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Review

Microbiota-Associated Metabolites in Tumor Immunity: Shared Regulatory Modules, Context-Dependent Outcomes, and Therapeutic Translation

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Abstract

Microbiota-associated metabolites across selected cancer contexts are likely to derive from biosynthetically distinct groups, ranging from metabolites directly synthesized by microorganisms, host metabolites modified by microbial enzymes, and microbiota-dependent host co-metabolites to primarily host- or tumor-derived mediators whose abundance or signaling is indirectly influenced by the microbiota. Microbiota-associated metabolites include, but are not limited to, short-chain fatty acids (SCFAs), microbial tryptophan (Trp)-derived metabolites, secondary bile acids (BAs), and trimethylamine N-oxide (TMAO), whereas kynurenine (Kyn), lactate, and prostaglandin E2 (PGE2) are classified separately as mainly host- or tumor-derived mediators within microbiota-linked metabolic networks. These molecules converge at shared molecular interfaces, including farnesoid X receptor (FXR), aryl hydrocarbon receptor (AhR), histone deacetylases (HDACs), and mechanistic target of rapamycin (mTOR)/general control nonderepressible 2 (GCN2)-associated signaling. Nevertheless, the functional outcomes of these recurrent molecular nodes vary across tissue, cellular, dose, and treatment contexts. Whether a metabolite supports antitumor immunity, immune suppression, or tumor-cell adaptation depends on anatomical exposure, cellular access, transporter and receptor expression, ligand sensitivity, intracellular metabolic fate, local immune composition, and treatment context. Butyrate inhibits colorectal cancer (CRC) growth but is associated with regulatory T-cell (Treg) expansion in metabolic dysfunction-associated steatotic liver disease-associated hepatocellular carcinoma (MASLD-HCC), whereas deoxycholic acid (DCA) exerts distinct effects in CRC and gastric cancer. Herein, this review puts together an operational context-filter framework whereby each signal is resolved as a metabolite–access route–sensor–cell state–metabolic fate combination that addresses how recurrent molecular modules generate divergent immune or tumor-cell outcomes across anatomical, cellular, dose, and treatment contexts. It has the potential to guide the development of context-resolved biomarkers, metabolite-targeted interventions, and combinations with immune checkpoint inhibitors (ICIs). However, clinical translation remains limited by pharmacokinetic uncertainty, interpatient variability, insufficient causal validation, and inadequate tissue- and cell-specific delivery.

Keywords: microbiota-associated metabolites; tumor immunity; context dependence; tumor microenvironment; cancer immunotherapy; clinical translation

1. Introduction

Cancer is a major global health burden[1]. Although surgery, radiotherapy, and systemic therapies may provide meaningful disease control, many patients present with metastatic disease or

experience recurrence after treatment, while treatment-related toxicities may adversely affect quality of life[2, 3]. ICIs have improved survival in several advanced cancers, such as melanoma and non-small-cell lung cancer (NSCLC)[4, 5]. However, acquired resistance may develop following an initial response to ICIs, thereby limiting durable clinical benefit[6].

Microbes residing in the gut and other sites of the body form communities that produce metabolites capable of modulating host metabolism, epithelial-barrier integrity, and immune function[7-10]. In cancer, microbiota-associated metabolites interact with recurrent molecular interfaces, but their downstream immune and tumor-cell effects vary according to tissue niche, target-cell identity, effective concentration, and treatment context[11-13]. Mechanistic interpretation therefore requires characterization not only of the pathway engaged by a metabolite, but also of the cell population that gains access to it, the transporter or receptor involved, and the competitive metabolic conditions within the tumor microenvironment (TME).

For instance, indole-3-propionic acid (IPA) enhances histone H3 lysine 27 (H3K27) acetylation at the T-cell factor 7 (TCF7) super-enhancer in progenitor-exhausted $CD8^+$ T cells, while butyrate modulates dendritic-cell development and T-cell priming through histone deacetylase 3 (HDAC3) inhibition[11, 14]. Although these metabolites stem from distinct microbial metabolic pathways, both exemplify how microbial metabolites converge on recurrent epigenetic regulatory modules[15, 16]. However, engagement of the same molecular module does not always yield the same functional outcome across tissues or cancer types.

A number of recent reviews centered on microbiota-derived metabolites and cancer immunity and immunotherapy have provided detailed background information on major metabolite classes and immune-cell targets for these compounds, while also describing immunotherapy outcomes, context-dependent effects, and therapeutic implications[17-19]. Recent work has elucidated the modulatory effects of microbial metabolites on immune-checkpoint blockade, allogeneic stem cell transplantation, and chimeric antigen receptor (CAR) T-cell therapy, as well as their biomarker and translational potential[19]. A more recent review proposed a metabolite–immune pathway–cancer framework to classify gut microbial metabolites and emphasized context-dependent effects across different tumor types[18]. Of note, an accompanying review covered metabolite-driven immune reprogramming in tumor immunotherapy and then defined concentration, receptor expression, metabolic context, host genetic background, and translational constraints as crucial determinants of metabolite activity[17].

To this end, these determinants have not been fully operationalized into a sequential framework linking anatomical exposure, cellular access, sensor engagement, cell state, intracellular metabolic fate, and causal evidence. Both the identification of individual metabolites and the recognition of context dependency are not new, but the distinctive contribution of the present review does not lie in cataloguing individual metabolites or in recognizing context dependence per se[20, 21]. Instead, this review will approach the issue differently, operationalizing context dependence via the sequential metabolite–access route–sensor–cell state–metabolic fate framework that is ideally suited to distinguish shared molecular modules from cancer-, cell-, dose-, and treatment-specific functional outputs. Based on this mechanistic framework, the present review connects effective exposure and cell-specific target engagement with causal evidence and translational applicability, interprets cross-cancer functional reversals, and defines the conditions under which a microbiota-associated metabolite may serve as a biomarker or therapeutic target[11, 22, 23]. In Section 3.5, the mechanistic basis of this framework is developed and subsequently applied to cross-cancer interpretation and translational evaluation.

A Level I–IV evidence hierarchy is used in this review to denote how closely the evidence approaches metabolite-specific causal inference. Importantly, none of these levels is indicative of an overall rank order of methodological quality or clinical strength of evidence. Level I evidence comprises direct human administration of a chemically defined metabolite with prospectively assessed clinical or pharmacodynamic outcomes. Mechanistic *in vivo* studies with defined metabolite exposure and cell-, receptor-, transporter-, or pathway-specific perturbation are considered Level II evidence. Level III evidence comprises *ex vivo* or *in vitro* studies that provide mechanistic support, although they remain limited by experimental context. Level IV evidence comprises human fecal, circulating, tissue, or microbiome–metabolome associations without direct metabolite intervention. Though microbiota-directed interventions provide interventional evidence for microbiota modification, including probiotics, live bacterial products, dietary modulation, and fecal microbiota transplantation (FMT), they remain indirect evidence for a specific metabolite unless altered metabolite exposure and causal mediation are directly demonstrated[21, 24-26].

2. A basic overview of microbiota-associated metabolites and tumor immunity

2.1 Classification of microbiota-associated metabolites by biosynthetic origin

For clarity, the molecules discussed in this review are classified according to biosynthetic origin rather than collectively designated as microbial metabolites. Category I includes metabolites directly synthesized by microorganisms, including SCFAs and many microbial Trp-derived indoles[27-29]. The second category is represented by host metabolites biotransformed by microbial enzymes, defined here as Category II, including secondary and iso-BAs derived from host-synthesized primary BAs[30, 31]. Category III comprises microbiota-dependent host co-metabolites that require sequential microbial and host metabolism, with TMAO being one of the most well-known examples[32]. Category IV comprises primarily host- or tumor-derived mediators whose abundance, production, or signaling may be indirectly shaped by microbiota-associated metabolic networks, including Kyn, lactate, and PGE2[33-36]. However, the coverage of the review is mainly tailored to metabolites in Categories I–III, whereas Category IV mediators are discussed separately only when they provide a mechanistically relevant interface with microbiota-dependent tumor–immune regulation. As succinate can be produced by both host and microbial cells, it is further classified according to its experimentally demonstrated source[21, 37]. Table S1 provides a summary of the biosynthetic origin, representative sources, signaling mechanisms, concentration-dependent effects, and immunomo dulatory functions of the metabolites considered in this review.

2.2 Immune-cell interfaces targeted by microbiota-associated metabolites in the TME

Innate and adaptive immune compartments orchestrate tumor immunity, which is constrained by immune-checkpoint signaling[38,43,44]. Within the TME, macrophages, dendritic cells (DCs), natural killer (NK) cells, $CD8^+$ T cells, $CD4^+$ T-cell subsets, and myeloid-derived suppressor cells (MDSCs) constitute the principal cellular interfaces through which microbiota-associated metabolites act[39]. Rather than revisiting their canonical recognition and cytotoxic mechanisms, this review focuses on metabolite-driven alterations in macrophage polarization, dendritic-cell antigen presentation, NK-cell cytotoxicity, T-cell activation and differentiation, and checkpoint-associated immune suppression[40-45].

Microbiota-associated metabolites and microbiota-mediated nutrient competition regulate NK-cell cytotoxicity, $CD8^+$ T-cell effector and memory programs, Treg suppressive activity, and polymorphonuclear myeloid-derived suppressor cell (PMN-MDSC) differentiation through mitochondrial remodeling and mTOR-dependent nutrient sensing, thereby shaping antitumor immunity and responses to immune-checkpoint blockade[46-49]. Here, this review summarizes these metabolite-dependent effects by metabolite category, core signaling mechanism, responding cell compartment, and context-dependent determinants. A conceptual overview of the integrated framework linking the biosynthetic categories of microbiota-associated metabolites to shared regulatory modules, context filters, cell-specific interfaces, divergent tumor–immune outcomes, and representative context-dependent contrasts is shown in Figure 1.

3. Metabolite-centered regulatory modules in tumor immunity

Instead of reviewing the effects of microbiota-associated metabolites according to individual immune-cell populations, this section integrates the available evidence using a metabolite-centered structure. Each metabolite class is organized according to its principal signaling pathways, epigenetic or metabolic mechanisms, responding immune and tumor-cell compartments, and contextual factors that determine the final functional outcome. This structure distinguishes recurrent molecular interfaces from cell- and tissue-specific responses while avoiding repeated descriptions of the same metabolite under different immune-cell headings.

3.1 SCFAs: G protein-coupled receptor (GPCR) signaling, HDAC inhibition, and metabolic reprogramming

This section summarizes how SCFAs, particularly acetate, propionate, and butyrate, modulate tumor immunity through three recurrent mechanisms: extracellular GPCR signaling, intracellular HDAC inhibition, and metabolic reprogramming. The dominant SCFA-responsive mechanism is shaped by receptor availability, transporter-dependent cellular access, intracellular metabolic capacity, and the identity of the responding cell[50, 51]. Figure 2 presents an integrated framework for SCFA action, outlining three shared regulatory modules, mapping the major immune-cell interfaces they engage, and highlighting the key contextual determinants that steer these signals toward enhanced effector immunity, immune regulation, or immune restraint.

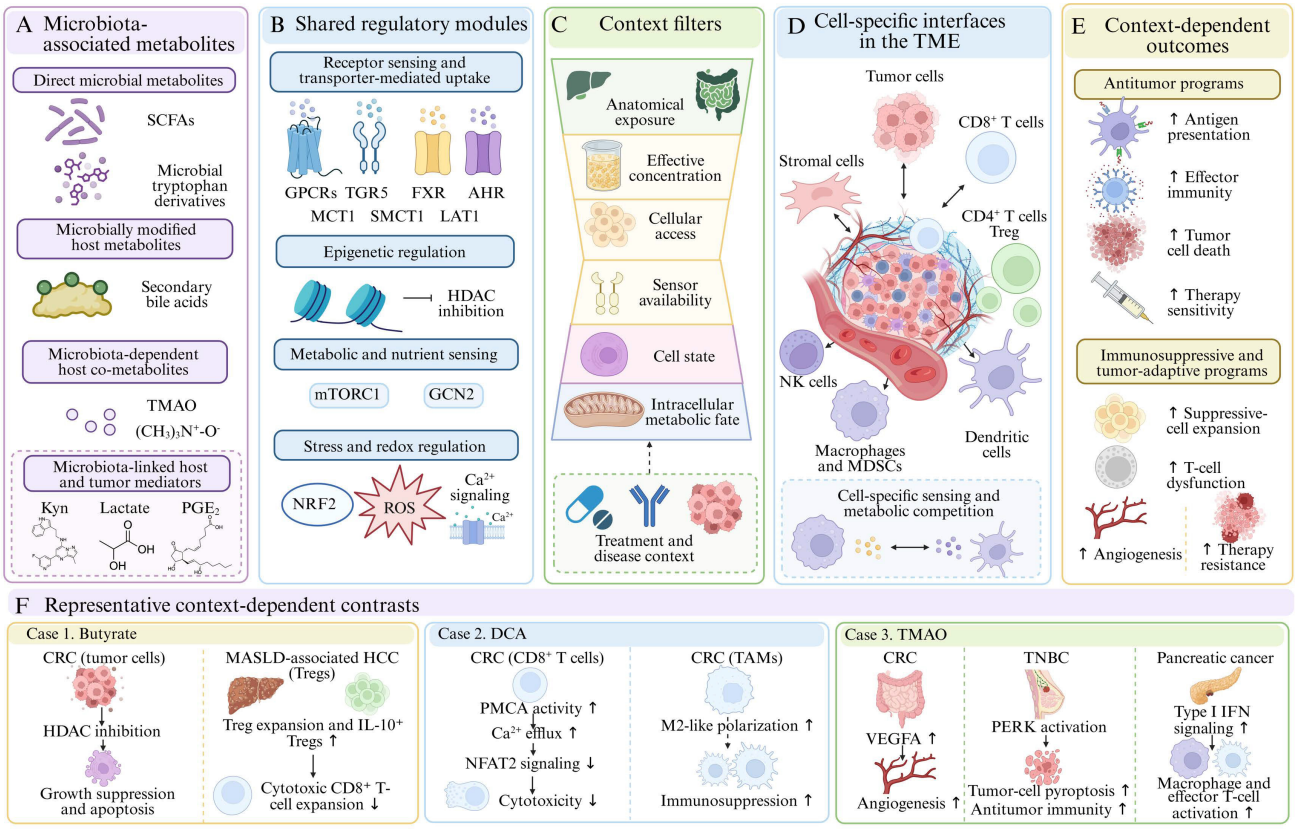

Figure 1. Integrated framework linking microbiota-associated metabolites to shared regulatory modules, context filters, cell-specific interfaces, and context-dependent tumor–immune outcomes: (A) Categories of microbiota-associated metabolites depending on their biosynthetic origin include direct microbial metabolites, such as SCFAs and microbial Trp-derived metabolites; microbially modified host metabolites, such as secondary BAs; microbiota-dependent host co-metabolites, including TMAO; and microbiota-related mediators mainly derived from the host or tumor, including Kyn, lactate, and PGE2. (B) The major metabolites and mediators coalesce on recurrent regulatory modules involving receptor sensing and transporter-mediated uptake, epigenetic regulation, metabolic and nutrient sensing, as well as stress and redox regulation. (C) Context filters further shape their biological effects, including anatomical exposure, effective concentration, cellular access, sensor availability, cell state, intracellular metabolic fate, and treatment and disease context. (D) Major interfaces in the TME include tumor cells, stromal cells, $CD8^+$ T cells, $CD4^+$ T-cell subsets and Tregs, NK cells, macrophages and MDSCs, and DCs, with metabolic competition and differential sensing contributing to the dominant response. (E) These pathways can promote antitumor programs characterized by enhanced antigen presentation, effector immunity, tumor-cell death, and therapy sensitivity or immunosuppressive and tumor-adaptive programs characterized by suppressive-cell expansion, T-cell dysfunction, angiogenesis, and therapy resistance, depending on the predominant metabolite–sensor–cell combination and contextual conditions. (F) Representative context-dependent differences demonstrate this principle. Although butyrate inhibits CRC tumor-cell growth through HDAC inhibition, a butyrate-enriched metabolic environment in MASLD-associated HCC is linked to Treg expansion and attenuated cytotoxic $CD8^+$ T-cell responses. DCA inhibits $CD8^+$ T-cell cytotoxicity through increased PMCA-mediated Ca^{2+} efflux and reduced NFATC2 signaling and can also promote M2-like TAM polarization and immunosuppression in CRC. Whereas TMAO has been associated with VEGFA-dependent angiogenesis in CRC, it promotes PERK-dependent tumor-cell pyroptosis and antitumor immunity in TNBC, as well as type I IFN-associated macrophage and effector T-cell activation in pancreatic cancer.

Metabolic reprogramming is a major mechanism through which SCFAs support $CD8^+$ T-cell activation and memory formation[52]. Butyrate enhances metabolic adaptation by increasing mitochondrial activity and shifting fuel utilization toward glutamine and fatty acids, thereby providing a metabolic basis for long-term T-cell persistence[53-59]. Such effects may support antitumor immunity when SCFAs act primarily on effector or memory $CD8^+$ T-cell populations.

The balance of $CD4^+$ T-cell subsets is also regulated by GPCR signaling and HDAC-dependent chromatin remodeling. Through G protein-coupled receptor 41 (GPR41; also known as free fatty acid receptor 3)-associated signal transducer and activator of transcription 3 (STAT3)–mTOR signaling, as well as HDAC-dependent chromatin remodeling, butyrate can promote Treg differentiation while restricting T helper 17 cell (Th17 cell) development[60-64]. Under defined in-vitro experimental conditions, butyrate can promote Th1-associated T-bet and interferon-γ (IFN-γ) expression while concomitantly driving the generation of IL-10-producing Th1-like populations, highlighting context-dependent dual immunomodulatory outputs [65, 66]. Such effects may regulate tumor-promoting inflammation, but excessive Treg accumulation may also restrict antitumor immune responses in established tumors.

Coordinated epigenetic and metabolic remodeling enables SCFAs to modulate antibody production as well as immune-regulatory programs in B cells. HDAC inhibition promotes the expression of genes involved in class-switch recombination and plasma-cell differentiation, while elevated acetyl-CoA

availability, glucose uptake, glycolysis, and mTOR activity provide metabolic support for B-cell proliferation and antibody secretion[67-70]. SCFAs can reinforce immune-regulatory B-cell programs. Butyrate promotes the differentiation of IL-10^{+}IgM^{+} plasma cells, whereas propionate stabilizes IL-10 expression in B10 cells[71, 72].

SCFAs have context-dependent effects on macrophages. Foundational studies established that butyrate directly reprograms intestinal macrophage function through HDAC inhibition[73]. More recent studies have described cancer-specific macrophage responses to SCFAs in tumor models. For example, SCFAs promoted M1-like macrophage polarization in glioblastoma models, while microbiota-derived butyrate reduced programmed death-ligand 1 (PD-L1) and IL-10 expression in tumor-associated macrophages (TAMs) in gastric cancer[74, 75]. These findings demonstrate that SCFA-induced macrophage polarization varies with tumor type, metabolite exposure, tissue origin, pre-existing inflammatory signaling, and myeloid-cell state.

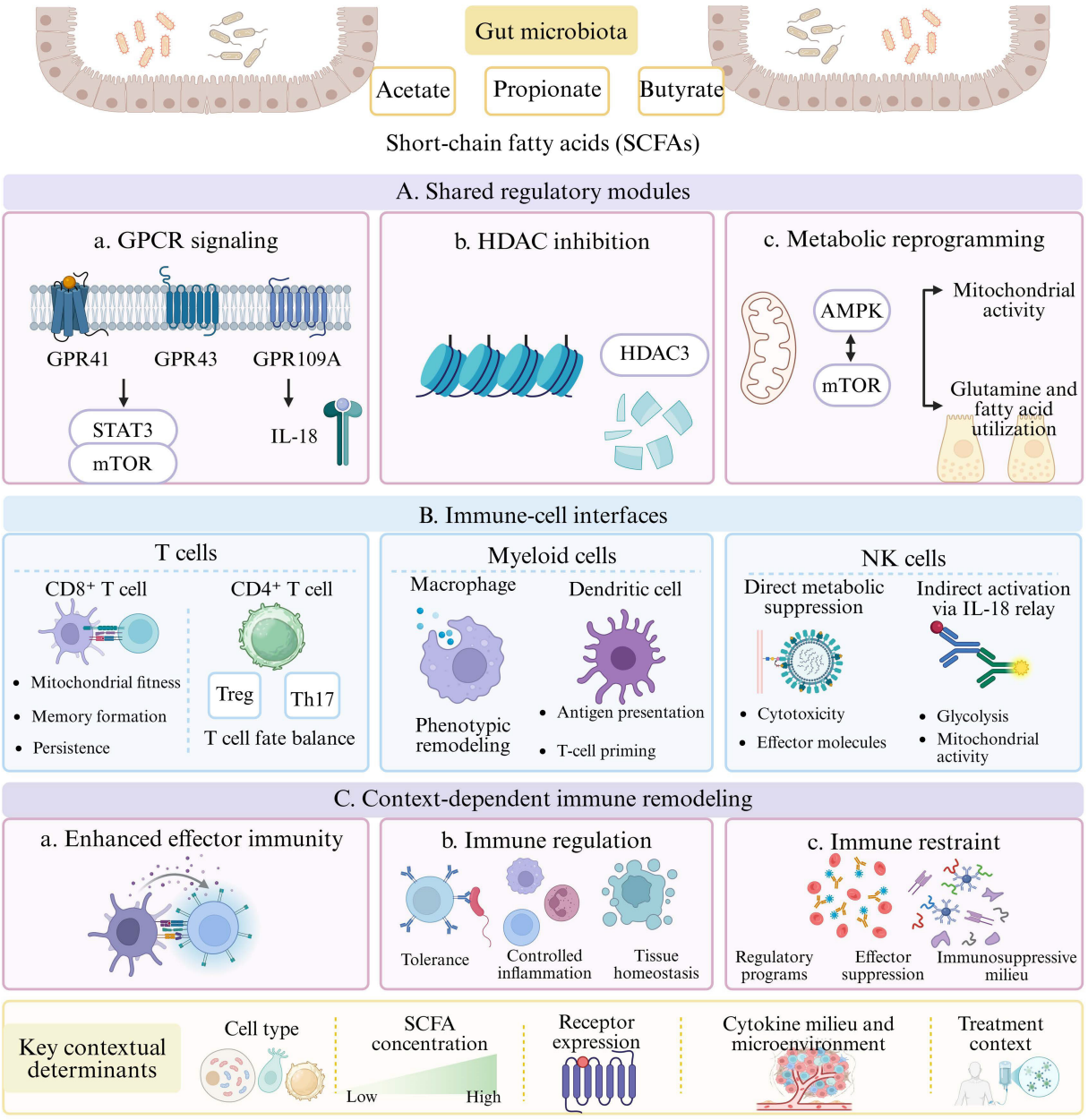

Figure 2. SCFAs regulate immune-cell programs through shared modules and context-dependent remodeling in the TME: Gut microbiota-derived acetate, propionate, and butyrate signal via three recurring mechanisms involving GPCR activation, HDAC inhibition, and metabolic rewiring. Shared regulatory modules include GPR41, GPR43, and GPR109A; HDAC3-associated chromatin regulation; and AMPK–mTOR-linked metabolic adaptation that enhances mitochondrial activity and glutamine/fatty-acid utilization. In the TME, these pathways shape core immune-cell interfaces involving T cells, myeloid cells, and NK cells. They influence CD8^{+} T-cell mitochondrial fitness, memory formation, and persistence; CD4^{+} T-cell fate balance; macrophage phenotypic remodeling; dendritic-cell antigen presentation and T-cell priming; and NK-cell function through either direct metabolic suppression or an indirect IL-18-mediated relay. SCFA signaling may promote enhanced effector immunity, immune regulation, or immune restraint depending on contextual determinants such as cell type, SCFA concentration, receptor expression, cytokine milieu, microenvironment, and treatment context.

The seemingly divergent effects of SCFAs on NK cells across different contexts are likely related to differences in cell source, metabolite concentration, activation state, cytokine environment, exposure duration, target-cell identity, and direct versus indirect signaling. In primary human peripheral-blood NK cells stimulated with IL-12 and IL-15, butyrate at millimolar concentrations reduced mechanistic target of rapamycin complex 1 (mTORC1)–S6 and cellular Myc (c-Myc) signaling, constrained glycolysis and oxidative phosphorylation, and decreased the expression of activating receptors, cytokines, and cytolytic molecules[76]. In this experimental setting, however, direct killing of K562 target cells was not significantly impaired. These findings suggest that butyrate-mediated metabolic restraint and reduced effector-molecule production do not necessarily represent a universal loss of NK-cell cytotoxicity. Additionally, this inhibitory effect occurred despite combined IL-12 and IL-15 stimulation, suggesting that the presence of IL-15 alone cannot explain the differences among studies.

In contrast, micromolar concentrations of acetate, propionate, and butyrate modestly enhanced NK-92-cell cytotoxicity against MM.1S multiple myeloma cells after 48 h of exposure and altered extracellular vesicle and IL-10 release[77]. A distinct tissue-dependent mechanism operates in liver-resident NK cells. In this context, butyrate primarily acts through a cell-extrinsic relay: G protein-coupled receptor 109A (GPR109A) signaling in Kupffer cells and hepatocytes increases IL-18 production, thereby supporting mitochondrial activity and the functional maturation of liver-resident NK cells[78]. Thus, the divergent effects of SCFAs on NK cells are best explained by differences in cell source, metabolite concentration, signaling route, cytokine context, exposure duration, and target-cell identity.

Butyrate regulates dendritic-cell development, antigen presentation, and T-cell priming primarily through HDAC3 inhibition. In conventional dendritic-cell precursors, butyrate can selectively suppress conventional type 2 dendritic-cell development and reduce naïve T-cell priming through HDAC3 inhibition in a GPCR-independent manner[14]. Importantly, these findings show that extracellular receptor signaling and intracellular HDAC inhibition can produce distinct functional outcomes even within the same metabolite class.

Collectively, GPCR signaling, HDAC inhibition, and metabolic reprogramming constitute common SCFA-responsive modules across immune-cell populations. However, their functional outputs vary according to cell-specific metabolite exposure, intracellular metabolic fate, and the prevailing immune and treatment context[79]. The final effects depend on which cell population receives an effective metabolite dose, whether the metabolite serves as a metabolic substrate or remains available for epigenetic regulation, and whether immune tolerance or effector function predominates in the relevant disease and treatment context.

3.2 Trp-derived metabolites: AhR, pregnane X receptor (PXR), STAT3, and nutrient-sensing pathways

Trp-derived metabolites engage recurrent immune-regulatory interfaces, including AhR signaling and PXR-dependent cytokine induction[80,81]. Other mechanisms, including epigenetic remodeling and amino-acid sensing, require separate pathway-specific evidence. Although they belong to the same broad metabolite family, individual Trp derivatives can promote antitumor immunity, immune tolerance, or tumor-cell adaptation according to their molecular structure and target-cell compartment. Figure 3 connects shared sensing modules with antitumor immunity, immune regulation, and tumor-cell adaptation across distinct cellular compartments by organizing individual ligands according to their receptors, responding cells, and downstream fates.

Indole-3-lactic acid (ILA) enhances $CD8^+$ T-cell activation and proliferation through complementary epigenetic and metabolic mechanisms. ILA produced by *Lactiplantibacillus plantarum* enhances H3K27 acetylation at the IL12A enhancer in DCs and suppresses SAA3-associated cholesterol accumulation in $CD8^+$ T cells, thereby promoting $CD8^+$ T-cell activation and proliferation[82]. These results demonstrate how a single metabolite can act indirectly through DCs and directly through metabolic regulation in $CD8^+$ T cells.

B-cell function is regulated by a distinct PXR–toll-like receptor 4 (TLR4)–IL-35 circuit involving indole-3-acetic acid (IAA). In the presence of lipopolysaccharide (LPS), IAA predominantly promotes the generation of $IL\text{-}35^+$ B cells through PXR- and TLR4-dependent signaling. IL-35 subsequently promotes further expansion of $IL\text{-}35^+$ B cells through STAT3 phosphorylation, thereby establishing a positive-feedback loop[83,84]. $IL\text{-}35^+$ B cells can also modify intestinal microbial composition and Trp-metabolite profiles and increase IAA abundance, indicating bidirectional crosstalk between IAA, regulatory B-cell programs, and the intestinal microbiota.

Another key interface through which Trp-derived metabolites influence tumor immunity is AhR. Microbiota-derived indoles, particularly IAA and ILA, can activate AhR-dependent programs in

TAMs, promote immunosuppressive macrophage phenotypes, and restrict intratumoral CD8⁺ T-cell activity[85]. In contrast, indole-3-aldehyde (I3A) produced by intratumoral *Limosilactobacillus reuteri* can activate AhR in CD8⁺ T cells, increase IFN-γ and granzyme B production, and enhance antitumor immunity in melanoma-related contexts[86]. Importantly, these findings suggest that distinct Trp-derived AhR ligands can elicit divergent immune outcomes according to the dominant responding cell compartment.

IPA primarily regulates CD8⁺ T-cell persistence through epigenetic remodeling. IPA enhances H3K27 acetylation at the TCF7 super-enhancer and maintains the stem-like features of progenitor-exhausted CD8⁺ T cells, thereby sustaining antitumor activity during immune-checkpoint therapy[11]. This mechanism is distinct from the macrophage-associated immunosuppressive AhR programs induced by other Trp metabolites and further demonstrates that membership within the same metabolite family does not confer a conserved functional outcome.

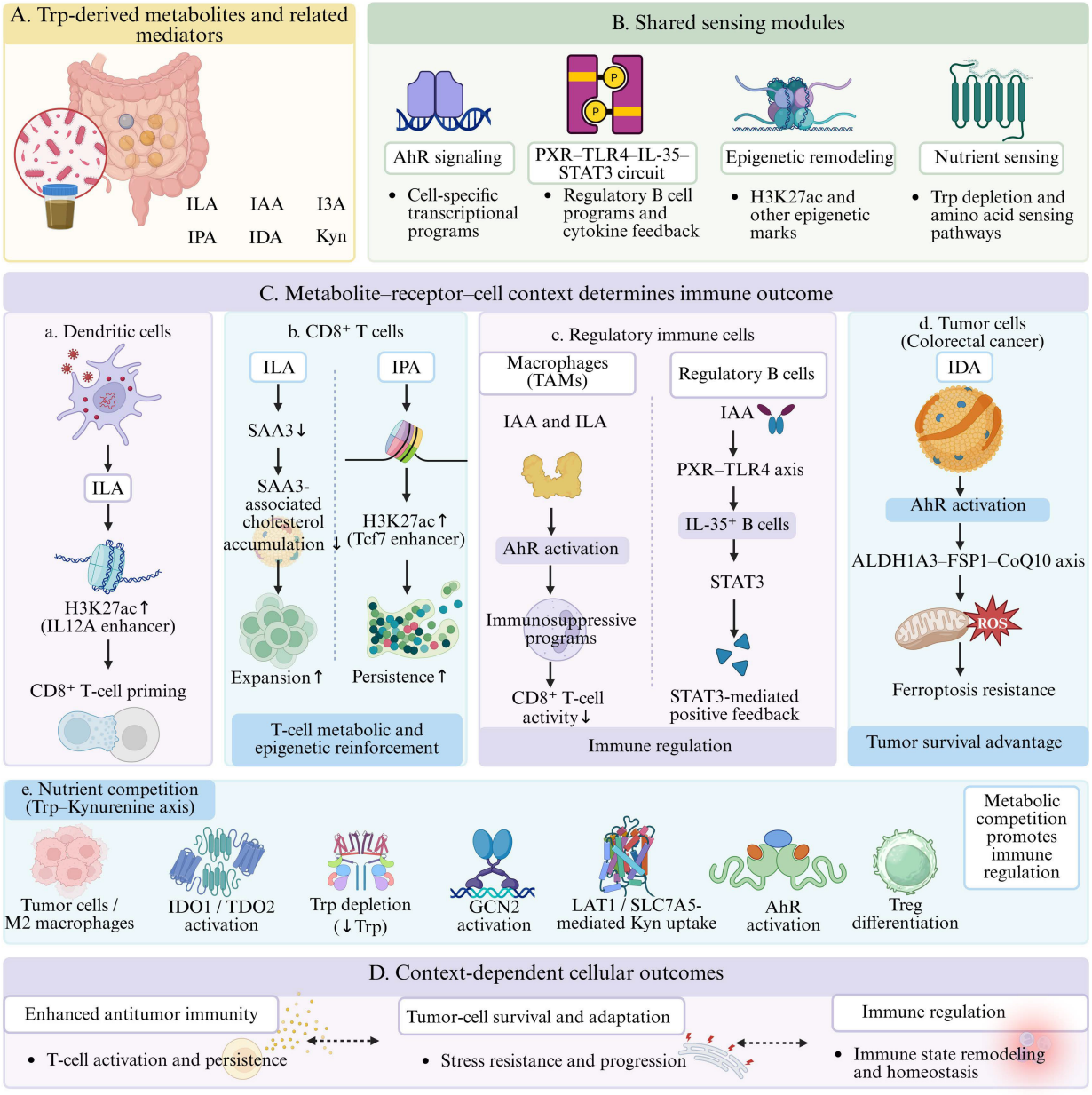

Figure 3. Trp-derived metabolites and related mediators drive cell-specific immune and tumor outcomes through shared sensing and nutrient-competition pathways: (A) Selected Trp-derived metabolites and related mediators include ILA, IAA, I3A, IPA, IDA, and Kyn. (B) These metabolites operate through recurrent regulatory circuits involving AhR signaling, the PXR–TLR4–IL-35–STAT3 circuit, epigenetic reprogramming, and amino-acid sensing. (C) Their functional effects are conditioned by specific metabolite–receptor–cell combinations. ILA increases H3K27 acetylation at the IL12A enhancer in DCs and reduces SAA3-associated cholesterol accumulation in CD8⁺ T cells, enhancing T-cell priming and expansion. IPA increases H3K27 acetylation at the TCF7 super-enhancer to sustain CD8⁺ T-cell persistence. IAA and ILA promote immunosuppressive AhR programs in TAMs, while I3A activates AhR-dependent effector programs in CD8⁺ T cells. In regulatory B cells, IAA induces IL-35⁺ B-cell generation through PXR and TLR4 signaling, followed by STAT3-mediated positive feedback. One experimental study indicated that IDA activates the AhR–ALDH1A3–FSP1–CoQ10 axis, inhibits lipid peroxidation in CRC cells, and increases ferroptosis resistance. Trp depletion and Kyn accumulation, in turn, promote GCN2-dependent LAT1/SLC7A5-mediated Kyn uptake, AhR activation, and Treg differentiation. (D) These cell-selective pathways may ultimately contribute to enhanced antitumor immunity, immune regulation and homeostasis, or tumor-cell survival and adaptation.

For example, trans-3-indoleacrylic acid (IDA) is a Trp-derived metabolite that can act directly on tumor cells. A recent experimental study found that IDA produced by *Peptostreptococcus anaerobius* activates the AhR–aldehyde dehydrogenase 1 family member A3 (ALDH1A3)–ferroptosis suppressor protein 1 (FSP1)–coenzyme Q10 (CoQ10) pathway and increases ferroptosis resistance in CRC cells. Current evidence therefore identifies this axis as an emerging tumor-cell-intrinsic mechanism in CRC[87]. In this setting, AhR activation supports tumor-cell survival, in contrast to the immune-cell differentiation programs mediated by AhR in other cellular compartments.

The Trp–Kyn axis provides another link between microbial and host metabolism, nutrient sensing, and immune-cell competition. Tumor cells expressing indoleamine 2,3-dioxygenase 1 (IDO1) or tryptophan 2,3-dioxygenase 2 (TDO2), as well as TDO2-expressing M2 macrophages, increase Trp catabolism and Kyn production, thereby elevating the extracellular Kyn/Trp ratio[33]. Trp depletion increases AhR expression and induces GCN2-dependent L-type amino acid transporter 1 (LAT1)/solute carrier family 7 member 5 (SLC7A5)-mediated Kyn uptake, thereby enhancing Kyn-driven AhR activation and promoting Treg differentiation[88]. This mechanism highlights that metabolite signaling depends not only on ligand abundance but also on nutrient depletion, transporter adaptation, and receptor sensitivity.

Collectively, Trp-derived metabolites converge on AhR, PXR, STAT3, epigenetic machinery, and nutrient-sensing pathways but elicit divergent outcomes across cellular compartments. Consequently, the relevant mechanistic distinction is not simply between different Trp metabolites but between specific metabolite–receptor–cell combinations[85, 86].

3.3 BAs: FXR, G protein-coupled bile acid receptor 1 (TGR5), retinoic acid-related orphan receptor γt (RORγt), and calcium-dependent signaling

Primary and secondary BAs regulate tumor immunity through nuclear-receptor signaling, cell-surface receptor pathways, transcription-factor activation, and cell-intrinsic antigen-presentation programs[89, 90]. Their effects are dictated by bile-acid composition, receptor localization, intracellular access, ligand potency, and the responding immune or tumor-cell population. The mechanistic framework presented in Figure 4 integrates bile-acid composition and receptor context with cell-specific signaling through FXR, TGR5, RORγt, and the plasma membrane Ca^{2+} ATPase (PMCA)–nuclear factor of activated T cells 2 (NFATC2) axis, thereby explaining divergent immune and tumor responses.

Secondary and iso-BAs regulate $CD4^+$ T-cell differentiation through distinct transcriptional mechanisms. Isolithocholic acid (isoLCA) suppresses Th17 differentiation through direct interaction with RORγt, whereas isoallolithocholic acid (isoalloLCA) promotes Treg differentiation by inducing mitochondrial reactive oxygen species and enhancing forkhead box protein P3 (FOXP3)-associated epigenetic regulation[91-94]. Thus, changes in local 3-oxoLCA, isoLCA, and isoalloLCA concentrations may alter the Treg‑Th17 balance and intestinal immune homeostasis.

DCA enhances PMCA-mediated Ca^{2+} efflux, suppresses NFATC2 activation, and impairs $CD8^+$ T-cell effector function[22]. This pathway impairs $CD8^+$ T-cell cytotoxicity and may contribute to T-cell dysfunction or exhaustion in CRC-related settings.

BAs also exert effects on macrophages and DCs. In CRC models, DCA promotes M2-like TAM polarization and remodels Wnt/β-catenin and nuclear factor kappa B (NF-κB) signaling[95]. In other settings, FXR-associated bile-acid signaling has been linked to myeloid-derived suppressor-cell expansion and M2 macrophage polarization. Secondary BAs regulate dendritic-cell maturation through TGR5–cyclic adenosine monophosphate (cAMP)–protein kinase A (PKA) signaling, thereby reducing pro-inflammatory cytokine production and altering T-cell differentiation[96]. These apparently divergent findings demonstrate that bile-acid effects on myeloid cells depend strongly on receptor expression, cellular state, and tissue context.

Bile-acid sensing through FXR regulates intestinal immune programs, whereas altered bile-acid synthesis can directly constrain tumor-specific T-cell responses in liver cancer[97, 98]. In other words, bile-acid sensing is not determined solely by the presence of ligands. For intracellular FXR signaling, transporter-dependent ligand access, bile-acid composition, relative ligand potency, and the endogenous ligand pool jointly shape the magnitude and threshold of receptor activation. At appropriate intracellular bile-acid concentrations, weak or modulatory BAs, such as ursodeoxycholic acid (UDCA) and selected iso-BAs, can cooperate with endogenous ligands[99]. In contrast, TGR5 is located on the cell surface and can respond without the same requirement for intracellular ligand accumulation. Thus, receptor localization can direct the same bile-acid pool toward different signaling outcomes in different cell types.

Collectively, these results define FXR, TGR5, RORγt, and PMCA–NFATC2 signaling as recurrent bile-acid-responsive interfaces. Their biological effects

vary according to BA identity, receptor context, and the responding cellular compartment.

3.4 Other microbial metabolites and microbiota-associated host mediators: inflammatory, stress-response, and stromal signaling

In addition to SCFAs, Trp-derived metabolites, and BAs, other microbial metabolites and microbiota-dependent host co-metabolites modulate tumor immunity through innate immune activation, cellular stress signaling, mitochondrial adaptation, and intercellular communication[21, 32, 49]. TMAO is a microbiota-dependent host co-metabolite, while succinate can be produced by both microbes and host cells. In gastric cancer, succinate produced by *Streptococcus anginosus* provides an example of a microbe-derived metabolite that promotes tumor progression through succinate receptor 1 (SUCNR1)–abraxas 1, BRCA1 A complex subunit (ABRAXAS1) signaling[37]. Lactate and PGE2 are primarily host-derived mediators produced by tumor and stromal cells under local metabolic and inflammatory conditions. These examples illustrate distinct routes involving myeloid-cell activation, dendritic-cell reprogramming, stromal–immune communication, and tumor-cell-mediated immune exclusion.

TMAO has context-dependent effects across tumors. It promotes proliferation and angiogenesis in CRC, but enhances macrophage-associated type I interferon signaling or tumor-cell stress responses and improves antitumor immunity in pancreatic and triple-negative breast cancer (TNBC) models[32, 100, 101]. In selected tumor contexts, TMAO activates protein kinase R-like endoplasmic reticulum kinase (PERK)-dependent endoplasmic-reticulum stress, promotes tumor-cell pyroptosis, and increases $CD8^+$ T-cell infiltration. These divergent effects suggest that the functional direction of TMAO depends on the dominant responding compartment and cancer context.

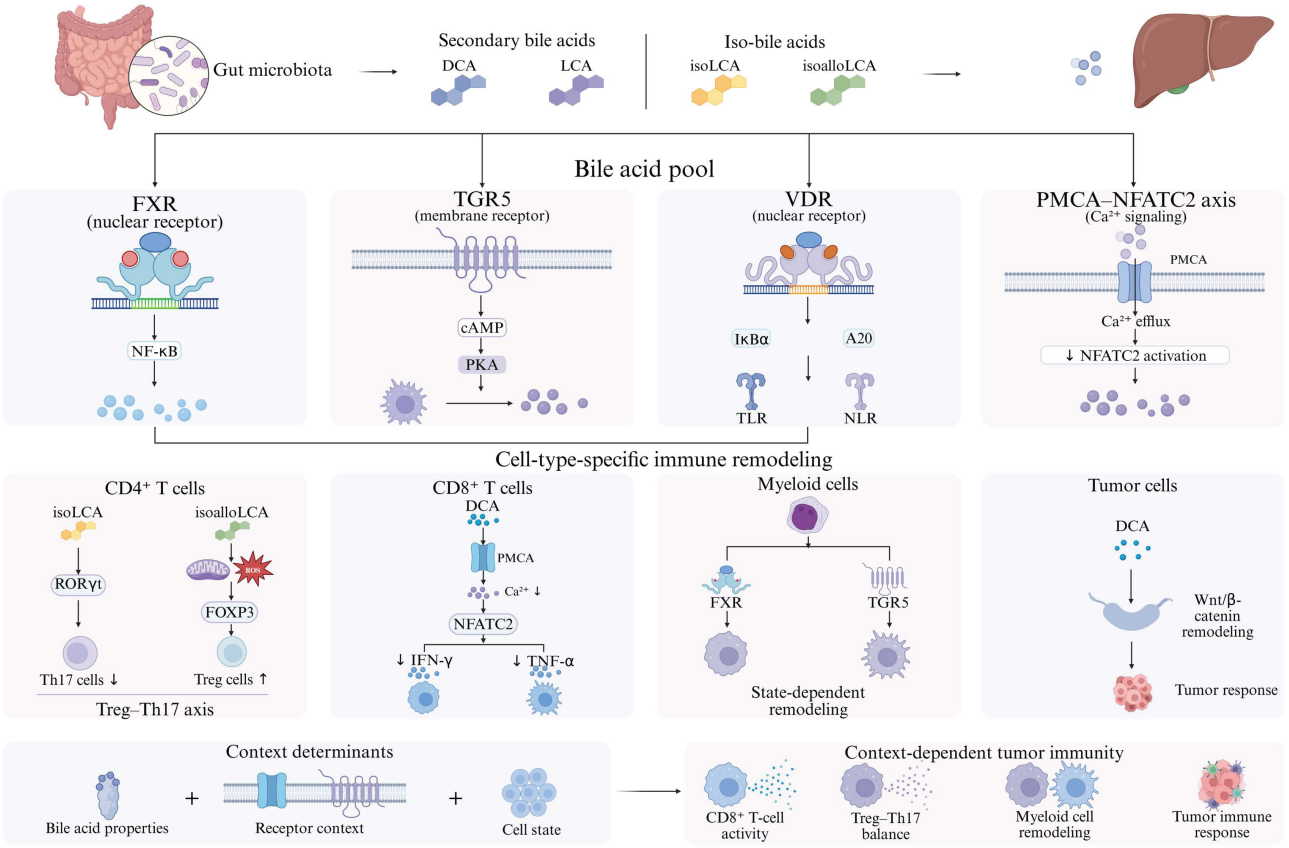

Figure 4. BAs drive context-dependent immune remodeling through receptor-selective and calcium-dependent signaling: Gut microbiota-derived secondary BAs and iso-BAs like DCA, LCA, isoLCA, and isoalloLCA remodel the bile-acid pool and interact with different signaling interfaces. Transcriptional, inflammatory, and calcium-dependent programs are regulated in a receptor- and cell-type-specific manner by FXR, TGR5, VDR, and the PMCA–NFATC2 axis. FXR- and TGR5-associated signaling drives state-specific remodeling of macrophages and other myeloid cells, while the TGR5–cAMP–PKA pathway modulates dendritic-cell maturation and inflammatory cytokine production. isoLCA directly inhibits RORγt-dependent Th17 differentiation in $CD4^+$ T cells, whereas isoalloLCA promotes mitochondrial reactive oxygen species production and FOXP3-associated Treg differentiation. DCA enhances PMCA-mediated Ca^{2+} efflux in $CD8^+$ T cells while suppressing NFATC2 activation and reducing IFN-γ and TNF-α production. These responses are shaped by bile-acid composition and potency, receptor localization, transporter-dependent intracellular availability, cellular state, and tissue context.

Lactate mainly functions through metabolic adaptation and transcriptional reprogramming. In the TME, tumor-derived lactate activates SREBP2-dependent metabolic programs in DCs, promotes their differentiation toward mature regulatory DCs, restricts antigen cross-presentation, and facilitates Treg differentiation and tumor progression. Lactate can also impair dendritic-cell migration, maturation, and antigen presentation and promote a tolerogenic phenotype in the TME[34, 35]. These findings indicate that lactate-mediated immune suppression involves mitochondrial and transcriptional reprogramming in addition to extracellular acidification.

PGE2 acts as a receptor-dependent immunosuppressive mediator linking stromal and senescence-associated programs to impaired antitumor immunity. Within the liver TME, PGE2 released from senescent hepatic stellate cells (HSCs) binds to prostaglandin E receptor 4 (EP4) on $CD8^+$ T cells, suppresses their proliferation, and reduces IFN-γ production[36]. This mechanism demonstrates how a metabolite or lipid mediator generated by one cellular compartment can determine the functional state of effector lymphocytes in another compartment.

In gastric cancer, succinate derived from *Streptococcus anginosus* activates the SUCNR1–ABRAXAS1 axis in tumor cells and promotes tumor progression. This mechanism is primarily tumor-cell intrinsic, whereas its direct effects on antitumor immune-cell recruitment or function remain to be established. Other microbial metabolites may contribute through less fully characterized pathways. In CRC cell models, exposure to a *Candida albicans*-derived metabolite mixture reduced cell viability, migration, and invasion while increasing extracellular ATP, lipid peroxidation, and apoptosis, although the active metabolites and direct immune-cell effects remain undefined[102]. Phenylacetylglutamine (PAGln) has been associated with $CD8^+$ T-cell exhaustion and reduced intratumoral T-cell infiltration[23]. Current evidence positions PAGln-associated regulation as an emerging mechanism requiring direct causal validation across tumor models.

Taken together, TMAO, lactate, PGE2, and succinate illustrate four complementary regulatory routes involving inflammatory sensing, cellular stress responses, metabolic reprogramming, and intercellular signaling. Their ultimate effects are determined by whether the dominant responding compartment consists of macrophages, DCs, stromal cells, effector T cells, or tumor cells. Less extensively characterized microbial metabolites may provide additional layers of regulation but are currently supported by weaker direct evidence in tumor immunity[103].

3.5 Context filters: metabolite access, sensor selection, intracellular fate, and human quantitative evidence

3.5.1 Sequential context filters

One key consideration is that the biological effect of a microbiota-associated metabolite is not determined solely by the downstream pathway that it may activate but is also influenced by cellular access, sensor availability, intracellular metabolic fate, and the identity of the responding cell[50, 51, 80]. Before pathway engagement, a metabolite must reach a defined anatomical compartment, encounter a transporter or receptor expressed at a sufficient level, and either persist intracellularly or escape rapid catabolism. Thus, metabolite signaling can be understood through four sequential mechanistic gates: spatial availability, cellular access, sensor engagement, and intracellular metabolic fate. Figure 5 models how sequential context filters shape the dominant responding compartment and ultimately determine cell-state-dependent outcomes of microbiota-associated metabolite signaling in the TME.

Metabolite exposure across distinct tissue and anatomical compartments, such as the intestinal lumen, portal circulation, mesenteric lymph, systemic blood, and target organs, is shaped by spatial availability[104, 105]. Intestinal tumors are directly exposed to high concentrations of gut-derived metabolites, while liver tumors receive portal blood enriched in microbial products. In contrast, lung, breast, and other extraintestinal tumors may depend more heavily on systemic circulation or local intratumoral microbial production[106]. These anatomical differences can determine whether epithelial cells, tumor cells, stromal cells, or infiltrating immune cells receive the dominant metabolite exposure. This distinction is all the more critical when interpreting human metabolomic associations, where fecal or circulating abundance is only an indirect measure of effective exposure, which ultimately depends on tissue distribution, cellular uptake, and intracellular availability.

Transporter abundance and membrane permeability determine cellular access. Butyrate can signal extracellularly through GPR41, G protein-coupled receptor 43 (GPR43), and GPR109A or enter cells through solute carrier family 5 member 8 (SLC5A8)/sodium-coupled monocarboxylate transporter 1 (SMCT1) and solute carrier family 16 member 1 (SLC16A1)/monocarboxylate transporter 1 (MCT1) to inhibit intracellular HDACs. Moreover, reduced SMCT1 expression is associated with butyrate

resistance in 5-fluorouracil-resistant CRC cells, whereas restoration of functional SMCT1 can reinstate butyrate-induced antiproliferative effects[107]. DCA, chenodeoxycholic acid (CDCA), tumor necrosis factor alpha (TNF-α), and IFN-γ can also reduce MCT1-mediated butyrate uptake and interfere with its intracellular activity[108]. As a result, equal extracellular concentrations do not necessarily produce equivalent intracellular exposure. Transient pharmacodynamic peaks after exogenous supplementation should be differentiated from steady-state physiological metabolite concentrations [109]. When transport activity approaches saturation at higher concentrations, additional increases in extracellular concentration may not result in proportional increases in intracellular exposure[110], such as may occur with butyrate uptake via MCT1[108] and Kyn uptake via LAT1[111].

Sensor engagement is determined by sensor localization and abundance, ligand affinity and potency, and competition among coexisting ligands[112]. Bile-acid signaling through TGR5, which is located at the cell surface, and FXR, which is intracellular, therefore involves different access requirements. Similarly, AhR activation depends on receptor abundance, ligand affinity, and intracellular ligand uptake. As described in Section 3.2, Trp depletion increases AhR abundance and LAT1/SLC7A5-mediated Kyn uptake, thereby lowering the threshold for AhR activation.

The intracellular metabolic fate of an internalized metabolite determines whether it acts as a signaling ligand, epigenetic regulator, or metabolic substrate. After entering a cell, butyrate may be oxidized as a metabolic substrate, thereby reducing the intracellular pool available for HDAC inhibition, or remain available at sufficient concentrations to inhibit HDACs[113]. A non-tumor metabolic study further showed that butyrate oxidation can attenuate a butyrate-responsive phenotype[114], providing a mechanistic precedent rather than direct evidence from tumor or immune cells. The balance between these fates is likely to vary according to the oxidative and metabolic capacity of the responding cell. However, this substrate-versus-epigenetic partitioning has not been directly examined across matched tumor and immune-cell populations.

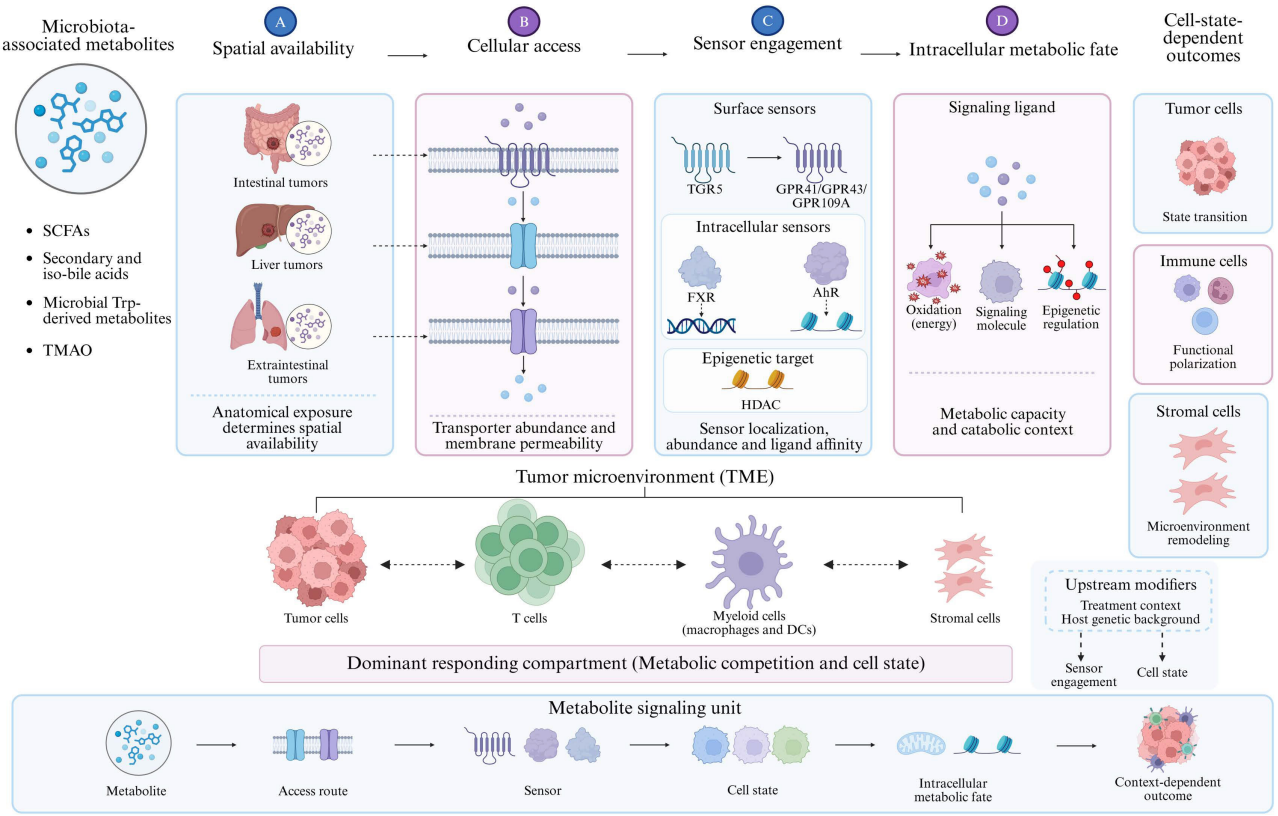

Figure 5. Sequential context filters determine the dominant responding compartment and cell-state-dependent outcomes of microbiota-associated metabolite signaling in the TME: Microbiota-connected metabolites, including SCFAs, secondary and iso-BAs, microbial Trp-derived metabolites, and TMAO, are processed through four consecutive but mechanistically distinct context filters. (A) Spatial presence determines whether metabolites arrive at intestinal, hepatic, or extraintestinal tumor compartments and thereby identifies the cellular populations potentially exposed to an effective concentration. (B) Cellular access depends on membrane permeability, transporter abundance, and accessibility to cell-surface sensing routes. (C) Sensor engagement is a function of sensor localization and abundance, ligand affinity and potency, and intracellular ligand availability. Representative surface sensors include TGR5 and GPR41/GPR43/GPR109A, whereas FXR and AhR are intracellular sensing systems with distinct access requirements; HDACs represent an additional intracellular epigenetic target. (D) The fate of internalized metabolites is determined by intracellular metabolic and catabolic capacity and dictates whether they will be oxidized as energy substrates, retained as signaling ligands, or routed toward

epigenetic regulation. In the TME, metabolic competition and exchange between tumor cells, T cells, myeloid cells, and stromal cells define the dominant responding compartment. Sensor engagement and cell state can be modified upstream by treatment and disease context and host genetic background. These sequential filters produce cell-state-dependent outcomes, including transitions of tumor-cell states, functional polarization of immune cells, and remodeling of stroma or the microenvironment. As such, the signaling unit defined by a metabolite is not a metabolite–pathway pair but rather an ensemble comprising a given combination of metabolite, access route, sensor, cell state, and intracellular metabolic fate.

The local availability and metabolic fate of nutrients, metabolites, and their precursors are further reshaped through metabolic competition and exchange among tumor cells, effector lymphocytes, myeloid cells, and stromal cells[115, 116]. While tumor cells expressing IDO1 or TDO2 can consume Trp and increase Kyn production, immune cells must adapt through transporter expression and nutrient-sensing pathways[33, 88]. Therefore, differences in substrate uptake and catabolism can determine which cellular compartment dominates the response, even when all cells occupy the same TME[115, 116]. Local oxygen tension, pH, substrate availability, inflammatory cytokines, and immune-cell composition can further modify metabolite production, degradation, cellular handling, and downstream signaling[117].

With regard to microbiota-derived metabolites, the specific signals and cellular processes they modulate are dictated not only by the metabolites themselves, but also by cell differentiation states and pre-existing epigenetic landscapes[118, 119]. Downstream, transcriptional competence is plastic and influenced by factors such as macrophage polarization, T-cell differentiation, tumor genotype, oxidative-stress status, receptor expression, and prior therapeutic exposure. In turn, this means that the same metabolite-responsive receptor can be expressed by multiple cell populations but can induce different transcriptional and functional responses in each population. Ideally, cell specificity would be defined in terms of measurable differences in metabolite uptake, receptor occupancy, intracellular concentration, and metabolic fate rather than solely through observed phenotypic differences[120].

Together, these findings support context-dependent selection among functionally non-equivalent cellular and molecular routes, with specific routes becoming dominant in particular tumor contexts[22, 121, 122]. The resulting biological effect therefore depends on which anatomically accessible cell population achieves effective target engagement and how the metabolite is processed intracellularly.

However, much of this framework is largely inferred by integrating complementary experimental models rather than by directly comparing metabolite uptake, receptor occupancy, intracellular concentration, and metabolic fate across matched tumor and immune-cell populations within the same TME[82, 85, 86]. Future studies should thus combine isotope tracing, spatial metabolomics, single-cell profiling, and cell-specific transporter or receptor perturbation to identify the dominant responding compartment for each metabolite. To complement the metabolite-centered organization of this section, Table S2 offers a cell-centered cross-reference of the immune populations influenced by microbiota-associated metabolites, together with the corresponding metabolites, regulatory mechanisms, experimental models, concentration ranges, and evidence levels.

3.5.2 Human spatial and cell-resolved evidence for quantitative context filters

Comparison between whole-tissue metabolite data and average metabolite concentrations from single-cell-resolved data reveals that metabolite exposure is heterogeneous across tumor compartments[123, 124]. Some additional quantitative evidence comes from human spatial and cell-resolved metabolomic studies. A single-cell spatial metabolomics framework integrating untargeted metabolite imaging with multiplexed protein profiling was used to quantify 19,507 individual cells and resolve their respective distributions of metabolites across tumor cells, T cells, $CD68^+$ myeloid cells, and $CD31^+$ vascular compartments in human lung cancer[123]. Radial gradients of normalized distance values and 20 spatial bins were used to characterize metabolite gradients as a function of distance from $CD31^+$ endothelial cells; local metabolite competition was assessed as the ratio of metabolite abundance in an individual cell to that of its neighboring cells. The mass channels associated with several metabolites showed opposite spatial distributions between tumor and immune cells, demonstrating that tissue-level metabolite abundance does not necessarily reflect the exposure experienced by individual cellular compartments.

This parallel example is then placed in the context of spatially resolved metabolite–immune coupling in human hepatocellular carcinoma (HCC)[125, 126]. Whereas spatial multi-omics revealed significant enrichment of lactate and long-chain polyunsaturated fatty acids defining the tumor–immune–cancer-associated fibroblast interface, single-cell mass-spectrometry imaging and functional coculture experiments showed increased glycolytic activity and lactate production in cancer-associated fibroblasts together with increased CD163-associated M2 macrophage polarization[125]. These findings link a compartment-enriched metabolite signal to a defined

immune phenotype. Because lactate is predominantly host- or tumor-derived, this finding serves as a human proof of principle for the context-filter framework rather than as evidence for a microbiota-derived lactate pathway[127, 128].

Importantly, the human spatial-metabolomic datasets currently available still offer much more insight into relative spatial gradients than absolute intracellular exposure. However, few studies have compared measurements of core microbiota-associated metabolites, including SCFAs, microbial Trp derivatives, secondary BAs, and TMAO, across fecal, circulating, tumor-tissue, and single-cell compartments[32, 129-131]. Thus, current human evidence supports quantitative spatial heterogeneity and cell-specific metabolite partitioning but does not yet provide complete absolute validation of the proposed context-filter sequence. To surmount this limitation, spatial metabolomics should be combined with stable-isotope tracing, absolute targeted quantification, and cell-resolved measurements of receptors or transporters in prospectively collected human tumors[132-135]. For quantitative context regarding these exposure differences, Table S3 summarizes the reported physiological and pathological concentration ranges of core microbiota-associated metabolites, including SCFAs, Trp-derived metabolites, BAs, and TMAO, across fecal, circulating, tissue, and other available biological compartments.

4. Cancer-specific examples and cross-cancer contextual divergence of microbiota-associated metabolite signaling

Although the molecular mechanisms presented in Section 3 recur across multiple cancer types, their final biological effects are modified by anatomical exposure, cellular access, sensor expression, intracellular metabolic fate, and the dominant responding cell compartment. Hence, this section does not recap the complete signaling pathways for each cancer type. Instead, representative cancers are used to demonstrate how common metabolite-responsive modules are routed toward cancer-specific immune activation, immune suppression, or tumor-cell adaptation. Representative cancers are selected to capture their distinct features in terms of metabolite-exposure architectures, including direct intestinal or portal exposure, distal systemic exposure, local–systemic interfaces, and hematological immune-cell exposure[101, 105, 136, 137]. These non-metabolite microbial components are noted only in cases where they modify or contextualize defined metabolite-associated pathways and are not treated as direct evidence of metabolite-mediated regulation[138, 139]. A cancer-centered summary of selected representative metabolites, associated immunoregulatory mechanisms, treatment-associated effects, and evidence levels is provided in Table S4.

4.1 Digestive system cancers as representative direct-exposure contexts

4.1.1 CRC

CRC provides a model of direct and prolonged local exposure to gut-derived metabolites. But distinct metabolite pools and concentrations might be encountered by epithelial, tumor, and immune compartments. As observed for acetate signaling through MCT4 in $CD8^+$ T cells and through GPR43 in CRC cells, the functional output therefore depends on spatial access as well as cell-specific sensing mechanisms[140]. Figure 6 connects anatomical delivery routes and dominant responding cell compartments to immune activation, immune suppression, and tumor-cell adaptation across cancer types by comparing direct-exposure, distal-exposure, and local–systemic interface settings.

Butyrate engages GPCR-, HDAC-, and metabolism-dependent pathways, as described in Section 3.1. In CRC, cellular access initially shapes the tumor-cell response to butyrate. Restoration of functional SLC5A8/SMCT1 increases the sensitivity of 5-fluorouracil-resistant CRC cells to the antiproliferative effects of butyrate, whereas BAs and pro-inflammatory cytokines reduce SLC16A1/MCT1-mediated butyrate uptake and attenuate its intracellular activity[107, 108]. In experimental CRC models, butyrate can suppress tumor growth and enhance immune clearance by activating cytotoxic $CD8^+$ T cells or reducing STAT1-dependent PD-L1 expression in tumor cells[141, 142]. Sodium butyrate has additionally been shown to enhance the antitumor efficacy of 5-fluorouracil through PINK1/Parkin-associated mitochondrial regulation and intestinal-microbiota remodeling[143]. However, a recent study reported that butyrate can activate CPT1A-mediated fatty-acid oxidation in CRC cells, reduce $CD8^+$ T-cell cytotoxicity, and promote resistance to anti-programmed cell death protein 1 (PD-1) therapy[144]. These apparently divergent findings indicate that the functional effect of butyrate in CRC depends on transporter expression, the dominant responding cell compartment, tumor-cell metabolic state, metabolite concentration, and treatment context.

An alternative tumor-cell-intrinsic example is IDA produced by Peptostreptococcus anaerobius. One experimental study suggested that IDA promotes CRC-cell ferroptosis resistance via an AhR–

ALDH1A3–FSP1–CoQ10-associated mechanism[87]. So far, this mechanism is mainly backed by the original experimental research and subsequent investigations building on that particular model; however, independent validation in primary human CRC organoids and prospective patient cohorts remains limited. In this sense, the IDA–AhR–ALDH1A3–FSP1–CoQ10 axis should be regarded as an emerging candidate mechanism rather than an established general feature of human CRC. In parallel, 4-hydroxyphenylacetic acid recruits PMN-MDSCs through GROγ-associated signaling and thereby suppresses CD8⁺ T-cell activity[145, 146]. As described in Section 3.4, succinate produced by *Fusobacterium nucleatum* can additionally suppress cyclic GMP-AMP synthase (cGAS)–stimulator of interferon genes (STING)-dependent chemokine production in CRC cells, thereby limiting CD8⁺ T-cell recruitment and promoting resistance to immunotherapy[21]. Colibactin-producing *Escherichia coli* can also establish an immunosuppressive, lipid-overloaded TME that facilitates CRC progression and chemoresistance[147]. Collectively, these findings suggest that CRC-associated microbial products can promote tumor progression through suppressive myeloid-cell recruitment, tumor-cell resistance to regulated cell death, or metabolic remodeling of the immune microenvironment[148].

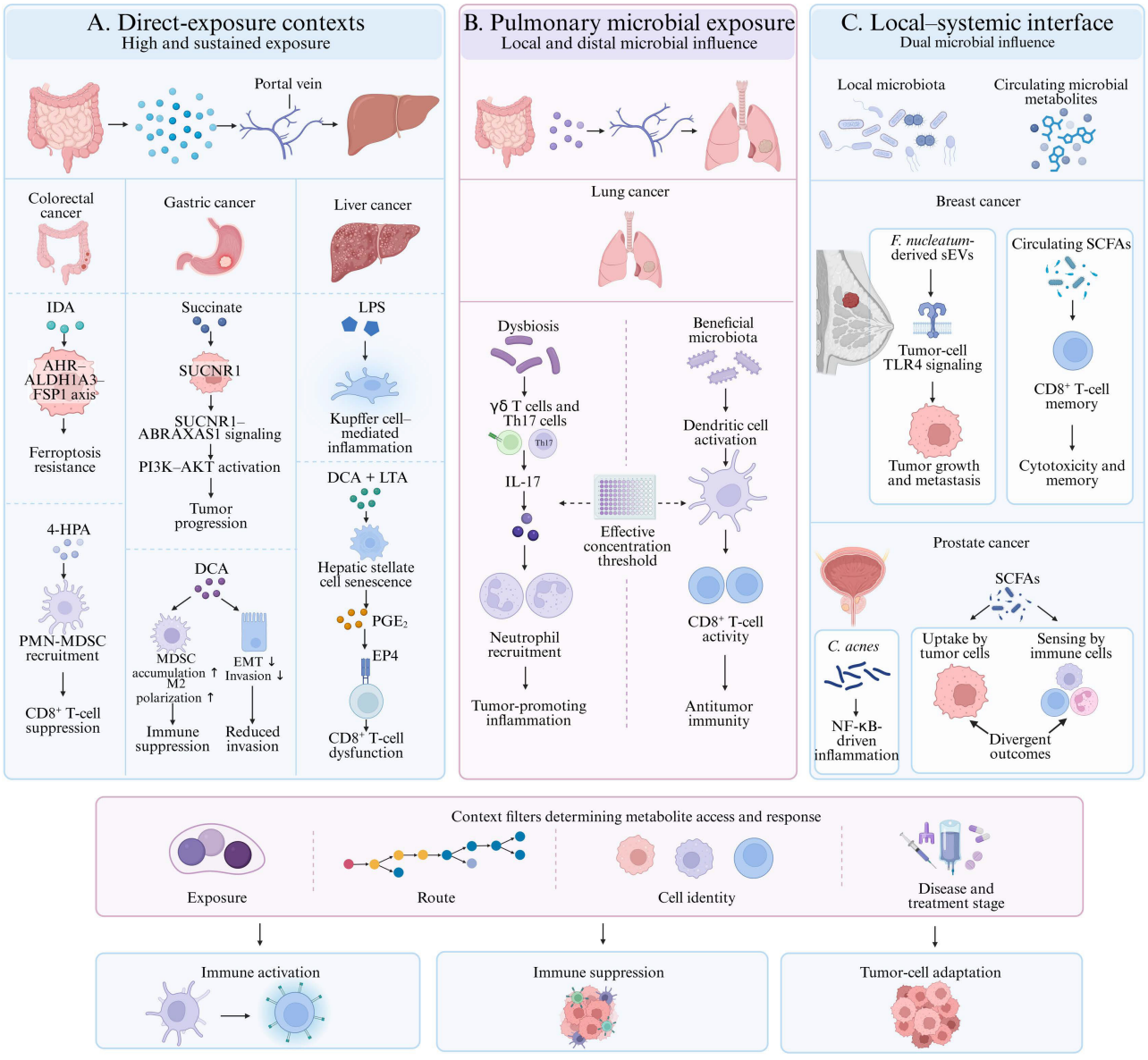

Figure 6. Anatomical exposure routes and cell-specific responses shape microbiota–metabolite effects across cancers: (A) Colorectal, gastric, and liver cancers are examples of direct-exposure settings where microbial metabolites and products enter tumor-associated compartments through continuous local exposure or the portal circulation. A single study in CRC indicated that IDA activates the AhR–ALDH1A3–FSP1–CoQ10 axis and induces resistance to ferroptosis, while 4-hydroxyphenylacetic acid recruits polymorphonuclear MDSCs and inhibits CD8⁺ T-cell activity. In gastric cancer, succinate activates the SUCNR1–ABRAXAS1 axis in tumor cells, and bile-acid-associated pathways may lead to different tumor-cell-intrinsic and myeloid-cell-mediated outcomes. In liver cancer, microbe-derived LPS stimulates Kupffer-cell-associated inflammation,

while DCA and lipoteichoic acid promote hepatic stellate-cell senescence and PGE2–EP2/EP4 signaling, suppressing $CD8^+$ T-cell function. (B) Lung cancer is an example of a distal-exposure setting where blood-borne gut-derived metabolites and locally derived microbial signals converge in the pulmonary microenvironment. Dysbiotic microbial communities can favor IL-17 production associated with γδ T cells and Th17 cells, together with neutrophil recruitment and tumor-promoting inflammation, whereas beneficial microbiota may support dendritic-cell activation and $CD8^+$ T-cell-mediated antitumor immunity. The outcome is determined by whether the metabolite reaches the relevant pulmonary cell population at a biologically effective concentration. (C) Breast and prostate cancers exemplify local–systemic interfaces. In breast cancer, direct quantitative evidence that circulating SCFAs or other defined microbiota-associated metabolites reach the breast TME at concentrations sufficient to reprogram specific tumor or immune-cell populations remains limited. In prostate cancer, local microbial inflammation and SCFA uptake or sensing can act through tumor-cell and immune-cell routes to induce divergent outcomes. The magnitude of exposure, the route of delivery, the identity of responding cells, and the disease or treatment stage collectively determine whether microbiota-associated signals facilitate immune activation, immune suppression, or tumor-cell adaptation across cancer types.

Accordingly, CRC represents a direct-exposure model in which epithelial uptake, tumor-cell AhR signaling, immune-cell GPCR sensing, and disease-stage-dependent immune tolerance jointly determine the final outcome. The key mechanistic distinction is whether a metabolite acts predominantly on tumor cells, inflammatory cells, regulatory lymphocytes, or effector lymphocytes.

4.1.2 Gastric cancer

For instance, gastric cancer illustrates how pathogen-associated factors and commensal metabolites can converge within the same anatomical niche. *H. pylori* virulence factors, including CagA, VacA, and γ-glutamyl transferase, can impair cytotoxic lymphocyte activity and promote an immunosuppressive microenvironment[149, 150]. Yet, metabolite-centered regulation in gastric cancer is more directly illustrated by butyrate, succinate, Trp-derived metabolites, and secondary BAs. Microbiota-derived butyrate has been reported to inhibit PD-L1 and IL-10 expression in TAMs, suggesting that butyrate can attenuate selected myeloid-cell-associated immunosuppressive programs in gastric cancer[75, 151].

In gastric cancer, *Streptococcus anginosus*-derived succinate activates the SUCNR1–ABRAXAS1 axis in gastric epithelial cells and promotes tumor progression[37]. This represents an indirect immune-regulatory pathway in which the primary metabolite-responsive compartment is the tumor cell rather than the lymphocyte.

In gastric cancer, tumor-derived Kyn hyperactivates Tregs and promotes chemoresistance through the IL-10–STAT3–BCL2 axis[152]. Because this core pathway is shared across cancers, its complete molecular sequence is not repeated here. Its significance in gastric cancer lies in the local combination of microbial Trp metabolism, immune-cell exhaustion, and pathogen-associated inflammatory signaling.

DCA presents a particularly informative example of cellular-compartment-specific divergence. Bile-acid signaling provides an additional pathway through which the gastric microbial environment can influence tumor development. In bile-reflux-associated gastric carcinogenesis, taurodeoxycholic acid and LPS-producing bacteria cooperatively activate IL-6–JAK1–STAT3 signaling[153]. This mechanism illustrates how bile-acid exposure and microbial inflammatory products can converge on a shared tumor-promoting pathway within the gastric niche. Thus, an inhibitory effect on tumor-cell invasion is insufficient to establish a uniformly antitumor effect when myeloid-cell-mediated immunosuppression occurs simultaneously.

Hence, gastric cancer serves as an example in which the same metabolite may elicit opposing tumor-cell-intrinsic and immune-cell-mediated effects. Determining the overall *in vivo* outcome requires direct comparison of metabolite exposure and pathway engagement across tumor cells, myeloid cells, and lymphocytes.

4.1.3 Liver cancer

Liver cancer develops in an organ directly exposed to gut-derived metabolites and microbial products through the portal circulation, where hepatocytes, HSCs, and potentially Kupffer cells may generate distinct cell-type-specific responses[105, 154, 155]. Although this anatomical arrangement increases hepatic exposure, it does not guarantee that all hepatic cell populations receive an equivalent intracellular metabolite dose.

LPS triggers TLR4-dependent inflammatory signaling in Kupffer cells[156]. In obesity-associated HCC models, gut microbiota-derived DCA induces senescence in HSCs[157], whereas lipoteichoic acid acts through Toll-like receptor 2 (TLR2) to further amplify the SASP and trigger GSDMD-mediated release of IL-1β and IL-33 from DCA-induced senescent HSCs[158]. PGE2 in the TME signals through prostaglandin E receptor 2 (EP2) and EP4 on tumor-infiltrating $CD8^+$ T cells, restricts the expansion and effector differentiation of stem-like $TCF1^+$ $CD8^+$ T cells, and consequently promotes tumor immune escape[36]. This pathway demonstrates how microbial signals can first remodel a stromal compartment and subsequently impair effector lymphocytes.

In obesity-associated HCC, DCA and lipoteichoic acid cooperatively remodel macrophage polarization through TGR5–STAT3 and TLR2–NF-κB signaling, respectively[159]. Because these pathways have already been described in Section 3, their importance here lies primarily in their routing through the gut–

liver axis and hepatic cell specialization. Recent single-cell, CyTOF, and spatial analyses identified an immunosuppressive niche enriched in Tregs and cancer-associated fibroblasts in steatotic liver disease-related HCC, with TNFSF14–TNFRSF14-mediated Treg–fibroblast interactions contributing to immunotherapy resistance[160]. However, the relative contributions of individual microbiota-associated metabolites to this hepatic immune state remain unresolved.

Butyrate may exemplify a context-dependent functional reversal in MASLD-HCC. Human metagenomic, metabolomic, and *ex vivo* data from patients with nonalcoholic fatty liver disease (NAFLD)-related HCC, which falls within the disease spectrum now termed MASLD-HCC, linked increased microbial SCFA-producing capacity and elevated butyrate levels to the expansion of total Tregs and IL-10$^+$ effector Tregs and the attenuation of cytotoxic CD8$^+$ T-cell responses[161]. These findings, however, demonstrate an association and a microbiota-induced immunosuppressive phenotype rather than providing direct evidence that a defined intrahepatic butyrate concentration alone is sufficient to cause Treg accumulation. Accordingly, the apparent functional reversal may reflect an interaction between microbial SCFA exposure and the pre-existing steatotic hepatic immune-metabolic state, while the relevant intrahepatic concentration threshold and dominant metabolite-responsive cell population remain unknown.

4.2 Lung cancer as a representative distal-exposure context

4.2.1 Lung cancer

Lung cancer serves as a distal-exposure context in which gut-derived metabolites must travel through systemic circulation to reach airway epithelial cells, tumor cells, and infiltrating immune cells. Of note, SCFAs are present at relatively low levels in the lower respiratory tract, and anatomical separation from the gut may limit the effective concentration reaching individual pulmonary cell populations[162-164]. Consistent with this distal-exposure model, higher circulating butyrate levels have been associated with response to anti-PD-1-based therapy in NSCLC, while experimental analyses indicated that butyrate can enhance T-cell receptor signaling and antitumor cytokine production in cytotoxic CD8$^+$ T cells[165].

Thus, the lung cancer-specific question with respect to central metabolites is whether circulating or locally generated metabolites reach airway epithelial cells, tumor cells, DCs, or effector lymphocytes at biologically effective concentrations. Microbiota composition, fecal SCFAs, and intestinal permeability have been investigated as potential biomarkers of ICI response in NSCLC cohorts; however, these studies remain predominantly associative, and no individual microbiota-associated metabolite has yet been validated as a causal predictor of treatment response[166].

4.3 Breast and prostate cancers as local–systemic interface examples

4.3.1 Breast cancer

Breast cancer illustrates a local–systemic interface in which mammary and gut microbiota may influence the TME through different exposure routes. Microbial communities associated with immune homeostasis are commonly found in healthy mammary tissue, whereas breast tumor tissue can contain microbiota associated with inflammatory cytokine production and MDSC accumulation[167-170].

Direct quantitative evidence demonstrating that circulating SCFAs or other defined microbiota-associated metabolites reach the breast TME at biologically relevant concentrations sufficient to reprogram specific tumor or immune-cell populations remains limited[171-173]. Accordingly, present associations between the breast or gut microbiota and breast-cancer immune phenotypes should not be construed as direct metabolite-dependent regulation unless the responsible metabolite, effective exposure, responding cell population, and downstream pathway are experimentally established.

Thus, the foremost unanswered question is whether local microbial products or circulating metabolites act predominantly on tumor cells, myeloid cells, or effector lymphocytes[81, 174, 175]. Microbiota–metabolite associations in breast cancer vary with anatomical source and target-cell exposure, which differ from those in intestinal tumors.

4.3.2 Prostate cancer

Prostate cancer offers a setting in which defined gut-derived metabolites may influence the tumor-cell and immune-cell compartments. This evidence also supports a link between SCFA exposure and tumor-intrinsic responses that modulate autophagy, NF-κB/MAPK-associated signaling, CCL20 production, and macrophage recruitment, thereby linking metabolite exposure to both tumor-intrinsic and myeloid-cell responses[176-179].

The most important mechanistic difference for prostate cancer is whether SCFAs are taken up by tumor cells and directed toward growth-associated signaling or sensed by immune cells and directed toward inflammatory or suppressive programs[179,

180]. Direct tumor-cell uptake and immune-cell sensing should therefore be evaluated separately before assigning an overall functional direction to SCFAs. Currently, controlled human evidence linking defined intratumoral SCFA exposure to prostate-cancer immune remodeling remains limited.

4.4 Cross-cancer synthesis: shared regulatory modules and context-dependent functional reversals

Melanoma is a clinically informative example where the treatment modality and systemic versus local metabolite exposure are key context filters. Higher concentrations of circulating butyrate and propionate were associated with less favorable treatment outcomes in two patient cohorts receiving cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) blockade, while pooled analysis revealed that lower baseline butyrate and propionate concentrations were associated with longer progression-free survival (PFS)[181]. Mechanistically, it was further demonstrated that butyrate restrained CTLA-4-blockade-induced activation of DCs and T cells. In contrast, in a prospective cohort of patients with solid tumors treated with PD-1 inhibitors, higher fecal butyrate was associated with longer PFS, while the associations observed in plasma differed across individual SCFAs[182]. These conflicting results suggest that the checkpoint target, biological compartment in which exposure occurs, concentration of specific metabolites, and the state of responding immune cells jointly determine the clinical direction of SCFA-associated signals.

An example of a second context filter specific to melanoma is one based on Trp-derived metabolites. Intratumoral I3A can activate AhR-dependent effector programs in $CD8^+$ T cells as well as enhance IFN-γ and granzyme B production, while other Trp-derived AhR ligands can preferentially engage immunosuppressive macrophage programs[86, 183]. Accordingly, melanoma shows that neither AhR activation nor SCFA exposure has a fixed functional direction. Instead, the resulting biological effect depends upon ligand identity, systemic versus intratumoral availability, the dominant AhR-expressing cellular compartment, and the specific checkpoint-blockade setting.

4.4.1 Shared molecular entry points

Collectively, evidence across cancer models argues against a single universal pathway or a fixed pro- or antitumor effect of microbiota-associated metabolites as a class, with the resulting outcome instead determined by metabolite identity, the responding cellular compartment, and the tumor context[37, 48, 184]. Instead, several molecular interfaces recur across tumors, including FXR signaling, AhR signaling, mTOR/GCN2 nutrient sensing, and nuclear factor erythroid 2-related factor 2 (NRF2)-associated ferroptosis control. GPCR signaling, HDAC inhibition, calcium-dependent signaling, and inflammatory stress responses provide additional recurrent entry points. These shared entry points can generate divergent outputs across cancers when routed through the context filters defined in Section 3.5.

Cross-cancer comparison therefore focuses on which cellular compartment dominates each shared molecular module under the relevant tumor context. General TME nutrient-partitioning studies show that tumor and immune-cell populations differ in their metabolic programs and nutrient-uptake capacities, resulting in cell-selective partitioning and competitive pressures when shared nutrients become limiting[185-187]. These studies provide mechanistic precedents for cell-specific metabolic competition but do not directly establish the regulation of tumor immunity by a defined microbial metabolite. Consequently, the dominant biological output of a microbial metabolite may depend partly on the competitive metabolic state of the TME rather than being an intrinsic and fixed property of the metabolite itself.

Within the BA–nuclear receptor module, FXR, TGR5, and vitamin D receptor (VDR) regulate epithelial and immune programs, whereas receptor localization, ligand potency, intracellular access, and the composition of the bile-acid pool determine which route predominates[91-94, 97, 99]. Within the AhR module, microbiota-derived indoles can promote immunosuppressive AhR programs in TAMs, whereas IPA supports the stemness of progenitor-exhausted $CD8^+$ T cells[11, 85]. In the nutrient-sensing module, direct metabolite evidence is provided by the Trp–Kyn axis, in which Trp depletion increases AhR expression and promotes GCN2-dependent LAT1-mediated Kyn uptake[88]. Studies of vitamin B6 competition and cellular nutrient transport provide broader mechanistic precedents for nutrient competition and cell-selective uptake in the TME[188, 189].

Another illustrative example is provided by the ferroptosis-regulatory module. In solid-predominant lung adenocarcinoma, $IL4I1^+$ macrophages and $TDO2^+$ myofibroblasts establish an AhR-dependent immunosuppressive and ferroptosis-resistant niche involving NRF2–GPX4–SLC7A11 signaling[183]. As described in Section 4.1.1, a single experimental study suggested that IDA may promote CRC-cell ferroptosis resistance through the AhR–ALDH1A3–FSP1–CoQ10 axis. These results illustrate potential convergence on

redox and cell-death regulation, although the specific IDA-associated pathway remains preliminary.

4.4.2 Representative functional reversals

Butyrate is the clearest example of context-dependent functional reversal. Butyrate exposure suppresses proliferation and promotes apoptosis in CRC cells[190, 191], whereas in NAFLD-HCC, a butyrate-enriched microbial and metabolic profile has been associated with Treg expansion and attenuated cytotoxic $CD8^+$ T-cell responses[161]. This contrast reflects differences in anatomical delivery, cell-specific access and sensing, the pre-existing hepatic immune-metabolic environment, and treatment context. In contrast, experimental HCC models show that microbiota-derived butyrate can suppress tumor growth by enhancing C-X-C motif chemokine ligand 11 (CXCL11)-dependent NK-cell infiltration[192]. Taken together, these findings suggest that butyrate activity depends on the dominant responding cell compartment and the disease and treatment context.

DCA represents a second representative example of context-dependent functional divergence. In CRC, DCA suppresses $CD8^+$ T-cell effector function through PMCA-mediated Ca^{2+} efflux and NFATC2 inhibition[22], whereas a distinct CRC model demonstrated DCA-associated M2-like TAM polarization[95]. The net effect of DCA therefore emerges from the combined contributions of lymphoid and myeloid pathways. Additional context-dependent reversals have also been reported for lithocholic acid (LCA), UDCA, TMAO, and Trp-derived metabolites. Although LCA has exhibited tumor-promoting activity in CRC and antitumor effects in selected breast cancer models, the biological effects of UDCA depend on dose and disease context. In CRC, TMAO has been linked to vascular endothelial growth factor A (VEGFA)-associated angiogenesis, whereas in TNBC it promotes PERK-dependent, gasdermin E (GSDME)-mediated tumor-cell pyroptosis and enhances $CD8^+$ T-cell-mediated antitumor immunity[100, 101]. In pancreatic cancer, TMAO instead promotes immunostimulatory macrophage programs and effector T-cell responses through type I interferon signaling. Trp-derived metabolites also exert divergent effects through cell-specific AhR and epigenetic programs: IAA- and ILA-associated AhR signaling can support TAM-mediated immunosuppression, whereas IPA supports $CD8^+$ T-cell stemness and I3A enhances $CD8^+$ T-cell effector activity in selected tumor contexts. Collectively, these functional reversals indicate that shared molecular modules do not imply uniform biological outcomes across cancer types. The shared metabolite-responsive modules, responding cellular compartments, representative outcomes, and major contextual determinants across cancers are summarized in Table 1.

Table 1. Shared microbiota-associated metabolite-responsive modules and context-dependent outcomes across cancers

Metabolite class	Representative molecular interface	Principal responding compartment	Direction of effect	Representative outcome	Main contextual determinant	References
SCFAs, particularly butyrate	Context-dependent mTORC1 inhibition and GPR109A–IL-18 signaling, with additional HDAC-associated effects	NK cells, macrophages, hepatocytes and tumor cells	⇅ Context-dependent immune activation or restraint	Enhanced antitumor immunity or suppression of immune-cell activation and effector programs	Concentration and exposure context, cell source, tissue niche and receptor expression	[75, 76, 78]
Trp-derived metabolites	I3A–AhR-dependent $CD8^+$ T-cell activation, IPA–H3K27 acetylation–TCF7 epigenetic regulation, and the emerging IDA–AhR–ALDH1A3–FSP1–CoQ10 ferroptosis-resistance mechanism	$CD8^+$ T cells and tumor cells	⇅ $CD8^+$ T-cell activation or tumor-cell adaptation	Enhanced antitumor $CD8^+$ T-cell immunity or tumor-cell ferroptosis resistance	Metabolite identity, responding cell type, AhR signaling competence and Trp availability	[11, 86, 87]
BAs	DCA–PMCA-mediated Ca^{2+} efflux and NFATC2 suppression, taurochenodeoxycholic acid-induced oxidative stress, LCA-induced endoplasmic reticulum stress, and BAAT-dependent conjugated bile-acid synthesis	$CD8^+$ T cells and BA-producing hepatocytes or liver tumor cells	↓ $CD8^+$ T-cell function; ↔ myeloid-cell polarization	Tumor-specific $CD8^+$ T-cell suppression and improved immunotherapy after bile-acid pathway modulation	Bile-acid species and concentration, tissue niche and efflux-dependent intracellular accumulation	[22, 98]
TMAO	PERK–caspase-3–GSDME-mediated pyroptosis or FXR–FGF15 suppression with Wnt/β-catenin activation	Tumor and intestinal epithelial cells, coupled to $CD8^+$ T-cell-dependent immunity in TNBC	⇅ Protumor angiogenesis or antitumor immunity	$CD8^+$ T-cell-dependent antitumor immunity in TNBC or accelerated intestinal tumorigenesis	Cancer type, tumor-cell signaling competence, exposure context and immune composition	[101, 313]

Note: The complete IDA–AhR–ALDH1A3–FSP1–CoQ10 axis is currently supported by one primary study and is presented as an emerging candidate mechanism requiring independent cross-cancer validation.

Table 2. Comparison of dominant context filters governing microbiota-associated metabolite effects in solid and hematological malignancies

Context filter	Solid tumors	Hematological malignancies	Cross-cancer implication	References
Anatomical exposure and delivery	Metabolite activity is strongly influenced by local tumor delivery and intratumoral availability. In melanoma, intratumoral *Limosilactobacillus reuteri*-derived I3A locally promoted IFN-γ-producing $CD8^+$ T cells and enhanced ICI efficacy.	Systemic circulation and the bone-marrow compartment may assume greater importance. In B-cell lymphoma models, *Akkermansia massiliensis* supplementation increased CAR T-cell accumulation in bone marrow and promoted Trp-derived indole production.	The biologically relevant exposure compartment differs between solid and hematological malignancies; fecal or circulating abundance alone should not be assumed to represent effective target-cell exposure.	[86, 314]
Dominant responding cell compartment	The dominant responding cells vary among tumor types. ILA regulated DC–$CD8^+$ T-cell interactions in CRC, whereas butyrate enhanced CXCL11-dependent NK-cell infiltration in HCC.	Circulating or marrow-associated NK cells and CAR T cells constitute prominent metabolite-responsive populations. SCFAs directly modified NK-cell activity against multiple myeloma cells, while butyrate altered CAR T-cell phenotype and antitumor activity in lymphoma models.	Metabolite function should be assigned to a defined responding cell population rather than generalized across the entire TME or immune system.	[82, 192, 193]
Metabolite concentration and exposure level	Effective local concentration depends on anatomical delivery, cellular uptake, and intratumoral metabolism. Experimental studies of I3A and ILA demonstrate defined local metabolite activity, but absolute cross-compartment thresholds remain incompletely established.	Concentration can reverse immune effects. Micromolar acetate, propionate, and butyrate enhanced NK-92-cell cytotoxicity against MM.1S cells, whereas 1 mM butyrate suppressed mTORC1–S6, c-Myc, cytokine production, and metabolic activity in primary human NK cells.	Concentration should be interpreted together with cell source, biological compartment, activation state, and exposure duration rather than as an isolated determinant.	[76, 82, 86]
Sensor and receptor engagement	In melanoma, the antitumor activity of I3A required $CD8^+$ T-cell-intrinsic AhR signaling, demonstrating that metabolite exposure alone is insufficient without the appropriate receptor context.	In B-cell lymphoma models, the benefit of *A. massiliensis* supplementation required AhR signaling in CAR T cells; however, AhR-agonistic indoles alone did not fully reproduce the bacterial effect.	Sensor availability and pathway dependence should be experimentally demonstrated before assigning causal metabolite-specific activity.	[86, 314]
Intracellular metabolic and epigenetic state	ILA enhanced H3K27 acetylation and chromatin accessibility in DC/$CD8^+$ T-cell programs in CRC, while butyrate induced chromatin remodeling associated with CXCL11 expression and NK-cell recruitment in HCC.	In primary human NK cells, butyrate suppressed mTORC1 and c-Myc-associated metabolic programs. In lymphoma, butyrate exposure induced phenotypic and transcriptomic changes in CAR T cells associated with enhanced antitumor efficacy.	The intracellular metabolic and epigenetic state of the responding cell can substantially modify the functional output of the same metabolite class.	[76, 82, 192, 193]
Treatment-specific context	Metabolite effects vary with therapeutic modality. I3A enhanced ICI efficacy in melanoma, whereas microbiota-derived 3-IAA enhanced chemotherapy efficacy in experimental pancreatic ductal adenocarcinoma through tumor- and neutrophil-dependent mechanisms.	Metabolite effects may directly intersect with cellular immunotherapy. Butyrate induced changes associated with improved CAR T-cell antitumor function in NHL, while *A. massiliensis*-dependent metabolic remodeling enhanced CAR T-cell potency in B-cell lymphoma models.	Treatment modality should be considered an active context filter because it changes the dominant responding cells, pathway dependencies, and metabolite-response thresholds.	[86, 130, 193, 314]

Note: The comparisons represent a cross-study synthesis of recent experimental evidence rather than direct head-to-head comparisons between solid and hematological malignancies. Context filters are presented as dominant determinants rather than mutually exclusive mechanisms.

4.5 Hematological malignancies as a distinct immune-cell exposure context

Because circulating and bone-marrow-resident immune cells can encounter systemic metabolites without being hindered by the same diffusion and stromal barriers present in many solid tumors, hematological malignancies represent a distinct exposure architecture. Butyrate at millimolar levels reduced mTORC1–S6 and c-Myc signaling, glycolysis, oxidative phosphorylation, and selected effector molecules in primary human peripheral-blood NK cells, yet direct killing of K562 target cells was not significantly impaired[76]. In stark contrast, 10 μM acetate, 2 μM butyrate, and 2 μM propionate modestly enhanced NK-92-cell cytotoxicity against MM.1S multiple myeloma cells after 48 h[77]. These opposing results underscore the complex roles of metabolite concentration, immune-cell source, activation state, exposure duration, and target-cell identity as dominant context filters in hematological settings.

The recent clinical evidence in non-Hodgkin lymphoma further supports a treatment-specific metabolite context. Among 84 patients receiving CD19 CAR T-cell therapy across multiple centers, circulating butyrate levels were positively associated with clinical outcome, and exposure to butyrate in experimental settings yielded phenotypic and transcriptional modifications associated with enhanced CAR T-cell activity[193]. In addition, exploratory associations between serum metabolites, including inosine and SCFAs, and CAR T-cell outcomes were identified by microbiome–metabolome analyses in relapsed or refractory diffuse large B-cell lymphoma[194]. This indicates that the effects of metabolites in hematological malignancies may be more strongly shaped by systemic or bone-marrow exposure, lineage-specific transporter and receptor expression, prior antibiotic exposure, and the activation state of circulating or marrow-resident immune cells compared with solid tumors. In order to systematically contrast the dominant context filters across solid and hematological malignancies, differences in anatomical exposure, responding-cell compartments, metabolite concentration, sensor engagement, intracellular state, and treatment context are summarized in Table 2.

4.6 A hierarchical operational framework for context-dependent metabolite effects

Within this operational framework, a metabolite should be assigned a direct immunomodulatory role only if demonstrable biologically relevant exposure is shown in the target compartment, the responding cell possesses the required access and sensing machinery, and pathway dependence has been experimentally established[89, 195]. This means that a direct local effect is unlikely regardless of fecal abundance if effective exposure is absent. A pathway being engaged will also be unlikely if the required receptor or transporter is absent or functionally insufficient, despite exposure being present. Exposure should additionally be interpreted with regard to its temporal profile. This is important because transient pharmacokinetic peaks that follow exogenous supplementation[196] may not translate proportionally into intracellular exposure because of transporter saturation or substrate competition[88, 110], and thus should be distinguished from steady-state physiological exposure. When these criteria apply to multiple cellular compartments, the dominant responding compartment should be determined by comparing metabolite exposure, target engagement, and functional dependence under the relevant treatment condition[122, 197]. This hierarchy transforms the descriptive context-filter concept into a testable and operational framework with which to evaluate context-dependent antitumor, immunosuppressive, or tumor-adaptive effects.

4.6.1 Treatment-specific context filters

Rather than being treated as a passive covariate, treatment should be thought of as an active context filter. PD-1/PD-L1 and CTLA-4 blockade can alter the functional importance of effector, memory, and progenitor-exhausted T-cell states, while SCFA-associated outcomes may be checkpoint target- and biological compartment-dependent, as indicated by currently available human studies. Butyrate can suppress radiation-induced STING–type I interferon signaling in DCs and also impair tumor-specific cytotoxic T-cell responses under radiotherapy[198]. Microbiota-derived IAA can modify treatment efficacy during chemotherapy by tumor-cell autophagy-related and neutrophil-associated mechanisms in pancreatic cancer. In addition, targeted therapy provides a further context where metabolite exposure might alter pathway dependence—physiologically relevant butyrate exposure has been shown to attenuate cetuximab activity in RAS/BRAF-wild-type CRC involving EGFR- and AMP-activated protein kinase (AMPK)–Wip1-associated signaling[199]. Treatment modality has the potential to rewire the dominant responding cell state, pathway dependence, effective metabolite-exposure threshold, and intracellular metabolic fate. Despite the plethora of studies addressing the role of metabolites in human health and disease, metabolite effects should be interpreted according to treatment modality, sequence, disease stage, and exposure timing rather than extrapolated across therapeutic settings.

4.6.2 Host and tumor genetic background as context modifiers

However, host genetic background should be considered a candidate upstream modifier of metabolite sensing, but the available evidence remains limited. The AHR rs2066853 is a variant that causes an Arg554Lys substitution within the transcriptional activation domain and is linked to altered AhR-related phenotypes as well as specific clinicopathological features in selected human cancer cohorts[200, 201]. Although human studies indicate context-dependent phenotypic effects of AHR rs2066853, direct evidence that this variant modifies responses to microbiota-derived AhR ligands in patients with cancer remains lacking[202]. In addition, the cancer-specific evidence directly linking FXR germline variants to microbiota-associated bile-acid responsiveness is also limited. Further, tumor somatic genotype may also alter signaling context downstream of receptor engagement. Such may be the case with KEAP1/NFE2L2 alterations in lung cancer and APC/CTNNB1 alterations in CRC, which may reconfigure NRF2- or Wnt/β-catenin-dependent signaling and immune states[203, 204], but direct evidence linking these alterations to microbiota-associated metabolite effects remains limited[205]. Host receptor genotype and tumor somatic genotype should therefore be viewed as complementary context filters for prospective testing, rather than established determinants of metabolite response.

5. Tumor immunotherapy strategies based on microbiota-associated metabolites

5.1 Microbiota-associated metabolites as biomarkers

5.1.1 Predicting response to immunotherapy

Microbial and microbiota-associated metabolite profiles may serve as candidate biomarkers of ICI outcomes because they capture integrated microbial metabolic activity and its interaction with the host clinical and immune context[206-208]. Most clinical studies available in the literature characterize aggregated circulating or fecal metabolic profiles, with

limited information on the contribution of specific metabolites. In patients with melanoma receiving anti-PD-1 therapy, baseline plasma metabolomic and circulating immune-bioenergetic profiles differed between responders and nonresponders, and several glycolysis-related features were associated with clinical outcomes. These findings support the potential utility of integrated metabolic signatures, while their microbial origin and independent predictive value require prospective validation[209].

The predictive value of microbiome-associated metabolic features may differ across patient populations[210]. A cross-cohort shotgun metagenomic analysis of patients with advanced melanoma identified gut microbial features associated with ICI responses or PFS, but also demonstrated limited reproducibility of individual signatures across cohorts[211]. These findings indicate that geographical background, dietary exposure, microbial ecology, treatment regimen, specimen processing, and host characteristics may influence biomarker performance[211, 212]. Thus, candidate metabolite signatures should be evaluated within defined cancer types and treatment settings rather than extrapolated across cohorts or tumor types[211].

In contrast, the few human studies of SCFAs and ICI response report heterogeneous associations that are either favorable, neutral, or treatment-dependent rather than a homogeneous predictive signal[166, 181, 182]. In another NSCLC cohort combining fecal SCFAs, gut microbiota composition and intestinal-permeability markers, neither the individual variables nor the combined analysis was able to identify a predictive biomarker of ICI response[166]. In contrast, a prospective cohort of 52 patients with solid tumors treated with nivolumab or pembrolizumab reported that higher fecal acetate, propionate, butyrate and valerate concentrations were significantly associated with prolonged PFS[182]. Conversely, high circulating butyrate and propionate levels are linked to poor clinical outcomes in CTLA-4 blockade[181]. These results suggest that the direction of metabolite associations is context-dependent and may differ across treatment contexts, biological compartments, cancer types, cohort characteristics, and analytical design[211]. Differences among studies should not simply be interpreted as biological contradictions. Intake of dietary fiber and probiotics can alter gut microbial ecology[24], while differences in the manner in which specimens are collected, stored, processed, normalized or analyzed may also alter measured metabolite abundance[213]. Future cross-cohort analyses should therefore report and adjust for diet, recent antibiotic and probiotic use, cancer stage, treatment regimen at the time of sample collection, specimen compartment such as serum or urine, preanalytical storage protocols and analytical platform before assigning predictive value to an individual metabolite.

Higher dietary fiber intake was associated with better PFS in patients with melanoma treated with immune-checkpoint blockade, whereas corresponding murine studies indicated that low-fiber diets or probiotic supplementation might impair responses to anti-PD-1-based treatment[24]. These results reinforce the need to record dietary and probiotic exposures a priori as covariates in metabolite-biomarker studies.

Candidate metabolite signatures require standardized specimen collection, analytical workflows, quality-control procedures, prespecified analytical strategies, and independent validation before clinical implementation[211, 214]. Further studies should assess whether metabolite measurements provide incremental predictive value beyond established clinicopathological and immunological variables[214, 215]. At present, microbiota-associated metabolic signatures remain candidate stratification biomarkers, while their use as predictors or treatment-selection tools requires independent validation[211, 214].

5.1.2 Evaluating tumor prognosis

Gut microbiota-derived and microbiota-associated metabolites may shape tumor progression by altering tumor-cell proliferation and apoptosis and by modulating immune activity within the TME, particularly in treatment-dependent settings. Their associations with treatment response and survival have prompted their evaluation as candidate prognostic and predictive biomarkers[216].

In CRC, location- and sex-specific differences in intratumoral bile-acid profiles have been observed, and selected conjugated-to-unconjugated bile-acid ratios have been associated with 5-year overall survival or recurrence-free survival. These findings, however, remain exploratory and require validation in independent prospective cohorts before bile-acid profiles can be considered clinically applicable prognostic biomarkers[131].

Taken together, intratumoral bile-acid profiles may yield complementary prognostic information alongside established clinicopathological variables in CRC[131]. Currently, bile acid profiles should be considered exploratory biomarkers for risk stratification, and they are not yet established as tools for treatment selection or routine prognostic assessment[131, 217].

5.2 Microbiota-associated metabolite supplementation or intervention therapy

5.2.1 Exogenous supplementation of beneficial microorganisms and their metabolites

As a strategy to modify the gut microbial–metabolic ecosystem and antitumor immunity during cancer immunotherapy, supplementation with selected beneficial microorganisms, donor microbiota, or microbiota-derived metabolite mixtures has been explored. Efficacy and underlying mechanisms vary across microbial strains or products, tumor types, host contexts, engraftment patterns, and treatment regimens[218-220]. The specific mechanisms of action, supplementation patterns and clinical application prospects are as follows:

Butyrate and other SCFAs may alter responses to cancer immunotherapy through several context-dependent mechanisms. They can help maintain epithelial-barrier integrity and decrease systemic exposure to microbial inflammatory products including LPS, directly influence tumor-cell proliferation and apoptosis, and modify effector and regulatory immune-cell programs[121, 191, 221, 222]. Most available evidence is preclinical or correlative, and controlled metabolite-administration studies are required to determine whether SCFA abundance directly contributes to enhanced immunotherapy efficacy. In fact, the dependence of SCFA activity on local concentration, target-cell identity, tissue exposure, and treatment context renders it improbable that these effects will be conserved across multiple cancer types.

Thus, probiotic supplementation has been studied as an indirect microbiota-directed strategy to influence antitumor immunity. In selected preclinical models, specific probiotics altered gut microbial composition, increased SCFA-producing bacteria or related metabolites, and were associated with increased immune-cell activity and decreased tumor growth[223, 224]. Probiotics simultaneously alter multiple microbial products and host pathways; their observed effects therefore reflect microbiota-level modulation involving SCFAs, calcium signaling, reactive oxygen species production, and other microbial and host factors. However, further evaluation of their clinical efficacy and generalizability in cancer immunotherapy is needed[225].

According to Section 5.1.1, probiotic supplementation and high-fiber dietary intervention constitute microbiota-directed approaches rather than direct administration of a chemically defined metabolite[24, 226]. These approaches modify the gut microbial context indirectly, with fiber-based interventions altering SCFA exposure through changes in microbial composition and metabolism rather than delivering a chemically defined metabolite at a controlled dose. Their biological effects therefore provide indirect evidence for SCFA-mediated antitumor activity rather than direct evidence for SCFA-specific therapeutic efficacy[226].

Probiotic and other microbiota-directed interventions exhibited immunomodulatory and antitumor activity in selected preclinical models, but their effects appear to depend on the microbial product, tumor context, and combination treatment [227, 228]. However, currently available evidence is insufficient to conclude that probiotic or live bacterial interventions consistently improve immunotherapy outcomes in patients[24, 25]. Personalized microbiome and metabolite profiles may support patient stratification in future studies, but these approaches have not yet been validated for guiding microbiome-directed interventions or improving treatment responses[229]. Substantial inter-individual variability persists in microbial engraftment and ecological response, while the durability of clinical benefit and longer-term safety require evaluation in adequately powered clinical trials[25, 229].

5.2.2 Targeting microbial metabolism and metabolite-producing bacteria

Adverse metabolic effects may be attenuated and antitumor immunity restored by targeting immunosuppressive microbial metabolic activities or specific pro-tumor bacteria, suggesting candidate strategies for context-specific therapeutic intervention [46, 230]. Representative approaches are described below.

AKR1D1 deficiency increases the abundance of *Bacteroides ovatus*, enhancing the conversion of CDCA into isoLCA in HCC. Accumulation of isoLCA suppresses hepatic NK-cell cytotoxicity via a phosphorylated CREB1-dependent mechanism, arguing that targeting the *B. ovatus*–isoLCA axis may reinstate antitumor immunity mediated by NK cells. Pharmacological targeting of this pathway could enhance the efficacy of immunotherapy. Spironolactone partially relieved isoLCA-induced inhibition of NK-cell antitumor activity and increased anti-PD-1 therapeutic efficacy in experimental models of HCC[231]. BAs from the gut microbiota might also function as endogenous receptor antagonists. In mouse tumor models, 3-oxo-Δ4,6-LCA antagonized the androgen receptor, augmented the presence of tumor-infiltrating stem-like $CD8^+$ T cells, inhibited tumor growth, and improved anti-PD-1 treatment efficacy through a $CD8^+$ T-cell-intrinsic androgen receptor-dependent mechanism[195]. Together, these results highlight two complementary intervention

approaches: lowering the microbial production or accumulation of immunosuppressive BAs and taking advantage of microbiota-derived BAs as endogenous antagonists of host immune-regulatory receptors. However, such strategies remain preclinical and require validation of bacterial targets, metabolite exposure, receptor selectivity, safety, and therapeutic efficacy in well-defined cancer contexts.

Engineered live bacteria and synthetic-biology platforms may nevertheless constitute an additional option for enhancing the spatiotemporal control of metabolite-targeted interventions through tumor-selective colonization, microenvironment-responsive genetic circuits, inducible expression systems, and localized payload release[232, 233]. Bacteria can also be engineered to colonize tumors and produce specific defined metabolites locally. In addition, they may reprogram metabolic pathways within the TME. An engineered Trp-overproducing strain of *Clostridium butyricum* selectively colonized tumors in preclinical mouse and rabbit tumor models following systemic administration.

Butyrate from the engineered strain inhibited indoleamine 2,3-dioxygenase activity and reduced Kyn levels, while bacterially released Trp supported $CD8^+$ T-cell activation and energy metabolism, thereby restoring $CD8^+$ T-cell function and delaying tumor growth[234]. In a separate study, engineered *Escherichia coli* Nissle 1917 locally produced IAA, activated AhR signaling, increased intratumoral CXCL9 and IFN-γ expression, and promoted T-cell infiltration and activation, thereby suppressing tumor growth and prolonging survival in syngeneic mouse models[235]. By contrast, engineered bacterial platforms represent a broader metabolite-delivery strategy than direct metabolite supplementation because their biological effects may involve bacterial colonization, microbial components, nutrient competition, and broader host responses in addition to the delivered metabolite. Challenges in translation involve context-dependent and sometimes persistent colonization[236], horizontal gene transfer, genetic instability or loss of engineered functions and containment circuits, and the need for robust, redundant biocontainment and conditional kill-switch mechanisms[237, 238]. Future studies will need to measure more precisely the intratumoral concentration, cellular uptake, and biological fate of the metabolite delivered by bacteria. Representative translational strategies, their current evidence stages, major advantages, and principal limitations are summarized in Table 3.

5.3 Clinical evidence and combination strategies

Current clinical and translational evidence can be classified into non-equivalent categories: directly administered chemically defined metabolites[239] versus relatively undefined live bacterial products[25], probiotic supplementation and dietary intervention [24], and FMT[240]. These categories are supportive of various degrees of metabolite-specific effects and should thus be interpreted independently. Table 4 summarizes the main clinical studies described in this section, classified by trial registration number, cancer type, study design, sample size, intervention and comparator, direct metabolite administration, primary endpoint(s), efficacy and safety results, including findings related to endpoint achievement and major limitations. While direct administration of a chemically defined metabolite represents the most unambiguous evidence for metabolite-targeted therapeutic activity, microbiota-directed interventions will simultaneously impact microbial community structure, multiple metabolites and systemic and tumor-associated immune states, complicating the attribution of an observed clinical effect with confidence to a single metabolite[26]. A major challenge for early-phase trials is the definition of compartment-specific pharmacokinetic/pharmacodynamic (PK/PD) endpoints, with local gut exposure and pharmacodynamic activity prioritized for locally acting metabolites[241, 242], while circulating exposure with relevant target engagement should be prioritized for systemically acting compounds[243].

Table 3. Translational strategies, evidence stages and major limitations of microbiota-associated metabolite-based interventions

Strategy	Representative approach	Current evidence stage	Main advantage	Principal limitation	References
Direct metabolite supplementation	Butyrate, IPA, TMAO or metabolite precursors	Predominantly preclinical for the representative approaches listed; oral inosine has entered randomized phase II clinical evaluation	Defined molecular intervention with experimentally controlled dose and route	Limited bioavailability and intratumoral exposure, model-dependent dosing and insufficient clinical validation	[11, 101, 143, 239]
Microbiota modulation	Defined live bacterial products such as CBM588	Early clinical, randomized phase 1	Potential multi-level modulation of microbial functions, metabolic pathways and immune signaling	Inconsistent microbiome remodeling, dietary and host heterogeneity and unresolved causal metabolite or mechanism	[25, 244]
FMT	Donor-derived microbial	Early phase I–II clinical	Broad restructuring of	Donor variability, infection risk,	[26, 245,

	communities combined with ICIs	investigation with inconsistent efficacy signals	microbial communities and functional capacity	non-randomized study designs, inconsistent efficacy, and uncontrolled transfer of microbial functions and metabolites	246]
Nanocarrier-mediated metabolite delivery	Enzyme-responsive SCFA-releasing nano-prodrugs	Preclinical	Sustained release, improved pharmacokinetic stability and reduced gastrointestinal toxicity compared with free SCFAs	Validation limited to melanoma models, with no demonstrated tumor- or cell-specific targeting and limited immune-mechanistic characterization	[276]
Engineered bacteria	Tumor-colonizing bacteria programmed to produce defined metabolites or reprogram local metabolic pathways	Preclinical	Localized and genetically programmable metabolic intervention	Route- and tumor-dependent colonization, limited dynamic control of metabolite output and insufficient long-term safety and biocontainment validation	[234, 235]

Note: Direction-of-effect coding is provided in Table 1 and Table S2 because the biological direction of microbiota-directed and delivery-based interventions depends on the delivered metabolite or microbial function, the target-cell compartment, and the treatment context.

Table 4. Clinical trials evaluating direct metabolite and microbiota-directed interventions in cancer therapy

Trial and cancer type	Phase/design and sample size	Intervention and comparator	Direct metabolite	Primary endpoint	Efficacy, safety and endpoint status	Major limitations	Reference
NCT05809336; advanced solid tumors	Phase 2; prospective, randomized, open-label; n=172	Inosine plus PD-1/PD-L1-based therapy vs the corresponding treatment without inosine	Yes; inosine	ORR	ORR: 26.7% vs 15.1% (P=0.061); median PFS: 7.0 vs 4.4 months (HR 0.63, P=0.011). Grade 3–4 adverse reactions: 29% vs 36%. Primary endpoint not met	Single-center study; heterogeneous tumor types and concomitant regimens; subgroup analyses were exploratory	[239]
NCT03829111; metastatic renal cell carcinoma	Phase 1; randomized, open-label, 2:1; n=30	CBM588 plus nivolumab and ipilimumab vs nivolumab and ipilimumab alone	No; live bacterial product	Change in relative abundance of *Bifidobacterium* spp.	Primary microbiome endpoint showed no significant difference. Median PFS: 12.7 vs 2.5 months (HR 0.15); ORR: 58% vs 20%. No significant toxicity difference. Primary endpoint not met	Small single-center phase 1 study; efficacy was secondary and the trial was not powered for definitive clinical comparison	[25]
NCT05122546; locally advanced or metastatic renal cell carcinoma	Phase 1; randomized, open-label, 2:1; n=30	CBM588 plus cabozantinib and nivolumab vs cabozantinib and nivolumab	No; live bacterial product	Change in relative abundance of *Bifidobacterium* spp.	Primary microbiome endpoint showed no significant difference. ORR: 74% vs 20% (P=0.01); 6-month PFS: 84% vs 60%. No significant toxicity difference. Primary endpoint not met	Small phase 1 study; 29 patients were efficacy-evaluable; clinical benefit represented a secondary preliminary signal	[244]
NCT03772899 (MIMic); previously untreated advanced melanoma	Phase 1; multicenter, open-label, single-arm; n=20	Healthy-donor FMT followed by nivolumab or pembrolizumab; no separate control arm	No; microbiota-directed intervention	Safety	No grade 3 adverse events were attributed to FMT alone; five patients developed grade 3 immune-related adverse events during combination therapy. ORR: 65%, including four complete responses (20%). Primary safety endpoint met	Small single-arm study; absence of an ICI-only comparator prevents attribution of efficacy specifically to FMT	[26]
NCT04951583 (FMT-LUMINate); NSCLC and melanoma	Phase 2; multicenter, open-label, single-arm; n=40	Healthy-donor oral FMT plus ICI therapy; no separate control arm	No; microbiota-directed intervention	ORR in the NSCLC cohort	NSCLC ORR: 80% (16/20); melanoma ORR: 75% (15/20). The NSCLC cohort met the primary endpoint. Safety was considered manageable within the respective ICI regimens	Only 20 patients per tumor cohort; single-arm design prevents separation of FMT effects from concurrent ICI therapy	[245]
NCT05286294 (MITRIC); ICI-refractory advanced solid tumors	Phase 2a; single-arm basket trial; n=12	FMT from long-term ICI responders plus continued/reintroduced ICI therapy; no control arm	No; microbiota-directed intervention	FMT-related safety and ORR	FMT was generally feasible and tolerated; no objective responses were observed, although five patients achieved stable disease. The efficacy component of the co-primary endpoint was not met	Very small heterogeneous cohort; no control arm; limited clinical activity and uncertain donor/patient selection	[246]

Note: Direct metabolite administration refers to interventions in which a chemically defined metabolite is administered directly to patients. CBM588 and FMT are classified as microbiota-directed interventions rather than direct metabolite therapies because they modify microbial communities and multiple downstream metabolites simultaneously. "Primary endpoint met" was determined according to the prespecified primary endpoint reported in the original clinical study. The PK/PD measures for early-phase metabolite trials should be consistent with the intended site of action. Local gut exposure and pharmacodynamic activity may be more suitable for locally acting metabolites, while circulating exposure and relevant target engagement may be more appropriate for systemically acting compounds[241,315]. These compartment-specific PK/PD measures were not consistently integrated into the early clinical studies summarized above.

5.3.1 Direct metabolite administration with ICIs

Among direct metabolite interventions, oral inosine combined with PD-1 or PD-L1 blockade was assessed in a single-center, randomized, open-label phase II trial (NCT05809336) involving 172 patients with advanced solid tumors[239]. Objective response rate (ORR) was the primary endpoint and was 26.7% in the inosine group compared with 15.1% in the non-inosine group, but the difference did not reach statistical significance. Median PFS was 7.0 months in the inosine group and 4.4 months in the non-inosine

group, with a hazard ratio (HR) of 0.63[239]. These results provide an initial clinical efficacy signal for purified inosine supplementation; however, the nonsignificant primary endpoint and single-center design preclude definitive confirmation of clinical benefit.

5.3.2 Live bacterial-product interventions with ICIs

Clinical trials of *Clostridium butyricum* MIYAIRI 588 (CBM588) represent live bacterial-product interventions rather than direct butyrate administration. A single-center, open-label, randomized phase I trial (NCT03829111) involving 30 treatment-naive patients with metastatic renal cell carcinoma examined nivolumab plus ipilimumab with or without CBM588[25]. The primary endpoint was prespecified as the change in the relative abundance of *Bifidobacterium* spp. from baseline to week 12 but was not met. Patients receiving CBM588 had a median PFS of 12.7 months compared with 2.5 months among those not receiving CBM588, with an HR of 0.15, while the ORRs were 58% and 20%, respectively; the difference in ORR did not reach statistical significance[25].

Another open-label, randomized phase I trial (NCT05122546) investigated cabozantinib plus nivolumab with or without CBM588 in 30 patients with advanced or metastatic renal cell carcinoma, of whom 29 were efficacy-evaluable[244]. The primary endpoint, defined a priori as the change in the relative abundance of *Bifidobacterium* spp. from baseline to week 13, was not met. However, the ORR was 74% with CBM588 compared with 20% without CBM588, and the corresponding 6-month PFS rates were 84% and 60%, respectively[244]. This limited evidence from early phase I studies suggests potential clinical utility and warrants further evaluation of CBM588. However, since CBM588 is a live bacterial intervention instead of direct butyrate delivery and these trials did not confirm modified butyrate exposure nor a butyrate-facilitated mechanism, it cannot be directly concluded that the clinical effects were caused by butyrate despite the fact that such a mechanism is plausible[25, 244].

5.3.3 FMT with ICIs

FMT represents a microbiota-level intervention rather than direct administration of a chemically defined metabolite. Healthy-donor FMT combined with nivolumab or pembrolizumab was evaluated in the multicenter phase I MIMic trial (NCT03772899), which enrolled 20 previously untreated patients with advanced melanoma[26]. The primary endpoint was safety. No grade 3 adverse events were attributed to FMT alone, while the ORR was 65%, including four complete responses (20%)[26].

The multicenter, open-label, single-arm phase II FMT-LUMINate trial (NCT04951583) assessed oral capsule FMT prior to first-line ICI therapy in 20 patients with NSCLC and 20 patients with melanoma[245]. In the NSCLC cohort, ORR was the primary endpoint. ORRs were 80% in the NSCLC cohort and 75% in the melanoma cohort. The lack of a randomized control group limits causal attribution of these outcomes specifically to FMT[245].

In contrast, the MITRIC basket trial (NCT05286294), a single-arm phase IIa study involving 12 patients with ICI-refractory solid tumors, evaluated FMT plus continued immune-checkpoint inhibition[246]. The co-primary endpoints were adverse events associated with FMT and ORR. No objective responses were seen, while five patients achieved stable disease. In this treatment-refractory population, these findings indicate that the intervention was feasible, generally well tolerated, and had limited clinical activity.

Altogether, these early-phase studies support the practical use of FMT and provide inconsistent signals for clinical activity by treatment setting[240, 245, 247]. Clinical outcomes following FMT are thus more appropriately understood as consequences of these wide-ranging microbiota remodeling events rather than representing direct causal evidence for the therapeutic efficacy of any given metabolite, likely due in part to simultaneous constellation-level changes in complex microbial communities, multiple metabolites and host immune pathways[240, 245].

Observational links between fecal or circulating metabolite concentrations and ICI efficacy should be distinguished from experimental evidence[206]. These associations can discover candidate biomarkers, but do not prove that the measured metabolite directly modulates treatment response, as exposure to metabolites may depend on other clinical factors such as diet, microbial ecology and antibiotic exposure[23]. Of the studies discussed here, direct oral inosine administration provides the most specific clinical test of a chemically defined metabolite intervention[239]. Instead, CBM588 and FMT are microbiota-targeted therapies and a clinical effect cannot be linked to modulation of a particular metabolite unless specific changes in metabolite exposure and mediation by microbial metabolites are demonstrated[240, 244].

5.3.4 Combination with chemotherapy, radiotherapy, and other anticancer therapies

Specific microbiota-associated metabolites have been reported to modify responses to standard anticancer therapies under defined experimental conditions. In pancreatic cancer, microbiota-derived IAA, referred to as 3-IAA in the original study,

enhanced chemotherapy effectiveness through tumor-cell autophagy-related and neutrophil-associated mechanisms. However, these results remain context dependent and do not provide evidence for pan-cancer efficacy[130]. Butyrate improved the potency of a p53-expressing telomerase-specific oncolytic adenovirus by augmenting viral infectivity and enhancing MHC-I/cGAS–STING signaling in CRC-related models[248]. An independent study showed that a microbial metabolite limited the growth of 5-fluorouracil-resistant colonic tumors by restoring drug-transporter sensitivity through regulation of the FOXO3–FOXM1 axis[249]. Importantly, however, these results indicate that selected metabolites can modulate the effectiveness of chemotherapy or oncolytic therapy in treatment-specific preclinical models, but do not confer generalizable therapeutic advantage.

Approaches targeting the microbiota, including FMT, have been examined as methods to reduce intestinal injury associated with treatment, but clinical evidence supporting FMT in chronic radiation enteritis is less robust[250]. Additional preclinical studies also propose that IPA of microbiota origin might mitigate the radiation-induced toxicity in specific experimental models[251].

In aggregate, microbiota-associated metabolite–treatment combinations are context dependent in their therapeutic efficacy or treatment-related toxicity in experimental models[252, 253] and need further validation for cancer-, dose-, and regimen-specific combinations. A summary of biomarker strategies, microbiota modulation, metabolite supplementation, combination therapies, delivery platforms, clinical evidence stages and major limitations is provided in Table S5.

6. Methodological and translational priorities

The major translational challenges are to establish quantitative exposure, causal target engagement, methodological reproducibility, intervention-specific safety, and patient-selection criteria within defined cancer and treatment contexts[144, 165, 195].

6.1 Quantitative exposure and causal validation

A primary difficulty is the separation of administered dose or measured metabolite abundance from biologically effective exposure. After administration, purified metabolites may be absorbed in the intestine, metabolized in the liver or kidney, enzymatically modified, and accumulate in specific tumor or immune-cell compartments[254]. Fecal, portal-vein, peripheral-blood, tumor-tissue and intracellular concentrations do not represent biologically equivalent exposures[255, 256]. Fecal abundance mainly represents the residual luminal pool, whereas peripheral-blood concentrations reflect metabolites and biotransformation products that enter the systemic circulation post-absorption and first-pass metabolism. Hence, tissue-level and, when possible, intracellular exposure should be confirmed before pharmacologically relevant activity is assumed from fecal or circulating abundance data alone. Pharmacokinetic characterization in humans remains incomplete for many microbiota-associated metabolites.

The pharmacokinetic profile could differ substantially between direct metabolite administration and continuous microbial production. Direct oral administration may result in brief systemic exposure, while metabolite-producing bacteria colonizing the tumor may sustain localized production[109, 257]. It should be noted that these exposure profiles should not be taken to imply equivalent transporter-mediated cellular uptake[258]. Colonization efficiency, nutrient availability, microbial competition, gut transit, antibiotic exposure and other host physiological parameters also impact microbiota-dependent production[259-261]. Hence, future translational studies should delineate the temporal profiles of absolute concentrations for all relevant metabolites in circulation, target tissues and intracellular compartments and correlate these concentrations with measurements of target engagement, therapeutic response and toxicity.

While human metabolomic studies can correlate metabolite abundance with tumor immunity, these associations cannot establish metabolite-specific causality and may instead reflect dietary context, microbial composition, host physiology, organ function or disease severity[11]. Likewise, mechanistic conclusions made from data collected with isolated populations of cells or experimental systems which are non-comparable may vary based on cell type, route of administration, exposure time, concentration range or treatment setting[11, 262]. Thus, rigorous causal inference demands defined context-dependent metabolite exposure coupled with selective functional manipulation of specific transporters or receptors in specific cell types, stable-isotope tracing, spatial or cell-resolved measurements of metabolites and direct assessment of downstream pathway engagement[11, 262, 263].

6.2 Standardized human metabolomics and multi-omics validation

Multiple stages of the metabolomic workflow,

including sample collection, storage, freeze–thaw processing, homogenization and extraction procedures, as well as the selection of analytical platforms such as nuclear magnetic resonance or mass spectrometry and targeted versus untargeted metabolomic workflows, contribute to substantial variability in measured concentrations and make cross-study comparisons difficult[213, 264, 265]. Standardization is critical because fecal, portal-vein, circulating, tissue, and intracellular measurements provide distinct information on metabolite production, distribution, and biologically active exposure[105].

For fecal metabolomics, future studies should prespecify collection timing, time to freezing, storage temperature, freeze–thaw limits, wet- or dry-mass normalization, extraction recovery, and the use of isotope-labeled internal standards. Blood-based studies should standardize fasting status, collection tubes, processing delays, centrifugation, storage conditions, and hemolysis assessment[266-269]. Tissue metabolomics should record ischemia time, tumor cellularity, spatial sampling location, preservation method, and extraction procedure. Targeted assays should report calibration ranges, limits of detection and quantification, intra- and inter-batch coefficients of variation, analytical recovery, and absolute concentration units whenever technically feasible.

6.3 Delivery-platform limitations and biosafety

Delivery platforms should be chosen based on anatomical target, responding cell population, required duration of exposure, and acceptable off-target exposure. Butyrate-prodrug micelles can deliver butyrate directly to its site of biological action and bypass limitations associated with traditional oral administration[270], while nanoparticles and local delivery systems can enhance chemical stability, tissue retention, or compartment-specific exposure[271-279]. Nonetheless, these strategies are still constrained by differences in cargo release, rapid gastrointestinal metabolism under the action of enzymes and acids[280], liver or splenic sequestration, heterogeneous tumor penetration, local inflammation, and limited use for anatomically inaccessible tumors. In this regard, absolute target-tissue and intracellular metabolite concentrations rather than administered dose or carrier accumulation alone should be the metric for assessing delivery efficacy.

No delivery platform is universally optimal. Nevertheless, direct head-to-head comparisons of intratumoral metabolite exposure among oral metabolite prodrugs, nanocarriers, and engineered bacterial platforms remain limited. Thus, colon-targeted formulations may be more suitable for intestinal exposure, while nanoparticles or local administration may support tissue-specific delivery. Direct delivery to tumor tissue could increase local concentrations of metabolites and therefore enhance local antitumor activity, while engineered bacteria may allow sustained local metabolite production[281]. Comparative evaluation should therefore focus on the ability of each platform to achieve a defined level of extracellular and intracellular exposure in the target cell population while remaining below tissue-specific toxicity thresholds.

Engineered bacteria and metabolite-producing live biotherapeutic products may selectively colonize tumors to continuously deliver therapeutic metabolites locally[282], but their clinical application is limited by concerns of variable colonization, uncontrolled metabolite output, systemic infection, and horizontal gene transfer, as well as the need for effective biocontainment and kill-switch systems. Further biosafety issues include off-target colonization or metabolite release in non-tumor organs, inadvertent systemic or organ-specific inflammation, loss of engineered metabolic pathways or conditional attenuation[283], environmental shedding, and failure of long-term containment mechanisms. As a result, evaluations of engineered strains should focus on longitudinal measures of biodistribution, genetic stability, shedding, horizontal transfer, systemic inflammation, and kill-switch failure rather than just short-term tumor-growth endpoints.

In immunocompromised populations, FMT has a unique infectious-risk profile and therefore needs careful donor screening and safety surveillance. Transmission through FMT of extended-spectrum β-lactamase-producing Escherichia coli has been reported in immunocompromised recipients, including a fatal case of sepsis[284]. Other supporting evidence from transplant populations highlights the possible transmission of multidrug-resistant organisms and occult pathogens[285]. Overall, these findings support intervention-specific microbiological screening and longer-term safety surveillance when considering FMT in patients with cancer.

Safety and development criteria should be specific to the intended intervention, rather than applied uniformly across microbiota-associated metabolite strategies. Toxicity assessments for purified metabolites require dose–exposure–response and formulation-specific toxicity assessment, while live bacterial products and engineered bacteria also require evaluation of systemic dissemination, colonization, genetic stability, horizontal gene transfer, and biocontainment. Donor screening and infectious-risk surveillance are necessary for FMT, whereas microbiota-directed interventions require

verification that the metabolite of interest is altered at the relevant physiological or target-tissue site before a metabolite-specific effect may be reliably inferred[240, 247, 254, 276, 286-289].

6.4 Precision stratification and prospective clinical validation

Microbiota composition and associated metabolite profiles vary according to geography, diet, the use of antibiotics, host factors, cancer type and treatment context[290-292]. This heterogeneity limits the generalizability of single-metabolite biomarkers and instead supports the need for context-specific patient stratification[293]. Differences in microbiota composition across geographical regions and populations can also affect metabolite production and confound cross-cohort comparisons, highlighting the need for external validation of findings across distinct populations and dietary backgrounds[294, 295].

Diet and antibiotic exposure are important modifiable confounders because they may alter microbial community structure, metabolite production, and ICI-associated immune responses [296-300]. Consequently, these variables should be prespecified and documented and incorporated into stratified or multivariable analyses rather than treated as unmeasured background factors.

Integrated microbiome–metabolome phenotyping may offer a stronger foundation for patient stratification compared with individual taxa or metabolites. Studies across multiple cohorts have identified microbial–metabolic patterns associated with response and built predictive models on the basis of metagenomic, metabolomic, clinical, or immune variables[23, 214]. Yet the metabolic subtypes identified by machine learning remain candidate predictive biomarkers, not validated treatment-selection tools. Prospective studies should prespecify multi-omics inputs, use locked classification models, define subtype-specific treatment-assignment rules and clinical endpoints, and investigate whether subtype-guided interventions improve objective response or PFS as compared with standard clinical stratification[301-303]. External validation across geographic populations, dietary backgrounds, antibiotic-exposure patterns, cancer types, and treatment regimens will be critical.

Multiple registered studies are underway to evaluate microbiome-based biomarkers or microbiota-directed interventions during immune-checkpoint therapy. NCT04264975 is a recruiting, open-label, single-center, non-randomized study comprising a microbiome biomarker-development component and a proof-of-concept FMT component in patients receiving immunotherapy for advanced solid tumors; initial results from the anti-PD-(L)1-refractory FMT cohort have already been reported[304]. NCT05251389 is a recruiting, randomized, double-blind phase Ib/IIa trial comparing FMT from anti-PD-1-responding and anti-PD-1-nonresponding donors in patients with anti-PD-1-refractory advanced cutaneous melanoma[305]. In contrast, clinical results from the FMT-LUMINate trial (NCT04951583) have been reported, and this study is therefore addressed together with completed clinical studies in Section 5.3.3. Notably, these trials primarily evaluate microbiome biomarkers or microbiota-directed interventions, whereas prospective validation of machine-learning-defined metabolic subtypes for treatment allocation requires dedicated clinical evaluation.

Context-resolved metabolite–immune–tumor maps that couple quantitative local and systemic metabolite exposure with cell-type-specific uptake, receptor dependence, intracellular metabolic fate, and functional pathway engagement will be important for future work. To this end, these studies are expected to integrate quantitative metabolomics with cell-resolved and perturbation-based approaches for defining the predominant metabolite-responsive compartment within specified tumor and treatment settings[85, 86, 252, 306].

Translational development should put further focus on site-matched delivery and prospectively validated patient stratification while strictly distinguishing direct administration of chemically defined metabolites from indirect metabolite changes elicited by live bacterial products, FMT, or broader microbiota remodeling. It is essential that these intervention classes are evaluated according to target-tissue exposure, functional response, safety, and causal evidence in specific cancer and treatment settings rather than being generalized across tumors[25, 240, 252, 257, 280].

In aggregate, clinical translation will require quantitative exposure measurements, metabolomic workflows that are reproducible, criteria for safety and delivery specific to interventions, as well as prospectively validated strategies of patient stratification[307-310]. These priorities should be assessed in specific cancer and treatment settings, rather than generalized across tumors, thus allowing for a more stringent foundation for the development of microbiota- and metabolite-based biomarkers and therapeutic modalities.

7. Conclusion

Microbiota-associated metabolites may not be fixed pro- or antitumor in the biological effects they exert but may act in a context-dependent manner as regulated by other metabolic factors within the tumor

niche[311]. The key part of this review is a sequential and experimentally testable framework, moving from the origin of the metabolite and its tissue exposure to cellular access, sensor engagement, cell state and intracellular fate while clearly disentangling direct metabolite causality from microbiota-level associations. Translation will necessitate quantification at a compartment-resolved level, human spatial and cell-specific validation, and intervention-specific evidence rather than extrapolation from fecal abundance or preclinical models in isolation[147, 304, 312]. This strategy may allow the identification of metabolite biomarkers and therapeutic strategies that are specific to tumor–cell–treatment settings, rather than assuming universality across cancers.

Abbreviations

ABRAXAS1: abraxas 1, BRCA1 A complex subunit; **AhR:** aryl hydrocarbon receptor; **ALDH1A3:** aldehyde dehydrogenase 1 family member A3; **AMPK:** AMP-activated protein kinase; **BAs:** bile acids; **cAMP:** cyclic adenosine monophosphate; **CAR T cell:** chimeric antigen receptor T cell; **CBM588:** *Clostridium butyricum* MIYAIRI 588; **CDCA:** chenodeoxycholic acid; **cGAS:** cyclic GMP-AMP synthase**; CoQ10:** coenzyme Q10; **CRC:** colorectal cancer; **CTLA-4:** cytotoxic T-lymphocyte-associated protein 4; **CXCL11:** C-X-C motif chemokine ligand 11; **DCA:** deoxycholic acid; **DCs:** dendritic cells; **EP2:** prostaglandin E receptor 2; **EP4:** prostaglandin E receptor 4; **FMT:** fecal microbiota transplantation; **FOXP3:** forkhead box protein P3; **FSP1:** ferroptosis suppressor protein 1; **FXR:** farnesoid X receptor; **GCN2:** general control nonderepressible 2; **GPCR:** G protein-coupled receptor; **GPR109A:** G protein-coupled receptor 109A; **GPR41:** G protein-coupled receptor 41, also known as free fatty acid receptor 3; **GPR43:** G protein-coupled receptor 43, also known as free fatty acid receptor 2; **GSDME:** gasdermin E; **HCC:** hepatocellular carcinoma; **HDAC:** histone deacetylase; **HDAC3:** histone deacetylase 3; **HR:** hazard ratio; **HSCs:** hepatic stellate cells; **I3A:** indole-3-aldehyde; **IAA:** indole-3-acetic acid; **ICIs:** immune checkpoint inhibitors; **IDA:** trans-3-indoleacrylic acid; **IDO1:** indoleamine 2,3-dioxygenase 1; **IFN-γ:** interferon gamma; **ILA:** indole-3-lactic acid; **IPA:** indole-3-propionic acid; **isoalloLCA:** isoallolithocholic acid; **isoLCA:** isolithocholic acid; **Kyn:** kynurenine; **LAT1:** L-type amino acid transporter 1; **LCA:** lithocholic acid; **LPS:** lipopolysaccharide; **MASLD-HCC:** metabolic dysfunction-associated steatotic liver disease-associated hepatocellular carcinoma; **MCT1:** monocarboxylate transporter 1; **MDSCs:** myeloid-derived suppressor cells; **mTOR:** mechanistic target of rapamycin; **mTORC1:** mechanistic target of rapamycin complex 1; **NAFLD:** nonalcoholic fatty liver disease; **NFATC2:** nuclear factor of activated T cells 2; **NF-κB:** nuclear factor kappa B; **NK:** natural killer; **NRF2:** nuclear factor erythroid 2-related factor 2; **NSCLC:** non-small-cell lung cancer; **ORR:** objective response rate; **PAGln:** phenylacetylglutamine; **PD-1:** programmed cell death protein 1; **PD-L1:** programmed death-ligand 1; **PERK:** protein kinase R-like endoplasmic reticulum kinase; **PFS:** progression-free survival; **PGE2:** prostaglandin E2; **PK/PD:** pharmacokinetic/pharmacodynamic; **PKA:** protein kinase A; **PMCA:** plasma membrane Ca^{2+} ATPase; **PMN-MDSC:** polymorphonuclear myeloid-derived suppressor cell; **PXR:** pregnane X receptor; **RORγt:** retinoic acid-related orphan receptor γt; **SCFAs:** short-chain fatty acids; **SLC7A5:** solute carrier family 7 member 5; **SMCT1:** sodium-coupled monocarboxylate transporter 1; **STAT3:** signal transducer and activator of transcription 3; **STING:** stimulator of interferon genes; **SUCNR1:** succinate receptor 1; **TAMs:** tumor-associated macrophages; **TCF7:** T cell factor 7; **TDO2:** tryptophan 2,3-dioxygenase 2; **TGR5:** G protein-coupled bile acid receptor 1; **Th17 cell:** T helper 17 cell; **TLR2:** Toll-like receptor 2; **SLC5A8:** solute carrier family 5 member 8; **SLC16A1:** solute carrier family 16 member 1; **TLR4:** Toll-like receptor 4; **TMAO:** trimethylamine N-oxide; **TME:** tumor microenvironment; **TNBC:** triple-negative breast cancer; **TNF-α:** tumor necrosis factor alpha; **Treg:** regulatory T cell; **Trp:** tryptophan; **UDCA:** ursodeoxycholic acid; **VDR:** vitamin D receptor; **VEGFA:** vascular endothelial growth factor A; **H3K27:** histone H3 lysine 27; **c-Myc:** cellular Myc.

Supplementary materials

Tables S1–S5 are available with the online version of this article. Across the supplementary tables, ↑ indicates an increase or enhancement, ↓ indicates a decrease or inhibition, ↔ indicates no clear directional effect, and ↑↓ indicates context-dependent or bidirectional effects. Concentrations are reported using the units provided in the original studies, with biological compartments and analytical methods specified where available. Evidence levels follow the criteria defined in the main text: Level I, direct human administration of a chemically defined metabolite; Level II, mechanistic *in vivo* evidence with defined pathway or cell-specific perturbation; Level III, *ex vivo* or *in vitro* mechanistic evidence; and Level IV, human observational or association-based evidence. These levels indicate proximity to metabolite-specific causal inference rather than overall methodological quality or clinical strength of evidence. NR indicates not

reported and NA indicates not applicable.
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Author contributions

Zhehan Xu, Shuya Jiang, Jiaqi Li, Haoling Zhang, Xiaohong Kang, Zhi-Jing Song contributed to the manuscript writing and figure preparation; Doblin Sandai, Wangzheqi Zhang, Zui Zou supervised the work. Zhehan Xu, Shuya Jiang, Jiaqi Li, Haoling Zhang reviewed the manuscript and verified the accuracy of the figures. All authors read and approved the final manuscript.

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Competing Interests

The authors have declared that no competing interest exists.

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