GIA: Gut microbiome, immune, and antioxidant; Nrf2: Nuclear factor erythroid 2-related factor 2; ROS: Reactive oxygen species; SCFA: Short-chain fatty acid.

Pre-clinical and translational work increasingly frames these interventions as GIA-axis tuners rather than purely gut-localized agents. For example, comprehensive analyses of microbial therapeutics in oncology highlight that probiotic and synbiotic formulations can expand butyrate-producing *Lactobacillus* and *Bifidobacterium* species, lower mucosal ROS, upregulate tight-junction proteins, and reduce IL-6 and TNF-α signaling, thereby shifting the colonic niche from a pro-oxidant, pro-tumor configuration toward one that favors epithelial repair and immune surveillance.[105]

In inflammation-associated CRC models, particularly AOM/DSS-induced colitis-associated carcinogenesis, probiotic interventions have demonstrated consistent chemopreventive effects. Strains such as *Lactobacillus rhamnosus* GG, *L. casei*, *Bifidobacterium longum*, and defined multi-strain consortia reduce tumor burden and dysplasia severity. These effects are accompanied by attenuation of mucosal oxidative stress, as evidenced by reduced ROS levels and decreased oxidative DNA damage. Probiotic administration also modulates the inflammatory milieu, characterized by suppression of pro-inflammatory cytokines (IL-6, IL-17, and TNF-α) and enhancement of the anti-inflammatory cytokine IL-10. Concomitantly, these interventions restore microbial ecological balance by enriching SCFA-producing commensals while reducing the abundance of pathobionts such as *Fusobacterium* species, collectively contributing to protection against colitis-associated tumorigenesis.[106]

These effects are consistently accompanied by enhanced

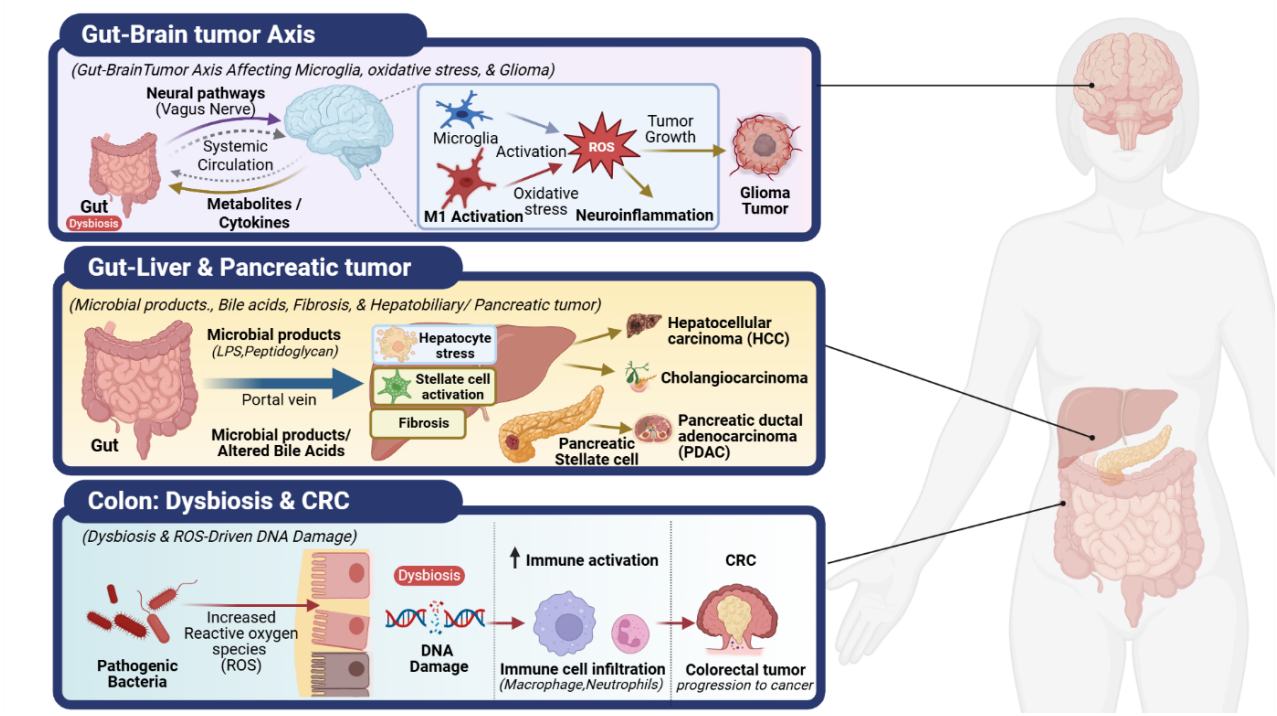


Figure 3. Route-specific propagation of the gut–immune–antioxidant (GIA) axis across tumor sites. The GIA axis influences different malignancies through distinct patterns of anatomical dissemination. In colorectal cancer (CRC), dysbiosis acts primarily through a local mucosal route within the colonic niche. In hepatobiliary and pancreatic malignancies, gut-derived microbial products and metabolite flux reach downstream tissues through the portal circulation. In glioma, gut signals influence the brain through multi-channel gut–brain communication involving immune, neural, and circulating metabolite pathways. This route-based framework highlights how a shared GIA concept manifests differently across organ systems. Schematic created by the authors.

antioxidant capacity (higher glutathione levels, induction of Nrf2-regulated enzymes) and improved barrier function, situating probiotics and synbiotics squarely as interventions that act along all three arms of the GIA axis: gut microbial ecology, redox homeostasis, and immune tone. Diet-based prebiotics (inulin, resistant starches, specific fibers, and polyphenol-rich substrates) further potentiate these effects by fueling beneficial taxa and increasing colonic butyrate, thereby reducing oxidative stress and suppressing colitis-associated tumorigenesis in rodent models.[107]

Postbiotics extend this concept by delivering defined microbial products without live organisms. Butyrate and other SCFAs, exopolysaccharides, and cell-wall components have demonstrated anti-proliferative, pro-apoptotic, and immunomodulatory effects in CRC models, often linked to reduced ROS, modulation of mitochondrial function, and interference with oncogenic signaling such as Wnt/β-catenin. Recent focused reviews on postbiotics in CRC underscore how butyrate and related metabolites can simultaneously constrain oxidative DNA damage, enhance DNA repair, and foster a more immunologically active TME.[108]

4.3. Treatment-related mucosal injury

Chemotherapy-, radiotherapy-, and targeted therapy-induced mucositis and enteritis represent prototypical GIA-axis injuries, characterized by epithelial barrier disruption, microbiota collapse, and ROS-driven inflammation. Pre-clinical and early clinical evidence indicate that microbiome-targeted interventions can attenuate these toxicities through coordinated redox and immune modulation. Probiotic and synbiotic formulations reduce chemotherapy-induced mucosal injury by decreasing epithelial ROS, suppressing pro-inflammatory cytokines, and promoting mucosal regeneration. In parallel, prebiotics restore SCFA-producing bacteria after cytotoxic therapy, increasing luminal butyrate, strengthening barrier integrity, and reducing bacterial translocation, thereby dampening systemic inflammation.[109] Postbiotic strategies, particularly butyrate-based interventions, further mitigate mucosal damage by enhancing tight junction integrity and reducing oxidative stress in CRC and therapy-induced mucositis models .[110]

Recent integrative reviews in cancer patients highlight

that targeted use of probiotics, prebiotics, and postbiotics can lessen gastrointestinal toxicity, protect against oxidative damage, and potentially preserve treatment intensity, with emerging data in breast, colorectal, and gastrointestinal malignancies. Mechanistically, these interventions reduce epithelial DNA damage, curtail NOX-mediated ROS generation, and maintain a more balanced microbiota, thereby maintaining a more favorable GIA axis during therapy and creating conditions that may support better immunotherapy and chemotherapy tolerance.[111]

The GIA axis is a key pathway influencing both treatment effectiveness and the adverse effects of therapy. Approaches such as probiotics, prebiotics, and postbiotics act as systemic modulators that help restore microbial balance and reduce ROS-associated inflammation, which is commonly seen in chemotherapy-induced mucositis. By elevating SCFA levels, particularly butyrate, these interventions activate Nrf2-mediated antioxidant pathways, strengthen epithelial tight junction integrity, and limit systemic endotoxin leakage. As outlined in Table 6, these integrated strategies connect experimental microbiome models with clinical approaches to prevent mucosal damage.

Table 6. Mechanistic interventions targeting the gut microbiome–immune–antioxidant (GIA) axis and mucosal protection

Intervention category	GIA component impacted	Primary mechanism of action	Clinical/Protective outcome	Ref.
Probiotics & synbiotics	Gut microbiota / Immune system	Restoration of microbial balance; inhibition of pathogen colonization; enhancement of mucosal barrier; production of antimicrobial compounds; modulation of immune response (↑ anti-inflammatory cytokines, ↓ pro-inflammatory signals)	Prevention and management of gastrointestinal disorders (*e.g.*, antibiotic-associated diarrhea, irritable bowel syndrome, infections); improved intestinal integrity and systemic health support	112
Postbiotics (*e.g.*, butyrate, SCFAs)	Redox / Metabolic / Mitochondrial axis	Enhances mitochondrial respiration and biogenesis (ATP production); activates antioxidant defenses; regulates mitophagy and inflammatory signaling	Reduced oxidative stress and epithelial apoptosis; improved barrier integrity; attenuation of intestinal inflammation and inflammatory bowel disease severity	113
Prebiotic fibers	Metabolic / Gut microbiota	Plant-derived dietary fibers serve as substrates for beneficial gut microbes, supporting probiotic survival and activity, enhancing fermentation processes and SCFA production, and maintaining gastrointestinal functional balance.	Improved gut homeostasis, enhanced digestive and excretory function, and reduced risk of inflammatory gut disorders and colon-related dysfunction	114
FMT (Ecosystem Reset)	Gut–brain–immune axis (multi-tissue Trp–KYN network)	Reprogramming tryptophan metabolism via α-diversity restoration, IDO1/TDO blockade, circadian alignment, and engineered microbial consortia shifting the KYN pathway toward indole/kynurenic acid balance	Reduction of immunosuppressive kynurenine signaling; improved response to immunotherapy; protection from immune-related toxicity and restoration of immune–metabolic homeostasis	115

4.4. Fecal microbiota transplantation (FMT)

4.4.1. FMT as an ecosystem-level reset of the GIA axis

Unlike single-strain probiotics or isolated metabolite therapies, FMT is an ecosystem-level intervention that transfers a complete microbial community from donor to recipient. Within the GIA framework, FMT functions as a global reset of microbial-immune-redox homeostasis. At the intestinal level, it restores alpha-diversity, re-establishes keystone SCFA-producing taxa, and suppresses inflammation- and oxidative stress-associated pathobionts. Immunologically, FMT reshapes host signaling by modifying microbial-derived ligands, including TLR agonists, and altering antigenic exposure, thereby influencing both myeloid and lymphoid cell populations. At the redox level, the reconfigured metabolite landscape, comprising SCFAs, bile acids, and tryptophan derivatives, modulates key stress-response and inflammatory pathways, including Nrf2, NF-κB, and interferon signaling, ultimately improving ROS homeostasis locally and systemically. From this perspective, FMT extends beyond microbial replacement to a systems-level therapeutic strategy that simultaneously reprograms interconnected microbial, metabolic, and immune networks.[116]

4.4.2. Experimental colon carcinogenesis

In mouse models of colon carcinogenesis, FMT studies reinforce the idea that microbial communities can drive or restrain tumor development. Transferring microbiota from CRC-bearing or colitis-prone donors accelerates tumorigenesis, increases colonic oxidative stress, and amplifies inflammatory signaling. In contrast, FMT from healthy donors or from animals enriched in SCFA-producing taxa mitigates tumor burden, reduces mucosal ROS, and restores barrier integrity.[117]

Mechanistically, these effects are associated with reduced NOX-dependent ROS production and lipid peroxidation within the colonic epithelium, reflecting improved redox homeostasis. In parallel, antioxidant defense systems and DNA repair pathways are upregulated, supporting enhanced cellular resilience to oxidative stress. Immunologically, FMT and related microbiome interventions remodel the tumor and mucosal immune landscape, characterized by increased infiltration and activity of $CD8^+$ T cells, alongside reduced immunosuppressive populations, including MDSCs and regulatory T cells. These changes are accompanied by normalization of bile acid and SCFA profiles, collectively consistent with restoration of a balanced GIA axis.[118]

Recent reviews on the microbiome-immune interface in cancer synthesize these data and emphasize that FMT, together with dietary and prebiotic modulation, can be used experimentally to swap tumor-permissive versus tumor-protective GIA configurations, enabling mechanistic dissection of microbiota-dependent redox and immune pathways in CRC.[119]

4.4.3. Early clinical experience in oncology

Clinically, FMT has expanded beyond its established role in *Clostridioides difficile* infection to emerging applications in oncology, particularly as a strategy to modulate responses to ICB. Early-phase I studies in patients with anti-PD-1-refractory metastatic melanoma have shown that FMT derived from long-term ICB responders, when re-challenged with PD-1 inhibition, is safe and associated with objective clinical benefit in a subset of patients. These responses are accompanied by durable engraftment of donor-like microbial communities enriched in taxa previously linked to ICB responsiveness. At the tumor level, FMT is associated with increased intratumoral $CD8^+$ T-cell activation and reduced IL-8-producing myeloid populations. Systemically and within the TME, transcriptomic profiling reveals signatures consistent with enhanced interferon signaling alongside suppression of immunosuppressive and pro-oxidant pathways. Subsequent work, including research highlights, narrative reviews, and updated analyses, has framed these trials as first-in-human evidence that targeted modulation of the GIA axis via FMT can overcome primary or acquired resistance to PD-1 blockade.[120] More recently, clinical trials have extended this strategy to advanced solid tumors beyond melanoma, including gastrointestinal cancers: responder-derived FMT combined with anti-PD-1 in refractory solid tumors has shown sustained microbiota shifts and encouraging response rates, and has begun to identify specific bacterial strains that potentiate or inhibit anti-tumor immunity.[121]

Parallel efforts are exploring FMT in CRC and other GI malignancies, both to modulate immunotherapy responsiveness and to mitigate treatment-related toxicity. Pre-clinical and translational CRC-focused reviews describe how FMT from favorable donors, or from animals or patients with robust SCFA production and lower inflammatory tone, can enhance checkpoint inhibitor activity, improve mucosal healing, and potentially remodel ferroptosis and redox pathways within the TME.[122]

Collectively, these data position FMT as a powerful yet still experimental tool for rewiring the GIA axis in cancer patients. Key challenges remain: inter-individual variability in donor and recipient microbiomes, risks of pathogen transfer, lack of standardization in preparation and delivery, and uncertainty over how durable and specific the desired GIA reprogramming will be. Nevertheless, convergent pre-clinical and early clinical evidence suggests that FMT, especially when guided by a mechanistic understanding of microbial metabolites and redox-immune pathways, could become a cornerstone of future microbiome-based strategies to sensitize tumors to immunotherapy and to protect normal tissues from oxidative injury.

Despite these promising early clinical observations, it is imperative to acknowledge the current limitations in the clinical evidence supporting responder-derived FMT and defined microbial consortia. These interventions remain strictly investigational and are currently supported only by early-phase, small-cohort studies. They have not yet been replicated in adequately powered, randomized controlled trials, which are necessary to definitively establish their efficacy, safety, and reproducibility across diverse patient populations. Consequently, while FMT represents a compelling proof of concept for GIA axis modulation, its application outside of controlled clinical research settings remains premature. Future large-scale, multicenter trials are essential to validate these preliminary findings, establish standardized therapeutic protocols, and determine the long-term viability of ecosystem-level microbiome resetting in oncology.

5. The GIA axis and immunotherapy

5.1. Microbiome correlates of ICI response and toxicity

Association studies in melanoma, non–small cell lung cancer (NSCLC), and renal cell carcinoma have consistently shown that baseline gut microbiome composition correlates with ICI response. Responders typically harbor greater microbial diversity and enrichment of taxa such as *Akkermansia muciniphila*, *Faecalibacterium*, *Bifidobacterium*, and certain Ruminococcaceae, whereas non-responders exhibit expansion of pathobionts (*e.g.*, *Fusobacterium*, *Escherichia/Shigella*, *Enterococcus*) and reduced SCFA producers. Landmark studies in melanoma and lung cancer demonstrated that favorable microbiomes were associated with increased intratumoral $CD8^+$ T-cell infiltration, augmented interferon signaling, and improved progression-free survival under anti-PD-1 therapy. At the same time, unfavorable configurations correlated with myeloid-dominant, immunosuppressive TME and primary resistance to ICI. These findings have been extended and synthesized in recent reviews of the microbiome-immune interface, which emphasize that similar patterns are emerging in CRC and other solid tumors.[123]

Parallel analyses of ICI-related toxicity (particularly colitis) reveal partially overlapping but distinct signatures. Some cohorts show that taxa associated with robust ICI responses also predispose to immune-related adverse events, whereas others describe configurations enriched in *Enterococcus* and *Veillonella* that are linked to severe colitis and systemic inflammation. Together, these studies suggest that the GIA axis encodes both efficacy and toxicity signals, with microbial community structure shaping the balance between anti-tumor immunity and off-target tissue damage.[124]

Functionally, microbial metabolic pathways provide a mechanistic link between compositional shifts in the microbiome and immune checkpoint inhibitor outcomes. Metagenomic and metabolomic analyses of responder-associated microbiomes consistently demonstrate enrichment of SCFA production, particularly butyrate and propionate, which support epithelial barrier integrity, regulate Nrf2-dependent antioxidant responses (as detailed in Section 2.1), and enhance mitochondrial fitness and memory or effector T-cell function. In parallel, bile acid metabolism is reconfigured toward profiles that activate FXR and TGR5 signaling while limiting the accumulation of pro-oxidant secondary bile acids that contribute to inflammation and T-cell exhaustion. Tryptophan metabolism is likewise balanced, with increased production of indole derivatives that engage the aryl hydrocarbon receptor (AhR) to sustain mucosal and immune homeostasis, alongside reduced diversion toward the kynurenine pathway, which is associated with immunosuppression and T-cell dysfunction.[125]

Recent work on microbial-derived metabolites as metabolic mediators of anti-tumor immunity underscores that SCFA, bile acids, and tryptophan derivatives converge on redox-sensitive circuits (Nrf2, NF-κB, STATs, interferons) and T-cell metabolic programming, thereby linking microbiome configuration to both redox balance and T-cell durability during ICI therapy.[126]

5.2. Redox modulation of ICI efficacy

The efficacy of immune checkpoint inhibitors is critically dependent on a finely tuned redox balance within the TIME. While moderate levels of ROS and RNS are essential for immunogenic cell death, antigen processing, and effective T-cell activation, sustained or excessive oxidative stress shifts this balance toward immune suppression. Within the tumor milieu, ROS generated by mitochondrial dysfunction, NOX enzymes, and inflammatory myeloid cells can enhance tumor antigenicity and danger signaling at intermediate levels, thereby promoting immunogenic cell death. However, at higher levels, oxidative stress drives DNA damage and genomic instability, facilitating the selection of immune-evasive clones, downregulating the antigen presentation machinery, and increasing PD-L1 expression. In parallel, excessive ROS promotes lipid peroxidation and metabolic exhaustion in $CD8^+$ T cells, ultimately impairing effector function and limiting the therapeutic efficacy of ICI.[127]

Conversely, tumor and myeloid antioxidant systems (Nrf2, glutathione, thioredoxin) buffer ROS and blunt these danger signals. Hyperactivation of Nrf2 in cancer cells and tumor-associated myeloid cells reduces type I interferon and NF-κB-dependent inflammatory programs, promotes an immunologically cold tumor, and is increasingly recognized as a driver of ICI resistance. Redox-adapted tumors may thus appear poorly antigenic and microenvironmentally hostile to effector T cells, even when checkpoint pathways are pharmacologically blocked.[128]

Integration of microbiome-derived signals into redox-sensitive immune circuits is a central feature of the GIA axis during immune checkpoint inhibitor therapy. Microbial metabolites, including SCFAs, bile acid derivatives, and tryptophan catabolites, modulate mitochondrial biogenesis, oxidative phosphorylation, and ROS dynamics in T cells, thereby influencing the balance between memory and exhausted phenotypes. These metabolites also regulate key stress-response pathways, including Nrf2 and NF-κB, in both tumor and immune compartments,

reshaping cytokine landscapes and checkpoint molecule expression. In parallel, they influence the differentiation and suppressive activity of MDSCs and regulatory T cells, populations that are highly sensitive to changes in redox state and metabolic signaling.[129]

Systems-level analyses of systemic metabolism and tumor-immune interactions further emphasize that host metabolic and redox changes, including those driven by the gut microbiome, feed into antigen presentation, costimulatory signaling, and the relative abundance of effector versus suppressor populations under ICI. Conceptually, ICI is therefore acting on an immune system whose responsiveness has already been pre-tuned by the GIA axis.

5.3. Microbiome- and redox-based interventions to enhance immunotherapy

Given this mechanistic integration, multiple GIA-targeted interventions are being investigated as adjuvants to ICI. These can be grouped into microbiome-directed approaches (diet, probiotics/synbiotics, FMT, targeted microbial products) and redox-modulating strategies that intersect with microbiome effects.

5.3.1. Diet, probiotics/synbiotics, and targeted metabolites

High-fiber, plant-rich diets that increase SCFA production have been associated with improved ICI outcomes in observational cohorts, consistent with the enrichment of SCFA-producing taxa in responders. Pre-clinical models support a causal role: fiber or resistant starch supplementation enhances butyrate production, improves T-cell metabolic fitness, and augments anti-tumor immunity under checkpoint blockade.[130]

Building on this framework, probiotics and synbiotics are increasingly being investigated as adjuncts to immune checkpoint inhibitor therapy. Mechanistic and translational evidence suggests that selected strains, including *Bifidobacterium*, *Lactobacillus*, and *Faecalibacterium*-enriched consortia, can expand SCFA-producing microbial communities and normalize bile acid metabolism. These shifts are associated with reduced NOX-dependent ROS generation and attenuation of epithelial oxidative injury. In parallel, they enhance dendritic cell activation and improve $CD8^+$ T-cell priming, thereby strengthening antitumor immune responses. Collectively, these effects may increase effector lymphocyte infiltration within the TME, supporting improved responsiveness to ICI therapy. Postbiotics and targeted metabolites, such as butyrate, propionate, and defined microbial products, are also being evaluated for their ability to modulate redox and immune pathways without live organisms, with pre-clinical data showing reduced oxidative stress, altered checkpoint expression, and improved responses to cytotoxic and immune-based therapies in CRC and melanoma models.[131]

Across CRC, melanoma, and lung cancer, recent reviews describe combinations of ICI with microbiome-modulating diets, probiotics, or metabolite supplementation that enhance tumor control in mice, often by restoring a more responder-like microbiome, boosting SCFA levels, and improving T-cell mitochondrial fitness.

5.3.2. FMT and ecosystem-scale modulation

At the ecosystem level, FMT has provided the clearest human proof-of-concept that deliberate GIA reprogramming can recover ICI responsiveness. As discussed earlier, phase I trials in anti-PD-1-refractory melanoma showed that FMT from long-term responders, combined with renewed PD-1 blockade, induced objective responses in a subset of patients and re-established donor-like microbiomes enriched in favorable taxa. Immune profiling revealed increased intratumoral $CD8^+$ T cells, reduced myeloid-derived suppressor signatures, and enhanced interferon and antigen presentation pathways, consistent with a coordinated microbiome-redox-immune reset.[121]

More recent studies extending FMT to advanced solid tumors, including gastrointestinal cancers, report improved anti-PD-1 efficacy and durable microbiota shifts, and begin to define specific bacterial strains and metabolic outputs that potentiate ICI. In CRC and hepatobiliary tumors, pre-clinical models show that responder-derived FMT reduces oxidative stress, enhances ferroptosis sensitivity, and increases $CD8^+$ T-cell infiltration, suggesting a direct impact of the remodeled GIA axis on tumor redox biology and immune surveillance.[132]

In glioma and other CNS tumors, emerging work on the gut-brain-tumor axis indicates that microbiome-targeted strategies (diet, probiotics, and experimental FMT) can modulate microglial activation states, oxidative stress, and response to radiotherapy and ICI. However, clinical data remain early and largely exploratory.

5.3.3. Redox-targeted combinations

Finally, redox-modulating strategies are being investigated in combination with microbiome-targeted interventions to further enhance tumor sensitivity to ICB. Preclinical studies indicate that pharmacologic suppression of tumor-intrinsic antioxidant systems, including Nrf2 signaling, glutathione synthesis, and thioredoxin pathways, can elevate immunogenic ROS levels, thereby promoting antigen presentation, amplifying type I interferon responses, and improving the efficacy of checkpoint inhibition. In

contrast, selective reinforcement of antioxidant capacity in T cells, particularly through mitochondrial ROS buffering, helps prevent functional exhaustion and preserve effector activity under sustained antigenic stimulation. Together, these complementary approaches highlight the therapeutic potential of fine-tuning redox balance in both tumor and immune compartments to optimize antitumor immunity.[127]

Integrative reviews emphasize that successful combinations will likely require precision targeting: dampening tumor- and MDSC-centric antioxidant programs while supporting T-cell redox resilience, ideally in the context of a microbiome configuration that favors SCFA-rich, low-endotoxin, low-oxidative inflammatory tone. In this sense, microbiome-directed and redox-based interventions are not separate strategies, but complementary levers for tuning the GIA axis to maximize the therapeutic window of immunotherapy.

6. Translational perspectives and future directions

6.1. Towards "GIA-guided" combination strategies

A conceptual overview of this translational framework is presented in Figure 4.

As the field moves toward clinical application, it is essential to stratify proposed translational strategies by their current level of evidentiary support. First, preclinical and mechanistic evidence robustly supports the biological plausibility of microbiome-redox-immune crosstalk, particularly in murine models of CRC and melanoma. Second, early-phase clinical and observational studies provide emerging, albeit preliminary, support for specific interventions, such as FMT or targeted probiotic supplementation, to modulate immune checkpoint inhibitor responses in small patient cohorts. Finally, multidimensional approaches, including composite GIA-axis biomarker profiling, GIA-guided patient stratification, and algorithm-driven treatment allocation, remain purely hypothetical constructs. These advanced strategies currently lack prospective clinical validation and should not be misconstrued as established clinical tools. Recognizing these distinct evidentiary tiers ensures that future research priorities are appropriately aligned with the current maturity of the underlying science.

The emerging evidence across tumor types supports a shift from considering the microbiome, redox balance, and anti-tumor immunity as parallel, largely independent modifiers of outcome, to viewing them as components of an integrated GIA axis that can be deliberately manipulated. Within this framework, GIA-guided strategies aim to

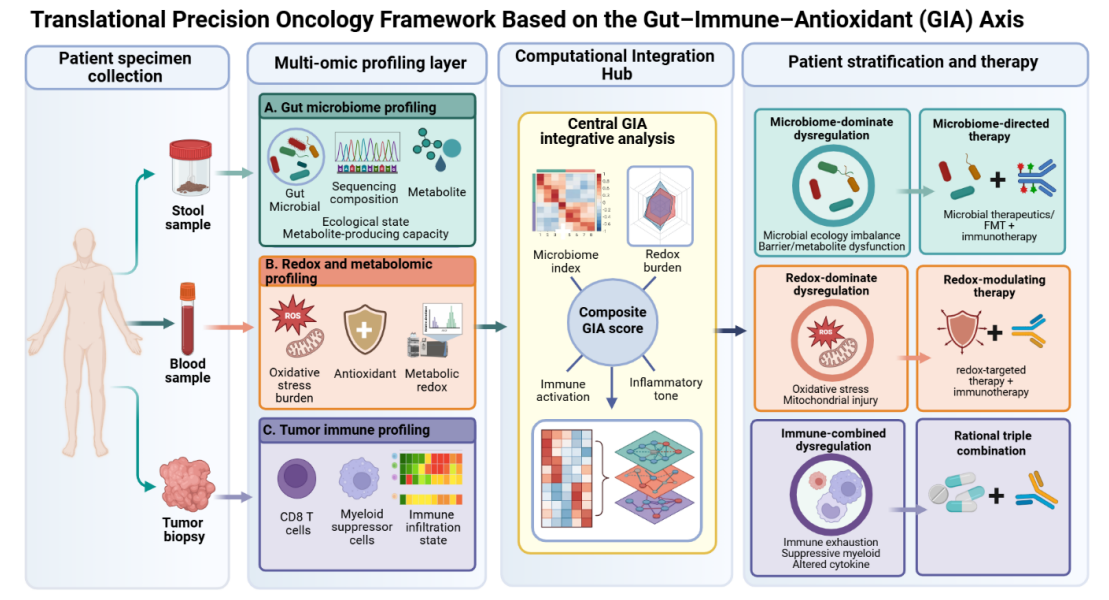


Figure 4. Translational precision oncology framework based on the gut–immune–antioxidant (GIA) axis. Schematic overview of a proposed GIA-guided precision oncology pipeline. Left panel: Patient biospecimens (stool, blood, and tumor biopsy) provide complementary information on microbial ecology, oxidative/redox balance, and immune contexture. Middle panel: Multi-omic profiling data are integrated into a central analytical framework to derive a composite GIA score reflecting microbiome status, redox burden, immune activation, and inflammatory tone. Right panel: Patients are stratified into dominant GIA dysregulation phenotypes and linked to matched therapeutic approaches, followed by longitudinal response monitoring and biomarker-based treatment adaptation. Schematic created by the authors.
Abbreviation: FMT: Fecal microbiota transplantation.

co-target microbial ecosystems, redox homeostasis, and immune checkpoints to recondition the TIME, enhance response durability, and limit treatment-related toxicity.[133]

Translating the GIA framework into clinical practice requires developing a precision oncology pipeline guided by GIA principles that integrates multi-omics data to classify and stratify patients. This approach uses defined microbial and redox biomarkers, such as the balance between commensal *Akkermansia* and pathobiont *Enterococcus*, as well as systemic GSH/GSSG ratios, to forecast patient responsiveness to ICB therapies. Early identification of these dysregulated signatures enables clinicians to apply targeted strategies, including FMT from responders or pharmacological modulation of redox pathways, to reshape the TME into an immunologically active state. Table 7 summarizes the key biological correlates and outlines priority areas for further research needed to standardize this systems-level therapeutic framework.

At the microbiota level, dietary interventions, probiotics, synbiotics, postbiotics, FMT, and next-generation live

Table 7. GIA-guided precision oncology: correlates and clinical roadmap.

GIA pillar	Favorable (responder) signature	Dysregulated (resistance) signature	Proposed translational action	Ref.
Microbial ecology	Enrichment of *Akkermansia muciniphila* and *Faecalibacterium prausnitzii* (anti-inflammatory, barrier-protective microbiota)	Depletion of beneficial taxa with a shift toward pro-inflammatory dysbiosis (loss of microbiome balance)	Probiotics/synbiotics, microbiome modulation, and targeted microbial restoration strategies for immune and cancer-related disorders	134
Metabolic output	High SCFA flux; Indole metabolites (*e.g.*, indole-3-aldehyde → AhR activation); effective VDR–AhR crosstalk promoting IL-22, autophagy, barrier repair	Reduced SCFA production; loss of indole–AhR signaling; impaired VDR activation; weakened IL-22–mediated epithelial repair and tight-junction integrity	Prebiotics to enhance SCFA production; strain-specific probiotics supplying indole ligands; standardized postbiotics for controlled AhR activation; vitamin D/ VDR modulation to restore AhR–VDR axis balance	135
Redox/ Immune tone	Controlled ROS homeostasis; strong antitumor immune activity with active dendritic cell maturation and IFN-related signaling	High ROS-related gene signature; suppressed antitumor immunity; impaired dendritic cell activation; poor immunotherapy response	ROS-targeted therapeutic modulation; patient stratification for immunotherapy; combination strategies to restore immune activation and redox balance	136
Knowledge gap: MetS biomarker landscape	Integrated multi-marker profile (hs-CRP, IL-6, TNF-α, adiponectin/ leptin ratio, SCFAs, miR-122/miR-223) indicating early metabolic imbalance detection	High inter-individual variability, inconsistent cutoff values, and overlapping signals between inflammation, obesity, and insulin resistance	Standardization of GIA-biomarker assays. AI-driven validation across large multi-ethnic cohorts + harmonized diagnostic thresholds	137

Abbreviations: AhR: Aryl hydrocarbon receptor; AI: Artificial intelligence; IFN: Interferon; hs-CRP: High-sensitivity C-reactive protein; GIA: Gut microbiome, immune, and antioxidant; IL: Interleukin; ROS: Reactive oxygen species; SCFA: Short-chain fatty acid; TNF-α: Tumor necrosis factor alpha; VDR: Vitamin D receptor.

biotherapeutic products are being developed to enrich health-associated taxa, restore SCFA production, normalize bile-acid and tryptophan metabolism, and suppress pro-oxidant, pro-inflammatory pathobionts. In parallel, redox-modulating approaches, including pharmacologic inhibition of tumor antioxidant programs, modulation of ferroptosis, and targeting metabolic pathways that govern ROS production, aim to create a redox environment that favors immunogenic stress in cancer cells while preserving the functional integrity of effector lymphocytes. These GIA-directed interventions are increasingly conceived as upstream conditioning tools for ICB and other immunotherapies, whose efficacy depends on antigenicity, interferon signaling, and the balance between effector and suppressor populations within the TME.[138]

The clinical positioning of GIA-guided strategies is likely to be stage-specific. In prevention and early interception, the emphasis will be on low-toxicity, primarily dietary and microbiome-friendly measures that sustain eubiosis, reduce mucosal oxidative stress, and dampen chronic inflammation in high-risk individuals such as those with long-standing inflammatory bowel disease, cirrhosis, or metabolic dysfunction. In perioperative and neoadjuvant

settings, short-term modulation of the GIA axis, for example, via perioperative synbiotics, antioxidant-tuned nutrition, and judicious use of antibiotics, may improve surgical outcomes, decrease infection and mucosal injury, and optimize immune competence at the time of curative-intent therapy. In advanced disease, rational combinations of immune checkpoint inhibitors with microbiome-directed therapies and selective redox modulators are emerging as a central translational focus, with the long-term goal of embedding GIA-guided decision-making into precision oncology algorithms.[139]

6.2. Candidate biomarkers of the GIA axis

Realizing a GIA-guided approach in practice will require biomarkers that capture the three pillars of the axis, microbiome, redox status, and immune function, in a clinically tractable manner. On the microbial side, numerous studies have identified taxa associated with improved or impaired responses to immune checkpoint inhibition, including enrichment of *Akkermansia*, *Faecalibacterium*, and *Bifidobacterium* in responders, and expansion of *Fusobacterium*, *Escherichia/Shigella*, and *Enterococcus* in non-responders or in patients with severe immune-related adverse events. However, single-taxon markers show limited reproducibility across cohorts. As a result, increasing attention is focused on functional descriptors, such as SCFA biosynthesis capacity, bile-acid transformation patterns, tryptophan metabolic routing, and microbiota-linked ferroptosis and redox pathways, as more robust readouts of the microbiome's contribution to the GIA axis.[140]

Beyond the gut, systemic and intratumoral redox measurements provide a second layer of candidate biomarkers. Circulating indices of oxidative damage (*e.g.*, 8-oxo-dG, F2-isoprostanes, protein carbonyls), plasma and tissue redox couples (GSH/GSSG, NADPH/$NADP^+$), and expression or activity of Nrf2, Keap1, glutathione, and thioredoxin pathway components in tumor and myeloid compartments are being explored as correlates of prognosis and immunotherapy responsiveness. Combining these redox measures with microbiome-derived features may help to identify patients with particularly maladaptive GIA states, for example, those harboring dysbiotic, low-SCFA microbiomes and tumors with strongly upregulated antioxidant signatures, who might benefit from aggressive GIA modulation in conjunction with immunotherapy.[141]

The third pillar comprises immune and cytokine signatures that integrate microbial and redox influences into measurable immune phenotypes. Established predictors of checkpoint inhibitor efficacy, such as tumor mutational burden, PD-L1 expression, and $CD8^+$ T-cell infiltration, can be augmented by type I/II interferon gene signatures, detailed profiling of exhausted versus stem-like $CD8^+$ T cells, regulatory T cells, and MDSCs, and plasma cytokine/chemokine panels reflecting systemic inflammatory and oxidative tone. Several recent frameworks propose composite GIA biomarker panels that weave together microbial taxa and pathways, metabolic and redox markers, and immune signatures to stratify patients, select appropriate GIA-modifying co-therapies, and monitor dynamic responses over time.[142]

6.3. Key knowledge gaps and research priorities

Notwithstanding the conceptual appeal of the GIA axis, current evidence is limited by substantial methodological and biological heterogeneity. Microbiome-immunotherapy studies often differ in sequencing depth, analytical pipelines, dietary and antibiotic confounders, and sampling timing, contributing to inconsistent taxonomic findings across cohorts. Redox and immune phenotyping are rarely standardized or longitudinal, making it difficult to capture the temporal evolution of the GIA axis during therapy. Most human data remain associative; causal inference relies heavily on pre-clinical models that, while mechanistically informative, may not fully recapitulate human tumor biology, microbial complexity, or environmental exposures. Even in the context of FMT and responder-derived consortia, the specific strains and metabolites responsible for clinical benefit are only beginning to be resolved.[143]

Despite the conceptual appeal of the GIA axis, translating this framework into clinical practice is currently constrained by substantial methodological and biological heterogeneity. Microbiome studies frequently exhibit significant inter-cohort variability, driven by differences in sequencing methodologies, bioinformatic pipelines, and analytical depths. Furthermore, the gut microbiome is highly susceptible to common clinical confounders, including recent antibiotic exposure, proton pump inhibitor use, dietary habits, obesity, and broader lifestyle factors, which can obscure disease-specific microbial signatures. Sampling-site heterogeneity presents an additional challenge, as stool-based analyses may not accurately reflect the mucosa-associated or intratumoral microbial communities that directly interact with the local immune and redox microenvironment. This discrepancy likely contributes to the observed differences in GIA axis manifestations across various cancer types. Compounding these microbiome-related challenges is the lack of standardized assays to measure systemic and intratumoral oxidative stress, making it difficult to reliably quantify the redox component of the axis in human cohorts. Consequently, the scarcity of prospective,

longitudinal clinical validation remains a critical barrier. Until these methodological inconsistencies are resolved through harmonized profiling and standardized redox measurements, the predictive and translational utility of the GIA framework will remain largely exploratory.

Questions of generalizability and safety further complicate translation. The bulk of microbiome-immunotherapy data originates from melanoma and a limited set of solid tumors in high-income settings; whether similar GIA configurations and intervention responses apply to colorectal, hepatobiliary, lung, and CNS malignancies in diverse populations remains uncertain. Moreover, FMT and live biotherapeutic products raise non-trivial safety and regulatory concerns, including the risk of pathogen transmission, unintended immune or metabolic consequences, and long-term ecological shifts that are not yet fully understood.[144]

Against this backdrop, several research priorities emerge. Mechanistically, gnotobiotic models, strain-resolved microbiome engineering, and targeted perturbation of redox and immune pathways are needed to disentangle causal microbial-metabolite-host interactions relevant to anti-tumor immunity. Clinically, prospective randomized trials should embed comprehensive GIA profiling into the design of immunotherapy combinations, testing, for example, responder-derived FMT or defined consortia, high-fiber and SCFA-augmenting diets, and redox-modulating agents alongside checkpoint blockade in CRC, melanoma, lung cancer, and glioma, with stratification by baseline GIA biomarkers. Harmonization of sampling, sequencing, redox assays, and immune profiling across studies will be essential to enable robust meta-analyses and the development of validated composite GIA scores. Finally, equitable representation of diverse dietary, environmental, and genetic backgrounds will be critical to ensure that future microbiome- and redox-based interventions are broadly applicable rather than tailored to a narrow subset of patients.[145]

If these challenges can be addressed, the GIA axis has the potential to evolve from a conceptual construct into a practical framework for designing and personalizing cancer prevention strategies, perioperative optimization, and combination treatments in advanced disease.

6.3.1. Systems biology and network-based approaches to the GIA axis

Realizing the composite, multi-omics stratification approaches discussed throughout this review will require methodological tools capable of integrating heterogeneous microbiome, redox, and immune data into coherent predictive models. Network medicine and systems biology approaches, which model disease states as perturbations of interconnected molecular and cellular networks rather than as isolated pathway abnormalities, provide a natural methodological foundation for this integration.[146] Furthermore, emerging multi-omics data-integration frameworks that combine metagenomic, metabolomic, transcriptomic, and immune-profiling data offer the computational architecture necessary to map these complex host-microbe interactions.[147] Applying these network-based and multi-omics approaches to GIA-axis data could support the development of the composite biomarkers and precision-oncology tools proposed in Section 6.2. We therefore identify this methodological integration as a critical research priority, alongside the clinical and mechanistic priorities discussed above. We also prioritize optimization and combination treatments in advanced disease.

6.4. Future directions: roadmap for GIA axis translation

Although the GIA axis provides a strong conceptual framework, significant knowledge gaps remain to be addressed before it can be translated into clinical practice. Key obstacles include substantial variability in microbiome sequencing methods, the absence of standardized assays for redox measurements, and the necessity for longitudinal sampling throughout therapeutic interventions. The table below outlines the main research priorities for establishing the GIA axis as a clinically reliable tool, with particular emphasis on conducting randomized, biomarker-informed trials across heterogeneous patient populations.[148]

7. Conclusions

The body of evidence reviewed in this article supports the GIA axis as a unifying framework for understanding how the microbiome, redox homeostasis, and host immunity jointly shape cancer risk, tumor evolution, and response to therapy. Rather than acting as isolated modulators, gut microbial communities, oxidative and antioxidant networks, and immune circuits form a tightly interwoven system in which changes in one component reverberate across the others. Dysbiosis-driven alterations in microbial metabolites remodel redox tone and immune polarization in local and distant tissues; redox signaling feeds back on microbial ecology and immune effector function; and, in turn, immunologic pressures select for specific microbial and metabolic configurations. Within this integrated view, cancer can be seen as arising and progressing within GIA states that either constrain or promote carcinogenesis and that strongly influence the efficacy and toxicity of modern treatments, particularly immune checkpoint inhibitors.

Translationally, this perspective opens the door to

GIA-guided oncology, in which microbiome- and redox-informed biomarkers and interventions complement conventional molecular and clinical stratifiers. In principle, composite GIA signatures could help identify individuals at elevated risk who might benefit from preventive modulation of diet and microbiota; guide perioperative strategies to protect barrier function, limit oxidative injury, and preserve immune competence; and inform combination regimens in advanced disease that pair ICB with microbiome-directed therapies and redox-targeted agents. At the same time, substantial challenges must be addressed before GIA-based approaches can be routinely incorporated into practice. Heterogeneity across studies, limited causal inference in humans, incomplete generalizability beyond selected tumor types and populations, and unresolved safety and regulatory issues with live biotherapeutic products and FMT underscore the need for rigorously designed, biomarker-embedded clinical trials.

Overall, the GIA axis provides a mechanistic scaffold that connects diverse observations in microbiome science, redox biology, and tumor immunology into a coherent systems model. If future work can translate this model into robust biomarkers, standardized assays, and safe, scalable interventions, GIA-guided strategies have the potential to refine cancer prevention, enhance the precision and durability of immunotherapy, and mitigate treatment-related toxicity, moving host-microbiome-immune integration from conceptual promise to clinical reality.

Acknowledgments

We sincerely appreciate Edigenomix Scientific Co., Ltd. (https://www.edigenomix-scientific.com/) for their expert editing and proofreading, which greatly improved the clarity and quality of our manuscript. Their meticulous attention to detail and support in refining the document for publication are gratefully acknowledged.

Funding

This work was supported by the National Research Foundation of Korea (NRF) grant, funded by the Korea government (MSIT) (RS-2020-NR049559); a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute, funded by the Ministry of Health and Welfare (RS-2020-KH087790); the Basic Science Research Program through the National Research Foundation of Korea (NRF), funded by the Ministry of Education (RS-2020-NR054734); the Starting Growth Technological R&D Program (RS-2024-00507224); and a grant from the National Research Foundation of Korea, funded by the Korea government (RS-2024-00350362).

Conflict of interest

The authors declare no competing interests.

Author contributions

Conceptualization: Muhammad Alaa Eldeen
Supervision: Bonglee Kim
Visualization: All authors
Writing–original draft: Muhammad Alaa Eldeen
Writing–review & editing: All authors

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

Further disclosure

The authors used the AI-assisted language tool ChatGPT (OpenAI) exclusively for minor English language editing and grammar improvement. The scientific content, study design, data analysis, interpretation of results, and conclusions were entirely developed and verified by the authors. Regarding figure preparation, AI-assisted image-generation tools, specifically ChatGPT (OpenAI), were utilized for the initial conceptualization and drafting of the figures. Subsequently, the authors manually and extensively revised every visual detail, structural layout, and scientific component of these figures to ensure complete scientific accuracy and data integrity. The final figures presented in this manuscript are the result of substantial human curation and verification by the authors, and no unverified AI-generated elements remain. The final graphical abstract and figures were assembled and formatted using Adobe Illustrator.

References

1. Sung H, Ferlay J, Siegel RL, *et al*. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*. 2021;71(3):209-249.

   doi: 10.3322/caac.21660

2. Bray F, Laversanne M, Weiderpass E, Soerjomataram I. The ever-increasing importance of cancer as a leading cause of premature death worldwide. *Cancer*. 2021;127(16):3029-3030.

doi: 10.1002/cncr.33587

3. Dagogo-Jack I, Shaw AT. Tumour heterogeneity and resistance to cancer therapies. *Nat Rev Clin Oncol*. 2018;15(2):81-94.

doi: 10.1038/nrclinonc.2017.166

4. Sharma P, Hu-Lieskovan S, Wargo JA, Ribas A. Primary, Adaptive, and Acquired Resistance to Cancer Immunotherapy. *Cell*. 2017;168(4):707-723.

doi: 10.1016/j.cell.2017.01.017

5. Binnewies M, Roberts EW, Kersten K, *et al*. Understanding the tumor immune microenvironment (TIME) for effective therapy. *Nat Med*. 2018;24(5):541-550.

doi: 10.1038/s41591-018-0014-x

6. Rajan RK, Bhattacharjee B, Hazarika H, *et al*. Piceatannol: a multifaceted polyphenol—from pharmacological actions to formulation development and clinical trials. *Adv Tradit Med*. 2025;25(4):837-884.

doi: 10.1007/s13596-025-00845-7

7. Garrett WS. Cancer and the microbiota. *Science*. 2015;348(6230):80-86.

doi: 10.1126/science.aaa4972

8. Zitvogel L, Ma Y, Raoult D, Kroemer G, Gajewski TF. The microbiome in cancer immunotherapy: Diagnostic tools and therapeutic strategies. *Science*. 2018;359(6382):1366-1370.

doi: 10.1126/science.aar6918

9. Mardinoglu A, Shoaie S, Bergentall M, *et al*. The gut microbiota modulates host amino acid and glutathione metabolism in mice. *Mol Syst Biol*. 2015;11(10):834.

doi: 10.15252/msb.20156487

10. Wong SH, Yu J. Gut microbiota in colorectal cancer: mechanisms of action and clinical applications. *Nat Rev Gastroenterol Hepatol*. 2019;16(11):690-704.

doi: 10.1038/s41575-019-0209-8

11. Louis P, Hold GL, Flint HJ. The gut microbiota, bacterial metabolites and colorectal cancer. *Nat Rev Microbiol*. 2014;12(10):661-672.

doi: 10.1038/nrmicro3344

12. Kostic AD, Chun E, Robertson L, *et al*. Fusobacterium nucleatum potentiates intestinal tumorigenesis and modulates the tumor-immune microenvironment. *Cell Host Microbe*. 2013;14(2):207-215.

doi: 10.1016/j.chom.2013.07.007

13. Routy B, Le Chatelier E, Derosa L, *et al*. Gut microbiome influences efficacy of PD-1–based immunotherapy against epithelial tumors. *Science*. 2018;359(6371):91-97.

doi: 10.1126/science.aan3706

14. Matson V, Fessler J, Bao R, *et al*. The commensal microbiome is associated with anti–PD-1 efficacy in metastatic melanoma patients. *Science*. 2018;359(6371):104-108.

doi: 10.1126/science.aao3290

15. Reczek CR, Chandel NS. ROS-dependent signal transduction. *Curr Opin Cell Biol*. 2015;33:8-13.

doi: 10.1016/j.ceb.2014.09.010

16. Hayes JD, Dinkova-Kostova AT, Tew KD. Oxidative Stress in Cancer. *Cancer Cell*. 2020;38(2):167-197.

doi: 10.1016/j.ccell.2020.06.001

17. Rojo de la Vega M, Chapman E, Zhang DD. NRF2 and the Hallmarks of Cancer. *Cancer Cell*. 2018;34(1):21-43.

doi: 10.1016/j.ccell.2018.03.022

18. Jones RM, Neish AS. Redox signaling mediated by the gut microbiota. *Free Radic Biol Med*. 2017;105:41-47.

doi: 10.1016/j.freeradbiomed.2016.10.495

19. Gopalakrishnan V, Spencer CN, Nezi L, *et al*. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. *Science*. 2018;359(6371):97-103.

doi: 10.1126/science.aan4236

20. Sena LA, Li S, Jairaman A, *et al*. Mitochondria are required for antigen-specific T cell activation through reactive oxygen species signaling. *Immunity*. 2013;38(2):225-236.

doi: 10.1016/j.immuni.2012.10.020

21. Kunst C, Schmid S, Michalski M, *et al*. The Influence of Gut Microbiota on Oxidative Stress and the Immune System. *Biomedicines*. 2023;11(5):1388.

doi: 10.3390/biomedicines11051388

22. Zhao J, Zhao F, Yuan J, Liu H, Wang Y. Gut microbiota metabolites, redox status, and the related regulatory effects of probiotics. *Heliyon*. 2023;9(11):e21431.

doi: 10.1016/j.heliyon.2023.e21431

23. Zünd JN, Caflisch M, Mujezinovic D, *et al*. Deciphering oxidative stress responses in human gut microbes and fecal microbiota: a cultivation-based approach. *FEMS Microbiol Ecol*. 2025;101(6):fiaf054.

doi: 10.1093/femsec/fiaf054

24. Sun Y, Wang X, Li L, *et al*. The role of gut microbiota in intestinal disease: from an oxidative stress perspective. *Front Microbiol*. 2024;15:1328324.

doi: 10.3389/fmicb.2024.1328324

25. Gupta P, Dutta S, Dutta K, *et al*. Interconnection between gut microbial metabolites and mitochondrial ROS production: implications for cellular health. *Mol Cell Biochem*. 2026;481(1):41-65.

doi: 10.1007/s11010-025-05397-7

26. Jiang S-S, Chen Y-X, Fang J-Y. Fusobacterium nucleatum: Ecology, pathogenesis, and clinical implications. *Nat Rev Microbiol*. 2026;24:197-214.

doi: 10.1038/s41579-025-01237-z

27. Luo F, Wang X, Ye C, Sun H. Microbial Biomarkers in Liquid Biopsy for Cancer: An Overview and Future Directions. *Cancer Control*. 2024;31:10732748241292019.

doi: 10.1177/10732748241292019

28. Zhu J, Qin S, Gu R, *et al*. Amuc_1434 From Akkermansia muciniphila Enhances CD8+ T Cell-Mediated Anti-Tumor Immunity by Suppressing PD-L1 in Colorectal Cancer. *FASEB J*. 2025;39(8):e70540.

doi: 10.1096/fj.202403295RR

29. Pei B, Peng S, Huang C, Zhou F. Bifidobacterium modulation of tumor immunotherapy and its mechanism. *Cancer Immunol Immunother*. 2024;73(5):94.

doi: 10.1007/s00262-024-03665-x

30. Galasso L, Termite F, Mignini I, *et al*. Unraveling the Role of Fusobacterium nucleatum in Colorectal Cancer: Molecular Mechanisms and Pathogenic Insights. *Cancers (Basel)*. 2025;17(3):368.

doi: 10.3390/cancers17030368

31. Zhou L, Zhang M, Wang Y, *et al*. Faecalibacterium prausnitzii Produces Butyrate to Maintain Th17/Treg Balance and to Ameliorate Colorectal Colitis by Inhibiting Histone Deacetylase 1. *Inflamm Bowel Dis*. 2018;24(9):1926-1940.

doi: 10.1093/ibd/izy182

32. Saito R, Shigematsu Y, Amori M, *et al*. Association of Enterotoxigenic Bacteroides fragilis with Immune Modulation in Colorectal Cancer Liver Metastasis. *Cancers (Basel)*. 2025;17(17):2733.

doi: 10.3390/cancers17172733

33. González-Bosch C, Boorman E, Zunszain PA, Mann GE. Short-chain fatty acids as modulators of redox signaling in health and disease. *Redox Biol*. 2021;47:102165.

doi: 10.1016/j.redox.2021.102165

34. Chen N, Chan CK, Khan FU, *et al*. Gut microbiota-derived metabolites as immune modulators in aging and age-related chronic inflammatory diseases. *Ageing Res Rev*. 2026;116:103036.

doi: 10.1016/j.arr.2026.103036

35. Shi J, Zhao C, Zhang D, *et al*. Xiayuxue decoction alleviates MASH by regulating gut microbiota, bile acid metabolism, and m6A modification. *Phytomedicine*. 2026;154:158023.

doi: 10.1016/j.phymed.2026.158023

36. Cornwell A, Badiei A. From Gasotransmitter to Immunomodulator: The Emerging Role of Hydrogen Sulfide in Macrophage Biology. *Antioxidants (Basel)*. 2023;12(4):935.

doi: 10.3390/antiox12040935

37. Islam SU, Lee JH, Shehzad A, *et al*. Decursinol Angelate Inhibits LPS-Induced Macrophage Polarization through Modulation of the NFκB and MAPK Signaling Pathways. *Molecules*. 2018;23(8):1880.

doi: 10.3390/molecules23081880

38. Kaisanlahti A, Turunen J, Hekkala J, *et al*. Gut microbiota-derived extracellular vesicles form a distinct entity from gut microbiota. *mSystems*. 2025;10(5):e0031125.

doi: 10.1128/msystems.00311-25

39. Weinberg SE, Chandel NS. Mitochondria reactive oxygen species signaling in immune responses. *Immunity*. 2025;58(8):1904-1921.

doi: 10.1016/j.immuni.2025.07.012

40. Shu P, Liang H, Zhang J, *et al*. Reactive oxygen species formation and its effect on CD4+ T cell-mediated inflammation. *Front Immunol*. 2023;14:1199233.

doi: 10.3389/fimmu.2023.1199233

41. Xiong B, Zhang Y, Liu S, *et al*. NOX Family: Regulators of Reactive Oxygen Species Balance in Tumor Cells. *FASEB J*. 2025;39(8):e70565.

doi: 10.1096/fj.202500238RRR

42. Konaté MM, Antony S, Doroshow JH. Inhibiting the Activity of NADPH Oxidase in Cancer. *Antioxid Redox Signal*. 2020;33(6):435-454.

doi: 10.1089/ars.2020.8046

43. Singh MK, Yun HR, Ranbhise JS, *et al*. Hypoxia, ROS, and HIF Signaling in I/R Injury: Implications and Future Prospects. *Antioxidants*. 2026;15(2):153.

doi: 10.3390/antiox15020153

44. Liang X, Weng J, You Z, *et al*. Oxidative stress in cancer: from tumor and microenvironment remodeling to therapeutic frontiers. *Mol Cancer*. 2025;24(1):219.

doi: 10.1186/s12943-025-02375-x

45. Song M-Y, Lee D-Y, Chun K-S, Kim E-H. The Role of NRF2/KEAP1 Signaling Pathway in Cancer Metabolism. *Int J Mol Sci*. 2021;22(9):4376.

doi: 10.3390/ijms22094376

46. Verza FA, GC DAS, Nishimura FG. The impact of oxidative stress and the NRF2-KEAP1-ARE signaling pathway on anticancer drug resistance. *Oncol Res*. 2025;33(8):1819-1834.

doi: 10.32604/or.2025.065755

47. Jiang X, Yu M, Wang WK, *et al*. The regulation and function of Nrf2 signaling in ferroptosis-activated cancer therapy. *Acta Pharmacol Sin*. 2024;45(11):2229-2240.

doi: 10.1038/s41401-024-01336-2

48. Lee J, Seo Y, Roh J-L. Ferroptosis and Nrf2 Signaling in Head and Neck Cancer: Resistance Mechanisms and Therapeutic Prospects. *Antioxidants*. 2025;14(8):993.

doi: 10.3390/antiox14080993

49. Chen T-H, Wang H-C, Chang C-J, Lee S-Y. Mitochondrial Glutathione in Cellular Redox Homeostasis and Disease Manifestation. *Int J Mol Sci*. 2024;25(2):1314.

doi: 10.3390/ijms25021314

50. Li J, Huang C, Tang P, *et al*. The distinct roles of ROS in tumor immunity: from mechanisms to immunotherapeutic applications. *J Hematol Oncol*. 2026;19(1):16.

doi: 10.1186/s13045-026-01780-z

51. Bjørklund G, Zou L, Peana M, *et al*. The Role of the Thioredoxin System in Brain Diseases. *Antioxidants*. 2022;11(11):2161.

doi: 10.3390/antiox11112161

52. Zhou M, Gao H, Wang X, *et al*. Nrf2 as a redox checkpoint in autoimmune joint inflammation: microenvironmental redox control across the arthritis spectrum. *Front Immunol*. 2026;17:1775908.

doi: 10.3389/fimmu.2026.1775908

53. Schaer DJ, Schulthess-Lutz N, Baselgia L, *et al*. Stress-NRF2 response axis polarizes tumor macrophages and undermines immunotherapy. *J Immunother Cancer*. 2025;13(10):e013063.

doi: 10.1136/jitc-2025-013063

54. Giulietti S, Bigini V, Savatin DV. ROS and RNS production, subcellular localization, and signaling triggered by immunogenic danger signals. *J Exp Bot*. 2024;75(15):4512-4534.

doi: 10.1093/jxb/erad449

55. Gülow K, Tümen D, Heumann P, *et al*. Unraveling the Role of Reactive Oxygen Species in T Lymphocyte Signaling. *Int J Mol Sci*. 2024;25(11):6114.

doi: 10.3390/ijms25116114

56. de la Lastra JMP, Andrés CMC, Munguira EB, Juan CA, Pérez-Lebeña E. Pathophysiology of reactive oxygen species (ROS). *Arch Toxicol*. 2026;100(2):475-513.

doi: 10.1007/s00204-025-04276-w

57. Ton Nu QC, Park P-H. Metabolic modulation of $CD8^+$ T cells by metformin: A promising adjuvant strategy for $CD8^+$ T Cell-Based Immunotherapies. *Pharmacol Res*. 2025;222:108015.

doi: 10.1016/j.phrs.2025.108015

58. Zhou Y, Bai M, Chen L, *et al*. Targeting inflammatory microenvironments: overcoming therapy resistance and immunosuppression. *Mol Cancer*. 2026;25(1):81.

doi: 10.1186/s12943-026-02583-z

59. Silva-Romeiro S, Flores-Campos RdC, Sánchez-León ML, Sánchez-Margalet V, De la Cruz-Merino L. Emerging Role of MDSCs as Novel Biomarkers and Therapeutic Targets for Cancer Immunotherapy. *ImmunoTargets Ther*. 2025;14:1267-1291.

doi: 10.2147/ITT.S485642

60. Stojanovic B, Milivojcevic Bevc I, Dimitrijevic Stojanovic M, *et al*. Oxidative Stress, Inflammation, and Cellular Senescence in Neuropathic Pain: Mechanistic Crosstalk. *Antioxidants*. 2025;14(10):1166.

doi: 10.3390/antiox14101166

61. Han I-H, Choi I, Kim S, *et al*. CD18-targeted peptide-drug conjugate remodels the immunosuppressive tumor microenvironment of prostate cancer by selective depletion of M2 macrophages. *npj Precis Oncol*. 2026;10:215.

doi: 10.1038/s41698-026-01377-2

62. Panda H, Rowland NG, Krall CM, *et al*. NRF2 immunobiology in cancer: implications for immunotherapy and therapeutic targeting. *Oncogene*. 2025;44(39):3641-3651.

doi: 10.1038/s41388-025-03560-4

63. Wen H, Suzuki T, Zhang A, *et al*. NRF2 activation in cancer cells suppresses immune infiltration into the tumor microenvironment. *iScience*. 2025;28(10):113519.

doi: 10.1016/j.isci.2025.113519

64. Kuang H, Chen Y, Yang X, *et al*. Macrophage polarization as a therapeutic target in lung diseases: From pathogenesis to precision intervention. *Int Immunopharmacol*. 2026;180:116660.

doi: 10.1016/j.intimp.2026.116660

65. Aboelella NS, Brandle C, Kim T, Ding ZC, Zhou G. Oxidative Stress in the Tumor Microenvironment and Its Relevance to Cancer Immunotherapy. *Cancers (Basel)*. 2021;13(5):986.

doi: 10.3390/cancers13050986

66. Joof AN, Bajinka O, Zhou Y, Ren F, Tan Y. The Central Role of NRF2 in Cancer Metabolism and Redox Signaling: Novel Insights into Crosstalk with ER Stress and Therapeutic Modulation. *Cell Biochem Biophys*. 2025;83(4):4145-4161.

doi: 10.1007/s12013-025-01821-3

67. Akter S, Madhuvilakku R, Kar AK, *et al*. Reactive oxygen species (ROS) in cancer: from mechanism to therapeutic implications. *Signal Transduct Target Ther*. 2026;11(1):111.

doi: 10.1038/s41392-026-02583-x

68. Chargui A, Hammami I, Hashem A, *et al*. Cd stabilizes HIF-1α under normoxic conditions via lysine-63-linked ubiquitination and induces ER stress and cell proliferation. *Toxicol Res*. 2025;41(3):221-234.

doi: 10.1007/s43188-024-00266-9

69. Gomar S, Bou R, Puertas FJ, *et al*. Current Insights into Glutathione Depletion in Adult Septic Patients. *Antioxidants*. 2025;14(9):1033.

doi: 10.3390/antiox14091033

70. Sánchez-Alcoholado L, Ramos-Molina B, Otero A, *et al*. The Role of the Gut Microbiome in Colorectal Cancer Development and Therapy Response. *Cancers (Basel)*. 2020;12(6):1406.

doi: 10.3390/cancers12061406

71. Paduraru DN, Palcau AC, Dinca VG, Ciuc DM, Constantinescu A. The Role of Gut Microbiota in Colorectal Cancer Pathogenesis: A Comprehensive Literature Review. *Int J Mol Sci*. 2025;26(24):11870.

doi: 10.3390/ijms262411870

72. Shah SC, Itzkowitz SH. Colorectal Cancer in Inflammatory Bowel Disease: Mechanisms and Management. *Gastroenterology*. 2022;162(3):715-730.e3.

doi: 10.1053/j.gastro.2021.10.035

73. Li J, Ji Y, Chen N, Dai L, Deng H. Colitis-associated carcinogenesis: crosstalk between tumors, immune cells and gut microbiota. *Cell Biosci*. 2023;13(1):194.

doi: 10.1186/s13578-023-01139-8

74. Bai B, Ma J, Xu W, *et al*. Gut microbiota and colorectal cancer: mechanistic insights, diagnostic advances, and microbiome-based therapeutic strategies. *Front Microbiol*. 2025;16:1699893.

doi: 10.3389/fmicb.2025.1699893

75. Irrazabal T, Thakur BK, Kang M, *et al*. Limiting oxidative DNA damage reduces microbe-induced colitis-associated colorectal cancer. *Nat Commun*. 2020;11(1):1802.

doi: 10.1038/s41467-020-15549-6

76. Gasaly N, Hermoso MA, Gotteland M. Butyrate and the Fine-Tuning of Colonic Homeostasis: Implication for Inflammatory Bowel Diseases. *Int J Mol Sci*. 2021;22(6):3061.

doi: 10.3390/ijms22063061

77. Chen JY, Wen JY, Lin JL, *et al*. Deoxycholic acid induces reactive oxygen species accumulation and promotes colorectal cancer cell apoptosis through the CaMKII-Ca(2+) pathway. *World J Gastrointest Oncol*. 2025;17(8):107453.

doi: 10.4251/wjgo.v17.i8.107453

78. Bautista J, Lamas-Maceiras M, Hidalgo-Tinoco C, *et al*. Gut microbiome-driven colorectal cancer via immune, metabolic, neural, and endocrine axes reprogramming. *NPJ Biofilms Microbiomes*. 2026;12(1):21.

doi: 10.1038/s41522-025-00883-8

79. Marroncini G, Naldi L, Martinelli S, Amedei A. Gut-Liver-Pancreas Axis Crosstalk in Health and Disease: From the Role of Microbial Metabolites to Innovative Microbiota Manipulating Strategies. *Biomedicines*. 2024;12(7):1398.

doi: 10.3390/biomedicines12071398

80. Mooli RGR, Mukhi D, Ramakrishnan SK. Oxidative Stress and Redox Signaling in the Pathophysiology of Liver Diseases. *Compr Physiol*. 2022;12(2):3167-3192.

doi: 10.1002/cphy.c200021

81. Han B, Lv X, Liu G, *et al*. Gut microbiota-related bile acid metabolism-FXR/TGR5 axis impacts the response to anti-α4β7-integrin therapy in humanized mice with colitis. *Gut Microbes*. 2023;15(1):2232143.

doi: 10.1080/19490976.2023.2232143

82. Hashem HR, Yehia T, Azab M, *et al*. Gut microbiome dysbiosis in hepatocellular carcinoma patients with persistent HCV viremia versus viral clearance: a cross-sectional study. *Gut Pathog*. 2025;17(1):88.

doi: 10.1186/s13099-025-00761-w

83. Schepis T, De Lucia SS, Nista EC, *et al*. Microbiota in Pancreatic Diseases: A Review of the Literature. *J Clin Med*. 2021;10(24):5920.

doi: 10.3390/jcm10245920

84. Ding T, Liu C, Li Z. The mycobiome in human cancer: analytical challenges, molecular mechanisms, and therapeutic implications. *Mol Cancer*. 2025;24(1):18.

doi: 10.1186/s12943-025-02227-8

85. Chai Y, Huang Z, Shen X, *et al*. Microbiota Regulates Pancreatic Cancer Carcinogenesis through Altered Immune Response. *Microorganisms*. 2023;11(5):1240.

doi: 10.3390/microorganisms11051240

86. Romeo M, Dallio M, Di Nardo F, *et al*. The Role of the Gut-Biliary-Liver Axis in Primary Hepatobiliary Liver Cancers: From Molecular Insights to Clinical Applications. *J Pers Med*. 2025;15(4):124.

doi: 10.3390/jpm15040124

87. Ying H, Kimmelman AC, Bardeesy N, *et al*. Genetics and biology of pancreatic ductal adenocarcinoma. *Genes Dev*. 2025;39(1-2):36-63.

doi: 10.1101/gad.351863.124

88. Laivacuma S, Oblate O, Derovs A. Gut Microbiota and the Gut-Liver Axis in Liver Disease: From Chronic Viral Hepatitis to Cirrhosis, Hepatocellular Carcinoma, and Microbiome-Based Therapies. *Microorganisms*. 2025;13(5):1053.

doi: 10.3390/microorganisms13051053

89. Damerell V, Klaassen-Dekker N, Brezina S, *et al*. Circulating tryptophan-kynurenine pathway metabolites are associated with all-cause mortality among patients with stage I-III colorectal cancer. *Int J Cancer*. 2025;156(3):552-565.

doi: 10.1002/ijc.35183

90. Toumazi D, Charalambous C, Constantinou C, Nicolaou N. From the gut to the brain: The involvement of the gut microbiota in the development and progression of glioblastoma. *Neurooncol Adv*. 2026;8(1):vdaf267.

doi: 10.1093/noajnl/vdaf267

91. Wang G, Zhong K, Wang Z, *et al*. Tumor-associated microglia and macrophages in glioblastoma: From basic insights to therapeutic opportunities. *Front Immunol*. 2022;13:964898.

doi: 10.3389/fimmu.2022.964898

92. Mohamed ZS, Wu Q, Jacome MA, Chen J, Etame AB. The Role of Gut Microbiome on Glioblastoma Oncogenesis and Malignant Evolution. *Int J Mol Sci*. 2025;26(7):2935.

doi: 10.3390/ijms26072935

93. Kaja E, Grupińska J, Budzyń M, *et al*. Disease- and chemotherapy-associated salivary microbiome changes in breast cancer patients. *Breast Cancer Res Treat*. 2026;216(1):2.

doi: 10.1007/s10549-026-07902-y

94. Wu H, He K, Wang H, *et al*. The gut-brain axis in the context of colorectal cancer. *Pharmacol Res*. 2025;217:107816.

doi: 10.1016/j.phrs.2025.107816

95. Yangyanqiu W, Jian C, Yuqing Y, Zhanbo Q, Shuwen H. Gut microbes involvement in gastrointestinal cancers through redox regulation. *Gut Pathog*. 2023;15(1):35.

doi: 10.1186/s13099-023-00562-z

96. Lu Y, Feng X, Wang Z, *et al*. Bile acid metabolism and hepatocellular carcinoma: mechanisms of drug resistance and intervention strategies. *Precis Clin Med*. 2025;8(3):pbaf020.

doi: 10.1093/pcmedi/pbaf020

97. Maneshi P, Mason J, Dongre M, Öhlund D. Targeting Tumor-Stromal Interactions in Pancreatic Cancer: Impact of Collagens and Mechanical Traits. *Front Cell Dev Biol*. 2021;9:787485.

doi: 10.3389/fcell.2021.787485

98. Nejadrostam S, Shadvar P, Jameie SB, Jameie M, Farhadi M. Gut microbiota and glioblastoma: composition, mechanisms, and therapeutic interventions. *Infect Agent Cancer*. 2026;21(1):15.

doi: 10.1186/s13027-026-00740-z

99. Hitch TCA, Hall LJ, Walsh SK, *et al*. Microbiome-based interventions to modulate gut ecology and the immune system. *Mucosal Immunol*. 2022;15(6):1095-1113.

doi: 10.1038/s41385-022-00564-1

100. Hou S, Yu J, Li Y, Zhao D, Zhang Z. Advances in Fecal Microbiota Transplantation for Gut Dysbiosis-Related Diseases. *Adv Sci (Weinh)*. 2025;12(13):e2413197.

doi: 10.1002/advs.202413197

101. Abouelela ME, Helmy YA. Next-Generation Probiotics as Novel Therapeutics for Improving Human Health: Current Trends and Future Perspectives. *Microorganisms*. 2024;12(3):430.

doi: 10.3390/microorganisms12030430

102. Du W, Zou ZP, Ye BC, Zhou Y. Gut microbiota and associated metabolites: key players in high-fat diet-induced chronic diseases. *Gut Microbes*. 2025;17(1):2494703.

doi: 10.1080/19490976.2025.2494703

103. Ngo V, Duennwald ML. Nrf2 and Oxidative Stress: A General Overview of Mechanisms and Implications in Human Disease. *Antioxidants (Basel)*. 2022;11(12):2345.

doi: 10.3390/antiox11122345

104. Eraghieh Farahani H, Pourhajibagher M, Asgharzadeh S, Bahador A. Postbiotics: Novel Modulators of Gut Health, Metabolism, and Their Mechanisms of Action. *Probiotics Antimicrob Proteins*. 2025;18(4):5037-5053.

doi: 10.1007/s12602-025-10832-8

105. Lei W, Zhou K, Lei Y, Li Q, Zhu H. Gut microbiota shapes cancer immunotherapy responses. *NPJ Biofilms Microbiomes*. 2025;11(1):143.

doi: 10.1038/s41522-025-00786-8

106. Tripathy A, Dash J, Kancharla S, *et al*. Probiotics: A Promising Candidate for Management of Colorectal Cancer. *Cancers (Basel)*. 2021;13(13):3178.

doi: 10.3390/cancers13133178

107. Tsao SP, Nurrahma BA, Kumar R, *et al*. Probiotic Enhancement of Antioxidant Capacity and Alterations of Gut Microbiota Composition in 6-Hydroxydopamin-Induced Parkinson's Disease Rats. *Antioxidants (Basel)*. 2021;10(11):1823.

doi: 10.3390/antiox10111823

108. Thorakkattu P, Khanashyam AC, Shah K, *et al*. Postbiotics: Current Trends in Food and Pharmaceutical Industry. *Foods*. 2022;11(19):3094.

doi: 10.3390/foods11193094

109. Abdolmohammadi P, Aali M, Lehmann C. Cytokine Toxicity and Bacterial Dysbiosis in Chemotherapy- and/or Radiotherapy-Induced Oral Mucositis: Pathophysiological Mechanisms and Therapeutic Interventions. *Life*. 2026;16(4):644.

doi: 10.3390/life16040644

110. Zeng J, Tan Z, Zhang K, *et al*. Butyrate enhances recovery of chemotherapy-induced oral mucositis by enhancing tight junction protein expression and inhibiting inflammatory responses. *Med Oral Patol Oral Cir Bucal*. 2025;30(5):e657-e663.

doi: 10.4317/medoral.27080

111. Ahmad MF, Ahmad FA, Alsayegh AA, *et al*. Probiotics and Cancer: Mechanistic Insights and Organ-Specific Impact. *Biomolecules*. 2025;15(6):879.

doi: 10.3390/biom15060879

112. Shimizu K, Ojima M, Ogura H. Gut Microbiota and Probiotics/Synbiotics for Modulation of Immunity in Critically Ill Patients. *Nutrients*. 2021;13(7):2439.

doi: 10.3390/nu13072439

113. Prajapati SK, Yadav D, Katiyar S, Jain S, Yadav H. Postbiotics as Mitochondrial Modulators in Inflammatory Bowel Disease: Mechanistic Insights and Therapeutic Potential. *Biomolecules*. 2025;15(7):954.

doi: 10.3390/biom15070954

114. Kaur AP, Bhardwaj S, Dhanjal DS, *et al*. Plant Prebiotics and Their Role in the Amelioration of Diseases. *Biomolecules*. 2021;11(3):440.

doi: 10.3390/biom11030440

115. Tanaka M, Vécsei L. From Microbial Switches to Metabolic Sensors: Rewiring the Gut-Brain Kynurenine Circuit. *Biomedicines*. 2025;13(8):2020.

doi: 10.3390/biomedicines13082020

116. Zikou E, Koliaki C, Makrilakis K. The Role of Fecal Microbiota Transplantation (FMT) in the Management of Metabolic Diseases in Humans: A Narrative Review. *Biomedicines*. 2024;12(8):1871.

doi: 10.3390/biomedicines12081871

117. Ionescu VA, Diaconu CC, Gheorghe G, *et al*. Gut Microbiota and Colorectal Cancer: A Balance Between Risk and Protection. *Int J Mol Sci*. 2025;26(8):3733.

doi: 10.3390/ijms26083733

118. Liu S, Liu J, Wang Y, Deng F, Deng Z. Oxidative Stress: Signaling Pathways, Biological Functions, and Disease. *MedComm*. 2025;6(7):e70268.

doi: 10.1002/mco2.70268

119. Barragan-Carrillo R, Zengin ZB, Pal SK. Microbiome Modulation for the Treatment of Solid Neoplasms. *J Clin Oncol*. 2025;43(24):2734-2738.

doi: 10.1200/jco-25-00374

120. Moon CM, Hong SN. Fecal Microbiota Transplantation beyond Clostridioides Difficile Infection. *Clin Endosc*. 2021;54(2):149-151.

doi: 10.5946/ce.2021.068

121. Zhang Y, Xu X, Wang S, *et al*. Fecal microbiota transplantation combined with anti-PD-1 therapy in refractory microsatellite-stable gastric cancer: a phase I feasibility and safety study. *J Immunother Cancer*. 2026;14(3):e013823.

doi: 10.1136/jitc-2025-013823

122. Kang X, Lau HC, Yu J. Modulating gut microbiome in cancer immunotherapy: Harnessing microbes to enhance treatment efficacy. *Cell Rep Med*. 2024;5(4):101478.

doi: 10.1016/j.xcrm.2024.101478

123. Petrelli F, Ghidini A, Dottorini L, *et al*. Clinical Evidence for Microbiome-Based Strategies in Cancer Immunotherapy: A State-of-the-Art Review. *Medicina (Kaunas)*. 2025;61(9):1595.

doi: 10.3390/medicina61091595

124. Malik A, Yousaf MN, Samiullah S, Tahan V, Mahdi A. Overlapping Hepatotoxicity and Colitis Associated with Immune Checkpoint Inhibitors. *J Community Hosp Intern Med Perspect*. 2023;13(3):75-78.

doi: 10.55729/2000-9666.1172

125. Yousefi Y, Baines KJ, Maleki Vareki S. Microbiome bacterial influencers of host immunity and response to immunotherapy. *Cell Rep Med*. 2024;5(4):101487.

doi: 10.1016/j.xcrm.2024.101487

126. Luu M, Riester Z, Baldrich A, *et al*. Microbial short-chain fatty acids modulate CD8+ T cell responses and improve adoptive immunotherapy for cancer. *Nat Commun*. 2021;12(1):4077.

doi: 10.1038/s41467-021-24331-1

127. Allegra A, Murdaca G, Mirabile G, Gangemi S. Redox Signaling Modulates Activity of Immune Checkpoint Inhibitors in Cancer Patients. *Biomedicines*. 2023;11(5):1325.

doi: 10.3390/biomedicines11051325

128. Jaganjac M, Milkovic L, Sunjic SB, Zarkovic N. The NRF2, Thioredoxin, and Glutathione System in Tumorigenesis and Anticancer Therapies. *Antioxidants (Basel)*. 2020;9(11):1151.

doi: 10.3390/antiox9111151

129. Zhao H, Wang D, Zhang Z, Xian J, Bai X. Effect of Gut Microbiota-Derived Metabolites on Immune Checkpoint Inhibitor Therapy: Enemy or Friend? *Molecules*. 2022;27(15):4799.

doi: 10.3390/molecules27154799

130. Antohi AL, Gheorghiță AD, Andronic O, Gradisteanu Pircalabioru G, Treteanu AR. Across the Social Network of the Gut: Bacterial, Fungal, and Viral Determinants of Checkpoint Inhibitor Efficacy and Toxicity. *Int J Mol Sci*. 2026;27(6):2538.

doi: 10.3390/ijms27062538

131. Kim K, Lee M, Shin Y, Lee Y, Kim TJ. Optimizing Cancer Treatment Through Gut Microbiome Modulation. *Cancers (Basel)*. 2025;17(7):1252.

doi: 10.3390/cancers17071252

132. Oh JJ, Lee YJ, Han YJ, *et al*. Inhibition of RBM23 induces ferroptosis in colon cancer cells via c-Myc regulation. *Cancer*

Cell Int. 2026;26(1):195.

doi: 10.1186/s12935-026-04262-x

133. Wang M, Zhang L, Chang W, Zhang Y. The crosstalk between the gut microbiota and tumor immunity: Implications for cancer progression and treatment outcomes. *Front Immunol*. 2022;13:1096551.

doi: 10.3389/fimmu.2022.1096551

134. Effendi R, Anshory M, Kalim H, *et al*. Akkermansia muciniphila and Faecalibacterium prausnitzii in Immune-Related Diseases. *Microorganisms*. 2022;10(12):2382.

doi: 10.3390/microorganisms10122382

135. Wang M, Guo J, Hart AL, Li JV. Indole-3-Aldehyde Reduces Inflammatory Responses and Restores Intestinal Epithelial Barrier Function Partially via Aryl Hydrocarbon Receptor (AhR) in Experimental Colitis Models. *J Inflamm Res*. 2023;16:5845-5864.

doi: 10.2147/jir.S432747

136. Guo Y, Chang G, Wan R, *et al*. Discovery of a novel ROS-based signature for predicting prognosis and immunosuppressive tumor microenvironment in lung adenocarcinoma. *J Cancer*. 2024;15(9):2691-2711.

doi: 10.7150/jca.93975

137. Di Maio G, Tafuri MG, Casillo M, *et al*. Physiological Regulation of Nutritional and Metabolic Biomarkers in Obesity: Implications for Precision Nutrition. *Nutrients*. 2026;18(6):1014.

doi: 10.3390/nu18061014

138. Chen C, Wang GQ, Li DD, Zhang F. Microbiota-gut-brain axis in neurodegenerative diseases: molecular mechanisms and therapeutic targets. *Mol Biomed*. 2025;6(1):64.

doi: 10.1186/s43556-025-00307-1

139. Prasad S, Singh S, Menge S, *et al*. Gut redox and microbiome: charting the roadmap to T-cell regulation. *Front Immunol*. 2024;15:1387903.

doi: 10.3389/fimmu.2024.1387903

140. O'Riordan KJ, Moloney GM, Keane L, Clarke G, Cryan JF. The gut microbiota-immune-brain axis: Therapeutic implications. *Cell Rep Med*. 2025;6(3):101982.

doi: 10.1016/j.xcrm.2025.101982

141. Msigwa SS, Mkwambe MC, Yu QY, *et al*. Comparative evaluation of oxidative stress biomarkers F2-isoprostanes and 8-OHdG in Parkinson's disease and Type 2 Diabetes Mellitus: a systematic review and meta-analysis of human studies. *Ann Med*. 2026;58(1):2654251.

doi: 10.1080/07853890.2026.2654251

142. Sun S, Liu L, Zhang J, *et al*. The role of neoantigens and tumor mutational burden in cancer immunotherapy: advances, mechanisms, and perspectives. *J Hematol Oncol*. 2025;18(1):84.

doi: 10.1186/s13045-025-01732-z

143. Lim ECN, Lim CED. Microbiome-Targeted Therapies in Gastrointestinal Diseases: Clinical Evidence and Emerging Innovations. *Acta Microbiol Hell*. 2025;70(3):36.

doi: 10.3390/amh70030036

144. Najmi M, Tran T, Witt RG, Nelson KC. Modulation of the Gut Microbiome to Enhance Immunotherapy Response in Metastatic Melanoma Patients: A Clinical Review. *Dermatol Ther (Heidelb)*. 2022;12(11):2489-2497.

doi: 10.1007/s13555-022-00810-1

145. Yang SY, Han SM, Lee JY, *et al*. Advancing Gut Microbiome Research: The Shift from Metagenomics to Multi-Omics and Future Perspectives. *J Microbiol Biotechnol*. 2025;35:e2412001.

doi: 10.4014/jmb.2412.12001

146. d'Andrea V, Loscalzo J, De Domenico M. Challenges and opportunities in the network medicine of complex diseases. *Med*. 2026;7(2):100920.

doi: 10.1016/j.medj.2025.100920

147. Hasin Y, Seldin M, Lusis A. Multi-omics approaches to disease. *Genome Biol*. 2017;18(1):83.

doi: 10.1186/s13059-017-1215-1

148. Tegegne HA, Savidge TC. Gut microbiome metagenomics in clinical practice: bridging the gap between research and precision medicine. *Gut Microbes*. 2025;17(1):2569739.

doi: 10.1080/19490976.2025.2569739