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REVIEW

Gut microecology empowers cancer immunotherapy: commensal microbiota-mediated mechanisms and translational prospects of PD-1/PD-L1 therapy

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ABSTRACT Anti-programmed cell death protein 1 (PD-1) or its ligand (PD-L1) are immune checkpoint inhibitors (ICIs) that have revolutionized cancer therapy. However, the efficacy of anti-PD-1 and anti-PD-L1 is limited by resistance and inter-individual variability. In recent years increasing evidence has highlighted the pivotal role of the gut microbiota in modulating the response to PD-1/PD-L1 immunotherapy. Extensive preclinical studies have demonstrated that commensal microbes can increase the efficacy of PD-1/PD-L1 blockade through multiple mechanisms, including the production of metabolites, such as short-chain fatty acids (SCFAs), tryptophan derivatives, and extracellular polysaccharides that remodel the tumor microenvironment, as well as the activation of immune pathways involving dendritic cells, $CD8^+$ T cells, and M1 macrophages to increase antitumor immunity. Moreover, clinical studies have shown that fecal microbiota transplantation (FMT) and targeted probiotic interventions show promise for improving the response to PD-1/PD-L1 therapy, while reducing the risk of immune-related adverse events (irAEs). This review systematically explores the multifaceted regulatory roles of the commensal microbiota in PD-1/PD-L1 therapy and examines the preclinical prospects of microbiota-based personalized immunotherapeutic strategies. The integration of multiomics technologies, synthetic biology, and precise microbiota interventions may further optimize PD-1/PD-L1 immunotherapy and offer novel insights into antitumor immune modulation.

KEYWORDS Gut microbiota; immune checkpoint inhibitors; commensal microbiota; PD-1/PD-L1; fecal microbiota transplantation

Introduction

In recent years the rise in immune checkpoint inhibitors (ICIs) has reshaped the landscape of cancer therapy, bringing unprecedented hope for patients with various cancers. Programmed cell death protein 1 (PD-1) and programmed cell death ligand 1 (PD-L1) antibody therapies, which block immune-inhibitory signals in the tumor microenvironment (TME) and reactivate the antitumor functions of T cells, have shown remarkable efficacy in melanoma, non-small cell lung cancer (NSCLC), as well as other solid tumors such as renal cell carcinoma (RCC), hepatocellular carcinoma (HCC) and notably, tumors with high microsatellite instability or mismatch repair deficiency (MSI-H/dMMR). The clinical development of PD-1 inhibitors began with the KEYNOTE-001 trial (2011), which investigated pembrolizumab. The clinical prognosis of various malignancies, such as melanoma and NSCLC, has significantly improved since the approval of the first PD-1 inhibitor in 2014 with some patients even achieving long-term survival[1,2]. However, in clinical practice, approximately one-half of patients are unresponsive or quickly develop resistance to PD-1/PD-L1 therapy and some are forced to discontinue treatment because of immune-related adverse events (irAEs)[3]. These limitations highlight the complexity of tumor immune evasion mechanisms and the profound impact of the host's endogenous regulatory network on treatment outcomes. Current research focuses on understanding the biological basis of heterogeneous responses to PD-1/PD-L1 therapy. Resistance is closely related to the immune-evasive phenotypes of tumor cells, the dynamic evolution of the immunosuppressive microenvironment, and the imbalance in the systemic immune status of the host. Moreover, traditional biomarkers, such as PD-L1 expression or tumor mutation burden, have significant predictive limitations, suggesting that systemic regulatory factors from host–environment interactions may play

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a key role in determining patient response to immunotherapy. In this context, leveraging the gut microbiota, a core hub connecting host metabolism, immunity, and the external environment, has emerged as a breakthrough for improving immunotherapy[4].

The gut microbiota modulates systemic immune homeostasis through metabolites, immune signaling, and microbial–host coevolution. Emerging evidence has shown that specific commensal bacteria can increase antigen presentation, promote effector T-cell infiltration, and inhibit checkpoint-mediated exhaustion, thereby increasing PD-1/PD-L1 therapy sensitivity. In 2015 Sivan et al.[5] reported that *Bifidobacterium* colonization in melanoma mouse models significantly increased PD-L1 inhibitor efficacy, reducing the tumor volume by 80%. This finding highlights gut microbiota modulation as a new target for improving immunotherapy efficacy. Subsequent clinical cohort studies revealed that patients responsive to PD-1 inhibitors have gut microbiota rich in *Akkermansia muciniphila* (Akk) *(A. muciniphila)*, *Bifidobacterium longum* (*B. longum*), and Ruminococcaceae, whereas resistant patients often have Enterobacteriaceae[6]. Notably, fecal microbiota transplantation (FMT) of "responder microbiota" into resistant patients can restore PD-1 inhibitor sensitivity in approximately 30% of advanced melanoma patients[7]. These findings highlight the systemic regulatory role of the gut microbiota in tumor immunotherapy and provide a foundation for developing microbiota-targeted interventions, such as probiotics, microbiota transplantation, or metabolic modulation. Recent studies have shown that gut microbiota and their metabolites not only influence the efficacy of immune checkpoint inhibitors but also regulate the effectiveness and toxicity of targeted therapies by modulating signaling pathways, such as EGFR and VEGF. Specific microbial metabolites, such as butyrate and ursodeoxycholic acid, exhibit anti-tumor effects[8]. As a systemic regulatory hub, the gut microecosystem impacts cancer immunotherapy and targeted therapy, offering novel strategies for enhancing treatment outcomes and overcoming drug resistance through modulation of the intestinal microenvironment. This article comprehensively discusses the molecular mechanisms underlying gut microbiota modulation by PD-1/PD-L1 therapy and explores clinical translational paths to optimize cancer immunotherapy.

Gut microbiota and immune system

The gut microbiota constitutes a complex ecosystem comprising bacteria, viruses, fungi, and archaea with a biomass reaching 10^{14}, which far exceeds the total number of host cells colonizing the intestinal mucosal surface to form a dynamically balanced "microbial organ"[9]. Within this vast community, the gut symbiotic microbiota, as mutualistic entities, have co-evolved with the host through long-term coevolution, transcending the biological definition of a mere microbial assemblage. The gut symbiotic microbiota fundamentally represents a "metabolic–immune functional unit" that is jointly shaped through host–microbe co-evolution. These microbial communities establish highly structured biogeographical distributions along the intestinal mucosa through genome-encoded ecological adaptation mechanisms (e.g., carbohydrate-active enzyme systems and bile acid transformation enzymes). Strictly anaerobic Bacteroidetes and Firmicutes dominate in the oxygen gradient spanning from the intestinal lumen-to-the crypts, forming stable nutritional networks through metabolic cross-feeding. These networks convert host-indigestible dietary components into immunomodulatory metabolites[10]. This metabolic transformation exhibits marked ecologic niche specificity, in which mucosa-adherent symbionts preferentially degrade mucin glycoproteins, whereas luminal planktonic microbiota primarily ferment dietary fibres. The resulting metabolites, including short-chain fatty acids (SCFAs) and tryptophan derivatives, establish spatially graded concentration profiles that generate differential immune-regulatory signals.

SCFAs bidirectionally regulate regulatory T-cell (Treg) differentiation and effector T-cell function through histone deacetylase (HDAC) inhibition and G protein-coupled receptor (e.g., GPR43) activation. Moreover, tryptophan metabolites dynamically balance T helper 17 (Th17)/Treg polarization *via* aryl hydrocarbon receptor (AHR) signaling, creating a precise regulatory interface between immune tolerance and activation[11]. This spatiotemporal dynamic of the metabolic–immune axis is particularly critical in anti-PD-1 therapy. The symbiotic microbiota increases dendritic cell antigen presentation efficiency through metabolic reprogramming, promotes $CD8^+$ T-cell mitochondrial metabolism while delaying exhaustion phenotypes, and concurrently suppresses excessive expression of immune checkpoint molecules (e.g., PD-L1)[12]. Clinical evidence has demonstrated that dysbiosis-induced metabolite imbalance (e.g., reduced SCFAs and accumulated secondary bile acids) significantly reduces PD-1 inhibitor efficacy, whereas specific microbial signatures restore T-cell anti-tumor activity through epigenetic remodeling of the TME[13]. This ecologic plasticity of the microbiota–immune network provides a theoretical foundation for the development of microbiota-directed intervention strategies (**Figure 1**).

Preclinical evidence for commensal bacteria increasing PD-1/PD-L1 immunotherapy efficacy

Akk: a key microbe in gut mucosal homeostasis and cancer immunotherapy

Akk, a member of the Verrucomicrobia phylum, is a core symbiont in the gut mucus layer. Akk promotes gut

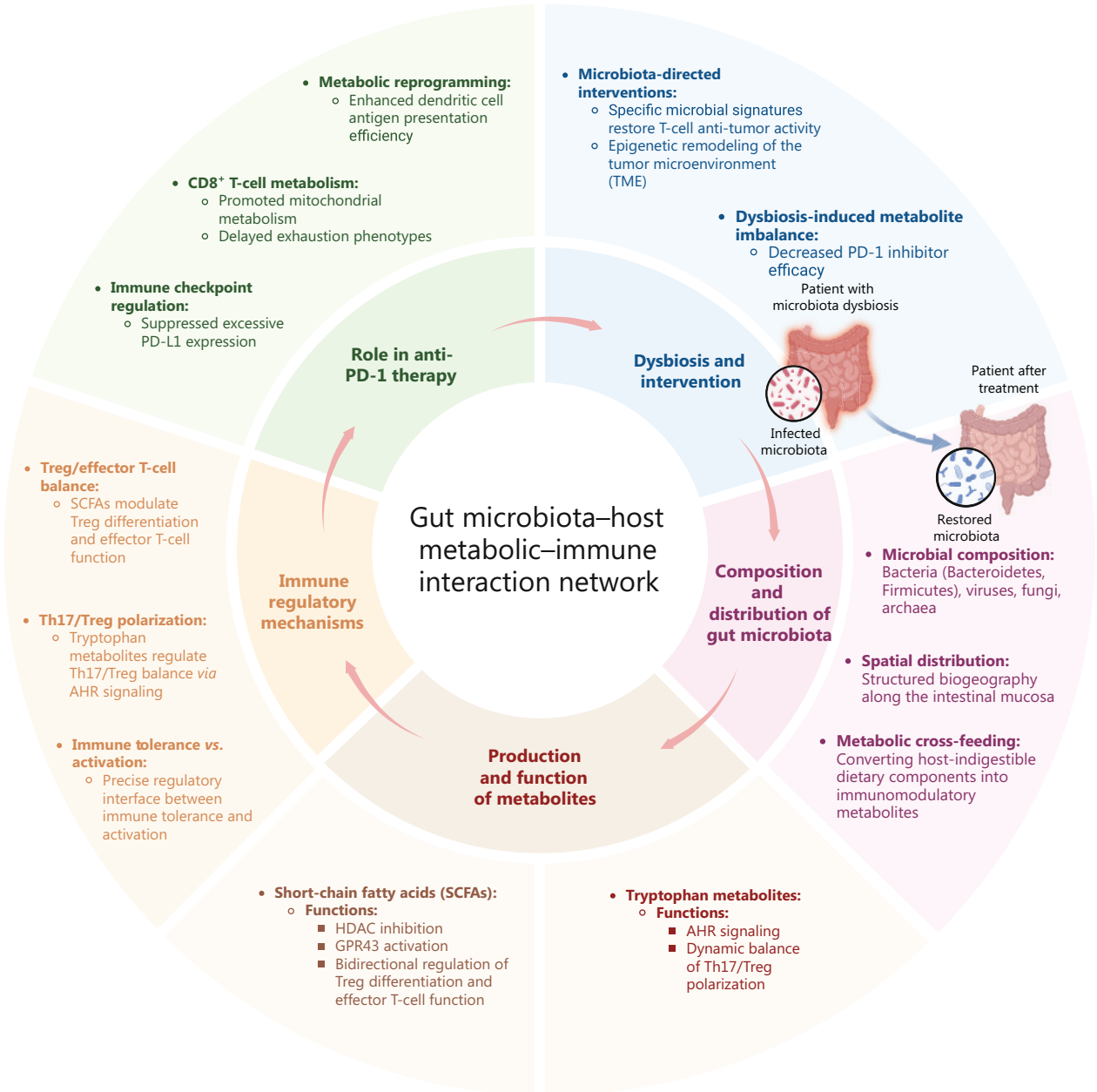


Figure 1 Gut microbiota–host metabolic–immune interaction network. This schematic illustrates the bidirectional crosstalk between the gut microbiota and host immunity that underpins the efficacy of PD-1-based cancer therapy. Microbes residing along the intestinal mucosa convert dietary fibres and mucins into immunomodulatory metabolites (SCFAs and tryptophan derivatives) that shape T-cell fate *via* HDAC inhibition, GPR43 activation, and AHR signaling. These metabolites establish spatially graded immune-regulatory signals, enhancing dendritic cell antigen presentation, promoting CD8⁺ T-cell mitochondrial fitness, and restraining PD-L1 expression. Dysbiosis-induced metabolite imbalance dampens anti-tumor immunity, while targeted nutritional or engineered microbial interventions restore the metabolic–immune axis, offering a programmable route to precision cancer immunotherapy. Created in BioRender. https://BioRender.com/xewsbgx.

barrier integrity by degrading mucin and modulating the host immune system through metabolites[14,15]. Live Akk activates MHC-II-dependent plasmacytoid dendritic cell (pDC) pathways, thereby increasing antitumor T-cell responses and downregulates PD-L1 in tumor cells to counteract immune checkpoint inhibition[16]. Akk with *Lactobacillus johnsonii* increased anti-PD-L1 therapy sensitivity by promoting Th1 responses and increasing the number of tumor-infiltrating T

cells in a colitis-associated colorectal cancer (CRC) model[17]. Routy et al.[18] demonstrated that Akk supplementation drives $CCR9^+CXCR3^+CD4^+$ T-cell homing to tumors through IL-12-dependent signals *via* FMT, restoring anti-PD-1 therapy efficacy in resistant CRC models.

Studies across cancer types have revealed both common and distinct mechanisms by which Akk modulates PD-1/PD-L1 therapy. Vancomycin-enriched Akk enhances $CD8^+$ T-cell function *via* glycerophospholipid metabolism in microsatellite-stable (MSS) CRC models, sustaining PD-1 antibody efficacy[19]. Zhu et al.[20] reported that live Akk blocks the CXCL3-PD-L1 axis in CRC by downregulating CXCL3 in Bgn^+Dcn^+ CAFs, reversing T-cell exhaustion. Akk reduces serum lipopolysaccharide (LPS) and pro-carcinogenic bile acids in metabolic-associated fatty liver disease (MAFLD) mice with HCC, decreasing myeloid-derived suppressor cell (m-MDSC) and M2 macrophage infiltration[21]. Lan et al.[16] reported that Akk-induced bile acid reprogramming elevates serum tauroursodeoxycholate (TUDCA), increasing PD-1 antibody efficacy in HCC by antagonizing immune suppression and downregulating tumor PD-L1. Akk maintains gut barrier function through mucin degradation and mucus layer renewal, preventing pathogen and pro-carcinogenic substance leakage. Akk repairs epithelial tight junctions in MAFLD-HCC models, lowering serum LPS and inhibiting hepatic inflammation and immunosuppressive cell recruitment[21]. Akk with *Lactobacillus johnsonii* synergistically reduces gut inflammation and inhibits macrophage hyperactivation in colitis-associated CRC models, maintaining barrier homeostasis and blocking the inflammation–cancer transition[17]. Overall, Akk enhances PD-1 therapy responses by modulating immune cells and the microbe–metabolite–immune axis and protecting mucosal barriers.

Bifidobacterium: a key genus in the gut microbiota with anticancer potential

Gut microbiota, particularly *Bifidobacterium* from Actinobacteria, ferment carbohydrates to produce lactic acid and SCFAs, maintaining gut acidity, inhibiting pathogens, and promoting vitamin synthesis, mineral absorption, and immune regulation[22].

Different *Bifidobacterium* strains have distinct roles in cancer immunotherapy. *B. longum* 420 with anti-PD-1 increases *Lactobacillus* (*Lacto.*) levels in RCC models, delivers wild type 1 (WT1) tumor antigen, activates antitumor immunity, and improves survival in mice[23]. *B. longum* RAPO with anti-PD-1 increases the number of tumor-infiltrating NK cells and $CD8^+$/$CD4^+$ T cells in breast cancer models, inhibits M2 macrophage polarization, and reduces the tumor burden[24]. *Bifidobacterium infantis* modulates PD-L1 to enhance Treg function *via* the PI3K–Akt–mTOR pathway[25]. *Bifidobacterium* colonization directly activates antitumor T cells through antigen cross-reactivity and the SVY epitope of *Bifidobacterium breve* cross-reacts with the tumor neoantigen, SIY, promoting melanoma recognition and extending survival[26]. Responders have *B. longum*-rich gut microbiota in metastatic melanoma patients and FMT in germ-free mice increases anti-PD-L1 efficacy and enhances T-cell responses, confirming the role of the symbiotic microbiota in human antitumor immunity[27]. These studies showed that *Bifidobacterium* enhances PD-1 therapy through microbiota modulation and direct immune cell interactions.

The microbiota–metabolite–immune network provides a mechanistic basis for the therapeutic efficacy of *Bifidobacterium* in modulating antitumor immunity. *Bifidobacterium pseudolongum*-derived inosine activates T cells *via* the adenosine A2A receptor, systemically translocates post-immunotherapy-induced gut barrier permeability, and improves PD-1 responses in melanoma and CRC models[28]. *Bifidobacterium bifidum* increases interferon-gamma (IFN-γ) signaling, synergizing with anti-PD-1 therapy or oxaliplatin in NSCLC[29]. These metabolite-driven pathways underpin personalized microbiota interventions. *B. longum* RAPO increases beneficial *Bifidobacterium* and *Clostridium*, reduces pathogenic *Mucispirillum*, maintains barrier integrity, and increases anti-PD-1 efficacy in triple-negative breast cancer[24]. High-salt diets increase *Bifidobacterium* abundance and gut permeability, promoting bacterial migration to the TME and activating NK cell-mediated immunity[30]. This microbiota–barrier–immune regulatory network supports the use of FMT or specific probiotics to repair mucosal damage and optimize immunotherapy responses.

Lactobacillus: gut commensals with antitumor and immunotherapeutic potential in CRC

Recent studies have shown that *Lactobacillus* (Firmicutes) in the gut microbiota significantly increases the efficacy of PD-1 immunotherapy through metabolite–immune regulatory networks. Key species, such as *L. johnsonii*, *L. gasseri*, and *L. rhamnosus*, activate immune responses *via* metabolites or cellular components. This bacterial genus lowers the gut pH to inhibit pathogens, strengthens the gut barrier through epithelial adhesion, and offers multidimensional immune regulation *via* strain-specific mechanisms[31].

Lactobacillus reshapes the tumor immune microenvironment. *L. johnsonii* increases $CD8^+$ T-cell infiltration in CRC models[32]. *L. rhamnosus* LR-DNA upregulates PD-L1 in enterocytes, inducing Th2 cell apoptosis and reducing Th2-related cytokines by 40%[33]. *L. casei* increases IFN-γ and granzyme B expression in tumors, increasing CRC $CD8^+$ T-cell infiltration 1.5-fold[34]. *Lactobacillus kefiranofaciens ZW18* elevates Akk and Prevotellaceae, achieving a 66.16% anti-PD-1 response in melanoma[35]. *Paracasei sh2020* increases anti-PD-1 sensitivity in triple-negative breast cancer by recruiting $CD8^+$ T cells *via* CXCL10 upregulation[36].

Different strains of commensal bacteria influence specific immune cells through metabolic networks. *L. johnsonii* and *Clostridium sporogenes*-derived indole-3-propionic acid (IPA) increase Tcf7 acetylation in $CD8^+$ T cells in CRC, promoting Tpex cell formation and increasing the anti-PD-1 response rate by 57%[37]. Indole-3-lactic acid (ILA) from *L. gasseri* induces CRC cell apoptosis[38]. Indole-3-carboxylic acid (ICA) from *L. gasseri* blocks the IDO1/Kyn/AHR axis, preventing Treg differentiation and increasing anti-PD-1 efficacy 3.2- and 2.8-fold in MC38 and CT26 models, respectively[39]. Indole-3-aldehyde (I3A) from *L. reuteri* activates $CD8^+$ T-cell AHR signaling in melanoma, increasing IFN-γ secretion. The objective response rate increases from 35%–62% in combination with PD-1 antibodies[40]. EPS-R1 from *L. delbrueckii* induces $CCR6^+$ $CD8^+$ T-cell infiltration in Peyer's patches, doubling tumor regression rates in anti-PD-1 combination therapy[41]. *L. rhamnosus* Probio-M9 increases α-ketoglutarate and pyridoxine levels, activating CTLs and suppressing Tregs, shrinking tumors by 48% and enhancing anti-PD-1 responses across CRC, melanoma, and breast cancer[42]. Tryptophan metabolites from *L. reuteri* reprogram $CD4^+$ T cells into DP IELs *via* AHR signaling, supporting mucosal immunity in CRC and melanoma[43]. *L. rhamnosus* GG induces DC type I IFN production through the cGAS/STING pathway, improving $CD8^+$ T-cell cross-presentation efficiency by 60% in CRC and melanoma[44].

Mucosal barrier protection is crucial. ILA from *L. gasseri* restores tight junction proteins, reducing pathogenic bacteria by 68% in CRC models[38]. *L. rhamnosus* Probio-M9 restores antibiotic-damaged microbial α diversity to 80% while increasing α-ketoglutarate and pyridoxine levels, which enhances anti-PD-1 responses in CRC and breast cancer[42,45]. This synergy between barrier repair and immune metabolism paves the way for personalized microbiota-based immunotherapy strategies.

Other bacteria

The gut microbiota modulates the efficacy of ICIs, such as PD-1/PD-L1 antibodies, *via* specific taxa and metabolites with significant effects on CRC and other solid tumors. Key bacteria include *Fusobacterium nucleatum* (Fn) *(F. nucleatum)*, *Faecalibacterium prausnitzii (F. prausnitzii)*, Lachnospiraceae (Lachno.) members (e.g., *Ruminococcus* and *Blautia*), and *Roseburia intestinalis (R. intestinalis)*, which directly or indirectly influence $CD8^+$ T-cell function. However, some bacterial species, such as *Enterococcus faecalis (E. faecalis)*, can metabolize phenylalanine to produce phenylacetylglutamine (PAGln), which inhibits the secretion of IFN-γ and TNF-α in $CD8^+$ T cells, promotes T cell exhaustion, and thereby significantly undermines the efficacy of anti-PD-1 therapy[46].

F. prausnitzii colonization mitigates gut toxicity and enhances antitumor effects in ICI-induced colitis models by inhibiting myeloid cell infiltration and inflammation[47]. *Clostridium* strains, such as *F. prausnitzii*, can directly activate tumor-infiltrating $CD8^+$ T cells in CRC and melanoma models, independent of PD-1 antibodies, indicating superiority over anti-PD-1 monotherapy[48]. These findings suggest that the microbiota can overcome PD-1 resistance by remodeling the immune microenvironment.

The microbiota–metabolite–immune axis has diverse yet convergent mechanisms across cancer types. Intratumoral enrichment of Fn causes butyrate accumulation in MSS CRCs, inhibiting $CD8^+$ T-cell HDAC3/8 and inducing Tbx21 promoter H3K27 acetylation, reversing T-cell exhaustion and enhancing effector function[49]. *R. intestinalis*-derived butyrate activates NF-κB signaling in microsatellite instability (MSI)-high CRC and MC38 models among $CD8^+$ T cells *via* TLR5, promoting granzyme B, IFN-γ, and TNF-α secretion and improving anti-PD-1 sensitivity in MSI-low CRC[50]. *Lachnospiraceae* members degrade lysophosphatidylcholine in the TME to relieve $CD8^+$ T-cell activation inhibition, suppressing CRC progression in immune-competent mice[51]. The anti-inflammatory effects of *F. prausnitzii*, which are mediated by SCFAs, inhibit pro-inflammatory cytokines (e.g., IL-6 and TNF-α) and balance Th17/Treg cells, reducing ICI-related colitis and increasing antitumor immunity[47]. These metabolic interventions focus on $CD8^+$ T-cell reshaping, indicating that microbiota metabolites may form synergistic networks *via* epigenetic modification, receptor signaling, or microenvironment remodeling.

Mucosal barrier protection is crucial for increasing PD-1 efficacy. *R. intestinalis* improves gut permeability by increasing tight junction protein (e.g., occludin and ZO-1) expression and *R. intestinalis* metabolite butyrate activates $CD8^+$ T cells and maintains epithelial integrity to prevent bacterial translocation, inhibiting tumorigenesis in *ApcMin/*$^+$ and AOM-induced CRC models[50]. *F. prausnitzii* increases gut microbial α diversity, increasing beneficial bacteria (e.g., *Lactobacillus*) and reducing pathogens (e.g., *Enterococcus*), repairing the intestinal mucosa in NSG mouse humanized models and alleviating ICI-related gut toxicity[47]. Overall, the microbiota enhances immunotherapy through dual metabolic–immune and mucosal barrier mechanisms, offering multitarget strategies for optimizing cancer treatment.

Emerging players: YB328, *Alistipes*, and fungal consortia

With recent research advances emerging roles of the microbiota are continuously being discovered and studied, particularly demonstrating remarkable potential in cancer immunotherapy. The gut microbiota, including both bacteria and fungi, has been confirmed to regulate the host immune system through multiple mechanisms, influencing the efficacy of ICIs. The gut microbiota are involved in the activation and migration of dendritic cells and the recruitment and functional

regulation of T cells but also shapes the TME through metabolites, offering new strategies to overcome immunotherapy resistance. Three representative microorganisms will be introduced below to systematically elaborate specific mechanisms in enhancing PD-1 therapy efficacy.

Alistipes finegoldii, a gram-negative anaerobic bacterium, has been shown to be significantly enriched in the gut of responders to immunotherapy across multiple studies. This bacterium secretes the lipoprotein, LIPOAF, which binds to Toll-like receptor 2 (TLR2), activating the NF-κB signaling pathway and thereby enhancing the expression of CXCL16 in $CCR7^+$ conventional dendritic cells. Subsequently, CXCL16 acts as a key chemokine to effectively recruit CXCR6-expressing $CD8^+$ T cells into the TME, significantly improving the sensitivity to anti-PD-1 therapy and inhibiting tumor growth[52]. In contrast, the newly identified strain *Hominenteromicrobium mulieris* YB328 (belonging to the Clostridiaceae family) also demonstrates promising immunomodulatory potential. This bacterium promotes the maturation and migration of $CD103^+CD11b^-$ conventional dendritic cells through the TLR7/9–MYD88–mTOR–STAT3 signaling axis. These activated dendritic cells further migrate to tumor-draining lymph nodes and the TME, facilitating the activation of tumor antigen-specific $CD8^+$ T cells and upregulating PD-1 expression, ultimately leading to a 3-fold improvement in anti-PD-1 efficacy in NSCLC and gastric cancer (GC)[53]. In addition, the composition of the fungal community has also been shown to be closely associated with the immunotherapy response. Recent studies have classified patients into "favorable-type" and "unfavorable-type" enterotypes based on the gut mycobiome with a high Basidiomycota ratio correlated with a better treatment response. This enterotype not only exhibits higher microbial α diversity but is also enriched with butyrate-producing bacteria and displays active butyric acid and sugar metabolism pathways. Further research has indicated that this enterotype promotes $CD8^+$ T cell infiltration in tumors and the potential to enhance anti-PD-1 therapy sensitivity has been validated through FMT experiments[54]. These emerging gut microbiota, including *Alistipes finegoldii*, *Hominenteromicrobium mulieris* YB328, and specific fungal enterotypes, significantly enhances the efficacy of anti-PD-1 therapy through distinct immune and metabolic mechanisms. These mechanisms involve the activation and migration of dendritic cells, the recruitment and functional regulation of $CD8^+$ T cells, and the immunomodulatory effects of microbial metabolites, such as butyrate. These findings not only deepen the understanding of microbe-immune interactions but also provide a critical foundation for developing microbiota-based adjuvant strategies, such as using specific bacterial strains or fungal enterotypes for patient stratification or combination interventions, thereby expanding the population benefiting from immunotherapy (**Table 1**, **Figure 2**).

Commensal bacteria for increased PD-1/PD-L1 immunotherapy efficacy: clinical studies

The correlation between the gut microbiota and response to PD-1/PD-L1 therapy

The link between the gut microbiota and the efficacy of PD-1/PD-L1 inhibitors has been verified in multiple cancer clinical studies. Responding patients have gut microbiota with high α diversity at the microbial composition level, including Akk[21,55], which repairs the gut barrier, reduces serum LPS and m-MDSC infiltration, and significantly increases anti-PD-1 efficacy, prolonging progression-free survival[18,21]. *Campylobacter jejuni* inhibits $CD4^+$ Tem cell recruitment in colon cancer mucosa, accelerating immune evasion and increasing disease progression risk[56]. Cross-cohort analyses have shown that Lachnospiraceae/Ruminococcaceae in Firmicutes produce SCFAs to activate dendritic cells, enhance $CD8^+$ T-cell function, and improve 1-year survival rates[57]. The abundance of TANB77 phylotype pilin-encoding genes is directly related to PD-1 treatment response[58]. Metabolomic evidence has indicated that PAGln weakens PD-1 efficacy by interfering with T-cell activation pathways[46]. *Lactobacillus* and *Bifidobacterium* modulate bile acid metabolism to inhibit immunosuppressive factors, such as IL-10, increasing disease control rates to 80%[59,60]. Dynamic monitoring has shown that the baseline Ruminococcaceae abundance is positively correlated with 12-month progression-free survival with persistence extending the median survival to 14.8 months[61]. Cancer-specific studies further revealed that high *Lactobacillus* abundance in gastric cancer doubles the objective response rate to anti-PD-1 therapy[60]. Elevated serum galactonic acid levels predict better immune therapy responses in HCC (AUC = 0.793)[62]. Amino acid metabolism-related microbial patterns increase clinical remission rates in ovarian cancer by promoting T/B-cell clonal expansion[63]. Machine learning integrating strain-specific single nucleotide polymorphisms (SNPs) (e.g., the Ala168Val variant in *Phocaeicola dorei*) and metabolomics data distinguishes baseline responders for predictive models with > 90% accuracy[64]. Overall, the gut microbiota dynamically shapes PD-1 treatment outcomes through metabolic reprogramming and immune cell regulation, offering new paradigms for precision immunotherapy as a biomarker and modulatory target. Indeed, the microbiome can serve as a biomarker for personalized immunotherapy.

The microbiome as a biomarker for personalized immunotherapy

Recent studies have established the core role of the gut microbiota in predicting the efficacy of PD-1/PD-L1 immunotherapy. Zhu et al.[46] identified microbial and metabolic

features linked to treatment response in 165 patients using multiomics analysis and reported that the metabolite, PAGln, significantly suppressed PD-1 efficacy. Similarly, a species co-abundance network was constructed using metagenomic data from NSCLC patients and a TOPOSCORE system that combines resistance-related microbiota (SIG1) and sensitive microbiota (SIG2) was proposed. The predictive power of this system has been validated across multiple cancer cohorts[65]. Recently, the TOPOSCORE system has been further enhanced by incorporating strain-specific SNP information (e.g., *Phocaeicola dorei* Ala168Val) and metabolomics data, achieving a prediction accuracy of 89% in a pan-cancer cohort. This improvement has been supported by a clinical trial (NCT03686202), a randomized study evaluating MET4, which is a microbial ecosystem therapy based on responsive bacterial consortia in combination with PD-1 inhibitors. Interim analysis of this trial indicated that MET4 treatment exhibited a favorable safety profile with only a small number of patients experiencing low-grade adverse events. Patients in the MET4 group showed significantly higher relative abundance and colonization levels of relevant bacteria, such as *Bifidobacterium*, *Collinsella*, and *Enterococcus*, compared to

Table 1 Key bacterial strains in preclinical research and their mechanism of action

Microbes	Cancer type	Key mechanism	Reference
Akk	CRC	Activates MHC-II-dependent plasmacytoid dendritic cell (pDC) pathway; synergizes with *L. johnsonii* to enhance Th1 response and anti-PD-L1	Hua et al. (2025)[17]
Akk	MSS-CRC	Activates glycerophospholipid metabolism, enhances $CD8^+$ T-cell function for PD-1 efficacy	Xu et al. (2020)[19]
Akk	HCC	Reprograms bile acid metabolism (↑TUDCA), downregulates PD-L1, increases $CD8^+$ T-cell cytotoxicity	Lan et al. (2024)[16]
Akk	CRC	Drives $CCR9^+CXCR3^+CD4^+$ T-cell homing *via* IL-12, restoring Anti-PD-1 therapy	Routy et al. (2018)[18]
Akk	CRC	Blocks CXCL3-PD-L1 axis in CAFs, reverses T-cell exhaustion	Zhu et al. (2024)[20]
B. longum 420	RCC	Delivers WT1 antigen; synergizes with anti-PD-1 to improve survival	Ueki et al. (2023)[23]
B. longum RAPO	Breast cancer	↑NK/$CD8^+$/$CD4^+$ T cells, ↓M2 macrophages, reduces tumor burden	Kim et al. (2021)[24]
B. breve	Melanoma	Cross-reactive SVY-SIY epitope promotes T-cell recognition and survival	Bessell et al. (2020)[26]
B. pseudolongum	Melanoma, CRC	Inosine activates T cells *via* A2AR, enhances PD-1 response	Mager et al. (2020)[28]
B. bifidum	NSCLC	↑IFN-γ signaling, synergizes with anti-PD-1 therapy or oxaliplatin	Lee et al. (2021)[29]
L. johnsonii	CRC	↑$CD8^+$ T cells; IPA production with *C. sporogenes* improves anti-PD-1 response	Jia et al. (2024)[37]
L. gasseri	CRC	Secretes ILA (apoptosis); inhibits IDO1/Kyn/AHR axis to block Tregs	Sugimura et al. (2022)[38]
L. rhamnosus LR-DNA	CRC	↑PD-L1 on epithelium, induces Th2 apoptosis, ↓Th2 cytokines	Song et al. (2025)[33]
L. reuteri	Melanoma	I3A activates AhR in $CD8^+$ T cells, ↑IFN-γ, improves PD-1 ORR	Bender et al. (2023)[40]
L. casei	CRC	Stimulates IFN-γ/granzyme B, ↑$CD8^+$ T-cell infiltration	Aindelis et al. (2020)[34]
L. delbrueckii EPS-R1	Melanoma	EPS induces the generation of $CCR6^+$ $CD8^+$ T cells, increases the number of anti-CTLA-4/PD-1 cells	Kawanabe-Matsuda et al. (2022)[41]
F. nucleatum	CRC	Butyrate inhibits HDAC3/8 to reverse T-cell exhaustion, ↓PD-1	Wang et al. (2024)[49]
F. prausnitzii	CRC	SCFAs ↓IL-6/TNF-α, balance Th17/Treg, alleviate ICI colitis	Gao et al. (2023)[47]
R. intestinalis	CRC	Butyrate-TLR5 activates NF-κB, ↑granzyme B/IFN-γ/TNF-α, ↑PD-1 sensitivity	Kang et al. (2023)[50]
Ruminococcus/Blautia	CRC	Degrades lyso-glycerophospholipids in TME, relieves $CD8^+$ T-cell suppression	Zhang et al. (2023)[51]

Table 1 Continued

Microbes	Cancer type	Key mechanism	Reference
Clostridium spp.	CRC, melanoma	Directly activates $CD8^+$ T cells, suppresses tumors independent of PD-1	Montalban-Arques et al. (2021)[48]
Alistipes finegoldii	CRC, NSCLC	LIPOAF binds TLR2→activates NF-κB→↑CXCL16 in DCs→recruits $CXCR6^+CD8^+$ T cells to TME	Wu et al. (2025)[52]
Hominenteromicrobium mulieris YB328	NSCLC, GC	TLR7/9→MYD88/mTOR/STAT3→matures $CD103^+CD11b^-$ DCs→activates $CD8^+$ T cells→↑PD-1 expression	Lin et al. (2025)[53]
Fungal Enterotype (high *Basidiomycota* ratio)	Pan-cancer	Enriches butyrate producers→activates metabolism→↑$CD8^+$ infiltration→FMT↑PD-1 sensitivity	Hu et al. (2025)[54]
E. faecalis	CRC	Produces PAGln → ↓$CD8^+$ T cell activation/cytokine (IFN-γ, TNF-α) → ↑T-cell exhaustion → ↓anti-PD-1 efficacy	Zhu et al. (2025)[46]

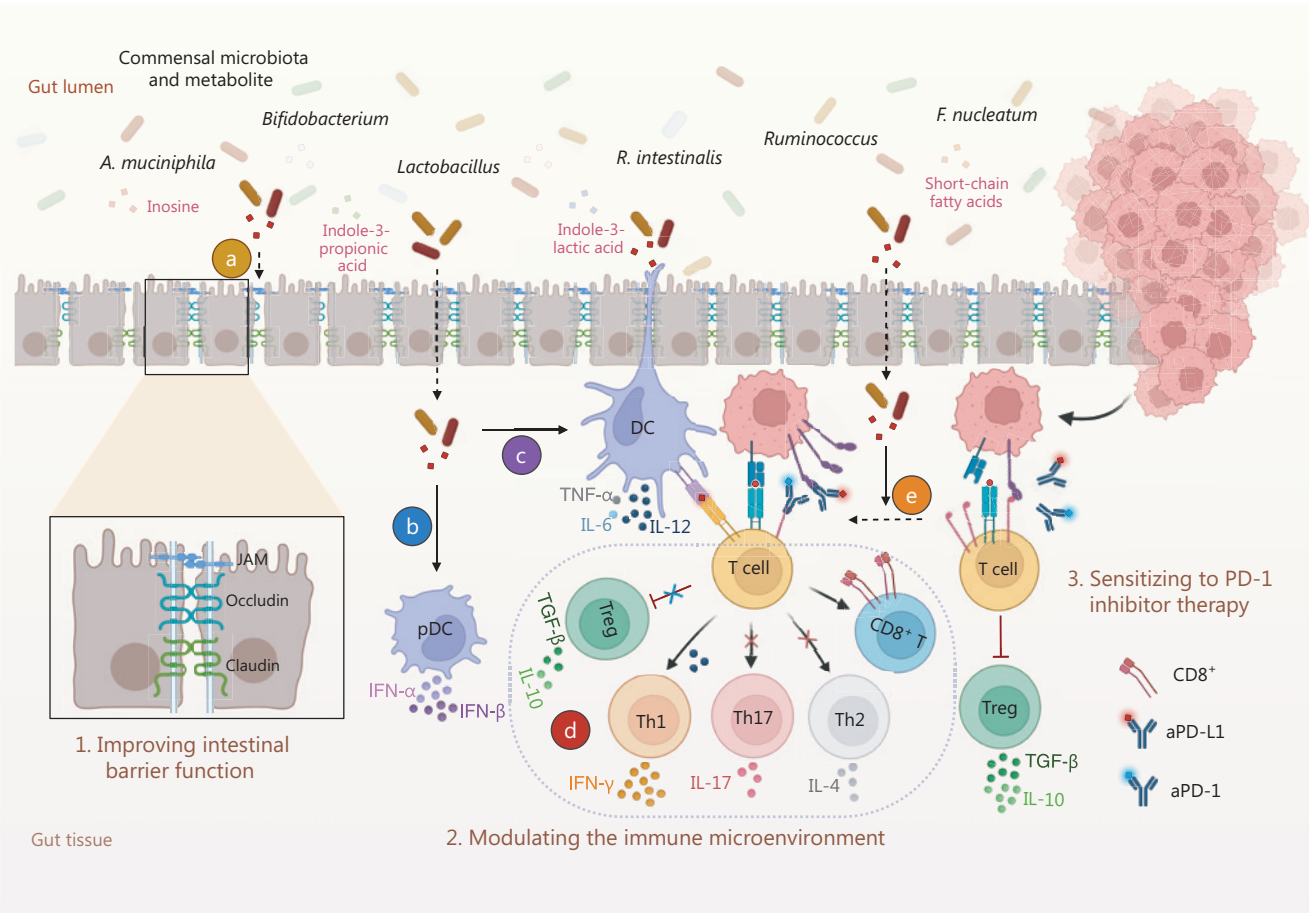


Figure 2 Core mechanisms by which the gut commensal microbiota and their metabolites increase anti-PD-1/PD-L1 efficacy. Improving intestinal mucosal barrier function and enhancing immune cell responses against tumors. Gut commensal microbiota, such as *A. muciniphila*, *Bifidobacterium*, *Lactobacillus*, *R. intestinalis*, and *F. nucleatum*, and their metabolites, such as inosine, indole-3-propionic acid, and SCFAs, enhance the efficacy of PD-1 therapy through three primary pathways: 1. Improving intestinal barrier function (a): Maintenance of barrier integrity: Maintaining intestinal barrier function and an anti-inflammatory environment, a process involving the stable expression of key tight junction proteins, such as JAM, occludin, and claudin. 2. Modulating the immune microenvironment (b–d): b. Activation of pDCs: Activating

pDCs and promoting the secretion of IFN-α and IFN-β, (c) Amplification of $CD8^+$ T-cell responses by DCs: Stimulating immune cells, like dendritic cells in the gut, to upregulate the production of IL-12, thereby enhancing the tumor-killing function of peripheral memory $CD8^+$ T cells; concurrently inhibiting pro-inflammatory factors, such as IL-6 and TNF-α, to alleviate tumor-associated immunosuppression. (d) Modulation of T-cell responses: Activating the Th1-type immune response, promoting the secretion of IL-12 and IFN-γ, which in turn enhances the infiltration capacity of $CD8^+$ T cells into tumor tissue; also inhibiting Th17 and Th2 cells and the release of related pro-inflammatory factors (e.g., IL-17 and IL-4), while simultaneously suppressing the differentiation of Tregs and reducing the levels of immunosuppressive cytokines, like IL-10 and TGF-β, in the tumor microenvironment, thereby creating favorable conditions for anti-PD-1/PD-L1 therapy. 3. Sensitizing to PD-1 inhibitor therapy (e): Potentiation of checkpoint blockade therapy: Upregulating the expression of PD-L1 on the surface of tumor cells, thereby improving the ability of antibody to recognize tumor antigens and significantly increasing the durability of anti-PD-1/PD-L1 treatment. Created in BioRender. https://BioRender.com/xewsbgx.

the control group with a reduced risk of microbial diversity loss. These findings suggest that targeted microbial interventions can safely and effectively enhance the predictive and regulatory functions of microbial biomarkers[66]. Notably, the abundance of Akk, a key symbiotic bacterium, has been consistently associated with treatment efficacy across various cancers. Reduced Akk is linked to PD-1 resistance in MAFLD-HCC patients, while supplementation can restore gut barriers and reduce the number of immunosuppressive cells, such as monocytic m-MDSCs[21]. Derosa et al.[67] and Yin et al.[68] confirmed baseline enrichment of Akk or a significant correlation of the Verrucomicrobiaceae family with the objective response and survival rates independent of PD-L1 expression in NSCLC and thoracic tumor patients. It is noteworthy that the gut microbiota influences the response to immunotherapy in CRC and is closely associated with molecular subtypes of the tumor. For example, anti-PD-1/PD-L1 antibodies exhibit significant efficacy in MSI-H/dMMR CRC but perform poorly in MSS/pMMR patients, highlighting the importance of the microbiota as a predictive biomarker and potential therapeutic target[69]. These studies suggest that single strains, such as Akk, and multispecies interaction networks serve as dynamic biomarkers for clinical stratification.

Further research highlights the significant impact of microbial functional heterogeneity and cross-domain interactions on immunotherapy responses. A cross-cancer cohort analysis revealed that microbial features, including bacteria (*Faecalibacterium prausnitzii*), fungi (*Nemania serpens*), and viruses, are associated with ICI responses. A random forest model built on these features performed well for melanoma, NSCLC, and RCC [area under the receiver operating characteristic curve (AUROC) = 72.27%–89.58%][70]. Furthermore, the mycobiotic enterotype has been proposed as a novel classification method for selecting FMT donors. Donors with a "favourable" mycobiotic profile were associated with a 65% increase in the response rate to immunotherapy among melanoma patients[54]. Macandog et al.[71] reported that complete responders have more stable gut microbial functions and identified flagellin-related peptides from Lachnospiraceae through longitudinal studies that activate $CD8^+$ T cells, suggesting that antigen mimicry from microbes may increase anti-tumor immunity. Strain-level analysis improves prediction accuracy with strain-specific functional features (rather than species abundance), which significantly improve the prediction of ICI responses in rare cancers. However, cross-cohort validity depends on consistent treatment regimens, implying that microbial diagnostics should be optimized in conjunction with treatment strategies[72]. In addition, Zhang et al.[73] reported that the abundance of specific gut genera in mesothelioma is positively correlated with $CD8^+$ T-cell infiltration but negatively correlated with tumor genomic instability, indicating that the microbiota can increase treatment sensitivity by modulating the TME.

In terms of clinical translation, microbial biomarkers are transitioning from basic research to application. TOPOSCORE has been converted into a quantitative real-time polymerase chain reaction (qPCR) scoring system based on 21 bacterial probes and validated for generalizability in CRC and melanoma[65]. It is also noteworthy that a study based on the NCT03686202 trial revealed that patients who developed irAEs exhibited higher pre-treatment IgG reactivity to autoantigens and steroid treatment reduced the IgG levels. This finding implied a close relationship between microbiome-immune interactions and the mechanisms underlying irAEs[74]. Usyk et al.[75] reported that the gut microbiota predict the risk of irAEs in melanoma patients based on metagenomic and metatranscriptomic analyses with a nearly 7-fold increase in the risk of irAEs associated with high-risk microbiota, such as *Bacteroides dorei*. Attention must be paid to the establishment of standardized donor screening protocols, which is crucial for controlling irAE risk. Proactively excluding carriers of high-risk microorganisms, such as *Bacteroides dorei*, through prospective microbial detection can significantly enhance treatment safety and the applicability of interventional strategies. However, challenges remain. Combining PD-L1 expression with TME stratification [e.g., tumor infiltrating lymphocyte (TIL) status] requires integrated microbial features to increase the prediction accuracy[76]. Treatment regimen dependence may limit the generalizability of microbial biomarkers[72]. Currently, donor screening still lacks unified standards and the sensitivity and specificity of detection methods require further optimization. Overall, the gut microbiota influences PD-1/PD-L1 efficacy

through multidimensional mechanisms, including species abundance, metabolites, functional pathways, and cross-domain interactions. The potential of the gut microbiota as a dynamic biomarker is well-established, but heterogeneity, complex host–microbe interactions, and treatment specificity require further exploration for precise intervention.

Probiotic intervention in clinical studies

The critical role of the gut microbiota in modulating anti-PD-1/PD-L1 therapy efficacy is underscored by clinical evidence demonstrating that antibiotic-induced disruption of commensal microbial communities impairs therapeutic outcomes. For example, vancomycin pre-treatment in melanoma patients receiving anti-PD-1 therapy not only depleted gut microbial diversity but also compromised systemic immune activation, leading to suboptimal responses despite subsequent administration of a spore-based probiotic[77]. This phenomenon aligns with broader observations that broad-spectrum antibiotics diminish the abundance of immunostimulatory taxa, such as Ruminococcaceae and *Bifidobacterium*, which are essential for priming cytotoxic T-cell responses and sustaining antitumor immunity. In contrast, FMT has emerged as a clinically viable strategy to reconstitute a favourable microbial ecosystem and reverse resistance to anti-PD-1 therapy. A pivotal study in 13 PD-1-refractory advanced solid tumor patients demonstrated that FMT from PD-1 responder donors combined with anti-PD-1 rechallenge induced durable microbial shifts in 46.2% of cases, accompanied by clinical benefits, including partial response (7.7%) and disease stabilization (38.5%)[78]. Longitudinal analyses revealed that responders presented increased systemic levels of cytotoxic T cells and pro-inflammatory cytokines compared to non-responders with TME remodeling characterized by increased $CD8^+$ T-cell infiltration and reduced immunosuppressive myeloid subsets. These findings were mechanistically validated by isolating *Prevotella merdae* Immunoactis from responder-derived FMT, which directly stimulated T-cell activity and suppressed tumor growth in murine models. Similarly, first-line FMT from healthy donors combined with nivolumab or pembrolizumab in treatment-naive advanced melanoma patients achieved an objective response rate of 65%, including 20% with a complete response, with FMT-driven enrichment of immunogenic species (*Faecalibacterium* and *Bifidobacterium*) and depletion of pathobionts (*Escherichia* and *Streptococcus*) correlating with improved survival[79]. Notably, microbial engraftment efficiency and sustained donor-recipient similarity were significantly greater in responders than in non-responders, suggesting that FMT success hinges on ecologic compatibility and persistent colonization. Refractory patients achieved 83% symptom resolution following FMT, even in severe immune-mediated colitis induced by PD-1 inhibitors, with restored microbial diversity marked by increased *Collinsella* and *Bifidobacterium* abundance, paralleled by reduced colonic $CD8^+$ T-cell infiltration and mucosal healing[80]. Controlled dietary interventions further corroborate the therapeutic potential of microbiota modulation because high-fibre diets enriched with Ruminococcaceae and Lachnospiraceae enhanced anti-PD-1 responses in melanoma patients by promoting SCFA production and $CD8^+$ T-cell activation[81]. Collectively, these clinical trials illuminate the multifaceted mechanisms through which FMT reshapes host–microbe interactions, reinvigorating antitumor immunity *via* metabolic reprogramming, epithelial barrier restoration, and direct immunomodulation, while highlighting the importance of donor selection, microbial strain specificity, and intervention timing in optimizing therapeutic outcome (**Table 2, Figure 3**).

Safety-first engineering: kill switches and autologous strains

Current FMT-based therapies show promise but face challenges due to complex composition and potential ecologic risks. Synthetic biology offers safer solutions through "safety-first" engineered bacteria. A key strategy involves suicide switches. Traditional kill switches often cause cytotoxicity and evolutionary pressure, leading to escape mutants[82]. Non-lethal CRISPR-based systems were developed to degrade engineered genes without killing cells. For example, a cellobiose-regulated circuit in *E. coli* Nissle 1917 (EcN) enabled complete elimination of engineered functions within 2 d after signal withdrawal without compromising host fitness[83]. Further advances include dual-input CRISPR-Cas9 kill switches (CRISPRks) responsive to chemicals (e.g., aTc) and temperature changes. These switches prevent environmental spread and exhibit high stability over 28 d of culture, achieving near-total clearance in mice[82].

A more promising approach is autologous strain therapy, in which native commensal bacteria (e.g., *E. coli* or *Lactobacillus*) are isolated from the patient, engineered to express immunomodulators, and reintroduced. These strains achieve lifelong colonization in conventionally raised hosts, continuously expressing therapeutic genes (e.g., *BSH* or *IL-10*) to modulate host physiology and avoid immune rejection[84].

Future work should focus on rigorous preclinical evaluation of these engineered live bacterial therapeutics (LBTs), especially in combination with ICIs, to advance programmable microbiome-assisted immunotherapy.

Challenges and future

The gut microbiota can increase the efficacy of PD-1-based cancer therapy, which has been robustly validated in preclinical experiments and clinical trials. Current clinical interventions involve probiotic supplementation or FMT, which artificially modulates microbial abundance to amplify the

Table 2 Summary of key bacterial strains in clinical settings

Cancer types and microbes enriched in responders	Microbial function	Reference
HCC		
A. muciniphila	Repairs gut barrier, reduces m-MDSC accumulation	Wu et al. (2025)[52]
Bifido. spp.	Modulates bile acid metabolism	Han et al. (2023)[60]
NSCLC		
A. muciniphila	Baseline abundance is positively correlated with survival	Derosa et al. (2022)[67]
Firmicutes (Lachno./Rumino.)	Pan-cancer response biomarker (Lachnospiraceae/ Ruminococcaceae)	McCulloch et al. (2022)[57]
CRC		
A. muciniphila	Increases anti-PD-L1 sensitivity	Hua et al. (2025)[17]
F. prausnitzii	Alleviates colitis, regulates Th17/Treg balance	Gao et al. (2023)[47]
Lacto. spp. (e.g., *L. reuteri*)	Improves therapeutic response	Xu et al. (2025)[85]
Melanoma		
Clade TANB77	Activates immunity *via* pilus proteins	Kim et al. (2024)[58]
P. merdae Immunoactis	Increases T-cell infiltration	Kim et al. (2024)[78]
Fungal Enterotype (high Basidiomycota ratio)	Serves as a donor selection criterion for FMT, improving response rates	Hu et al. (2025)[54]
Gastric cancer		
Lacto. spp.	Abundance is positively correlated with treatment response	Han et al. (2023)[60]
Mesothelioma		
Unsp. gut genus	Positively correlated with $CD8^+$ T-cell infiltration	Zhang et al. (2024)[73]
Ovarian cancer		
AA/lipid metab.-linked microbiota	Associated with T/B-cell activation	Rosario et al. (2024)[63]
Pan-cancer		
Firmicutes (Lachno./Rumino.)	Cross-cancer response biomarker	McCulloch et al. (2022)[57]
TOPOSCORE system (SIG1/SIG2 species network)	Integrates strain-specific SNPs and metabolomics to predict immunotherapy response	Derosa et al. (2024)[65]

therapeutic effects of PD-1 while ensuring safety. However, three core challenges persist after FMT treatment.

First, there is a colonization issue. Significant uncertainty exists regarding whether the transplanted microbiota can successfully colonize the gut or tumor microenvironment. For example, Fn requires intratumoral colonization to exert antitumor effects[49], whereas systemic colonization may trigger pro-inflammatory responses. Kennedy et al.[86] concluded that dietary resource environments are decisive factors for microbial colonization. Specific dietary components (e.g., fibre) shape microbial metabolic networks to foster symbiotic relationships between colonizing bacteria and the host. This finding suggests that future strategies could employ dynamic nutritional intervention systems to adjust dietary regimens in real time on the basis of individual metabolic profiles, thereby increasing the precision and stability of microbial colonization[86]. Second, there are ecologic perturbation risks. Greater than 60% of FMT-transplanted microbiota consists of unculturable, unknown species, leaving functional mechanisms and an ecologic impact on the recipient microbiota unclear. Rozera et al.[87] proposed a multiomics artificial intelligence (AI) platform that deciphers the metabolic pathways and immunomodulatory potential of unknown microbiota *via* machine learning, enabling predictions of adaptability to host ecologic

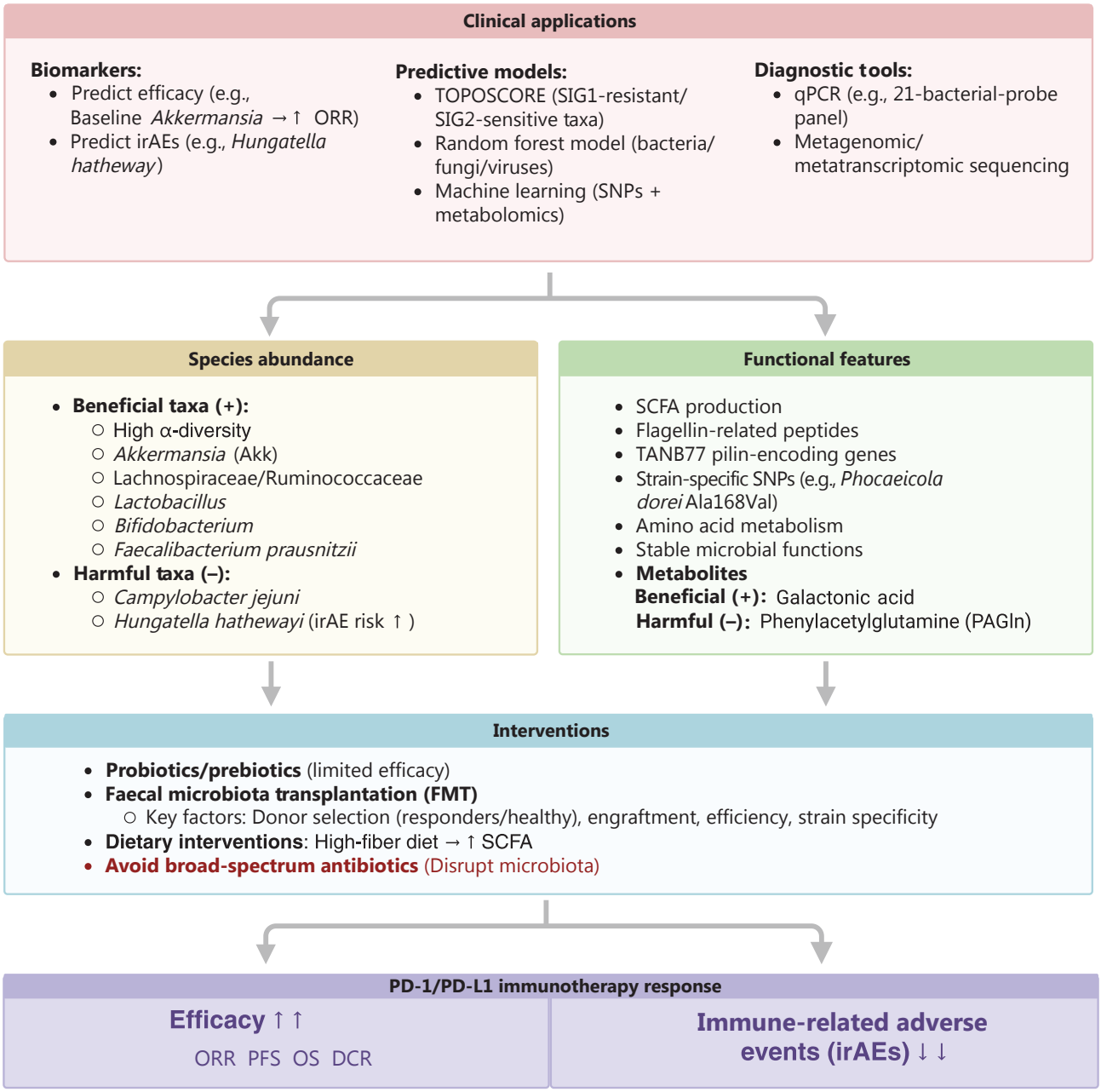


Figure 3 Interplay between gut microbiota features and clinical outcomes in PD-1/PD-L1 immunotherapy. Commensal gut bacteria modulate PD-1/PD-L1 immunotherapy efficacy through compositional and functional features. Beneficial taxa (*Akkermansia*, Ruminococcaceae, and *Bifidobacterium*) correlate with treatment response, while harmful bacteria (*Campylobacter jejuni*) promote immune evasion. Key functional markers include SCFAs production enhancing $CD8^+$ T-cell activity, strain-specific SNPs (e.g., *Phocaeicola dorei* Ala168Val), and the inhibitory metabolite, PAGln. Clinically, FMT restored treatment response in 46.2% of refractory patients. Predictive models (TOPOSCORE) and diagnostic tools (qPCR panels) enable microbiota-guided precision immunotherapy. Created in BioRender. https://BioRender.com/xewsbgx.

niches. This innovation could be used to establish novel criteria for FMT donor screening. Third, there is a lack of microbial synergy. Current interventions predominantly focus on single-strain effects but synthetic metabolic interactions (e.g., cross-feeding) among microbiota are critical for ecologic stability. Future solutions may involve synthetic biology to reconstruct functional microbial consortia. For example, engineering bacterial combinations that mutually supply essential metabolites (e.g., SCFAs or tryptophan derivatives) to amplify immunomodulatory effects[88].

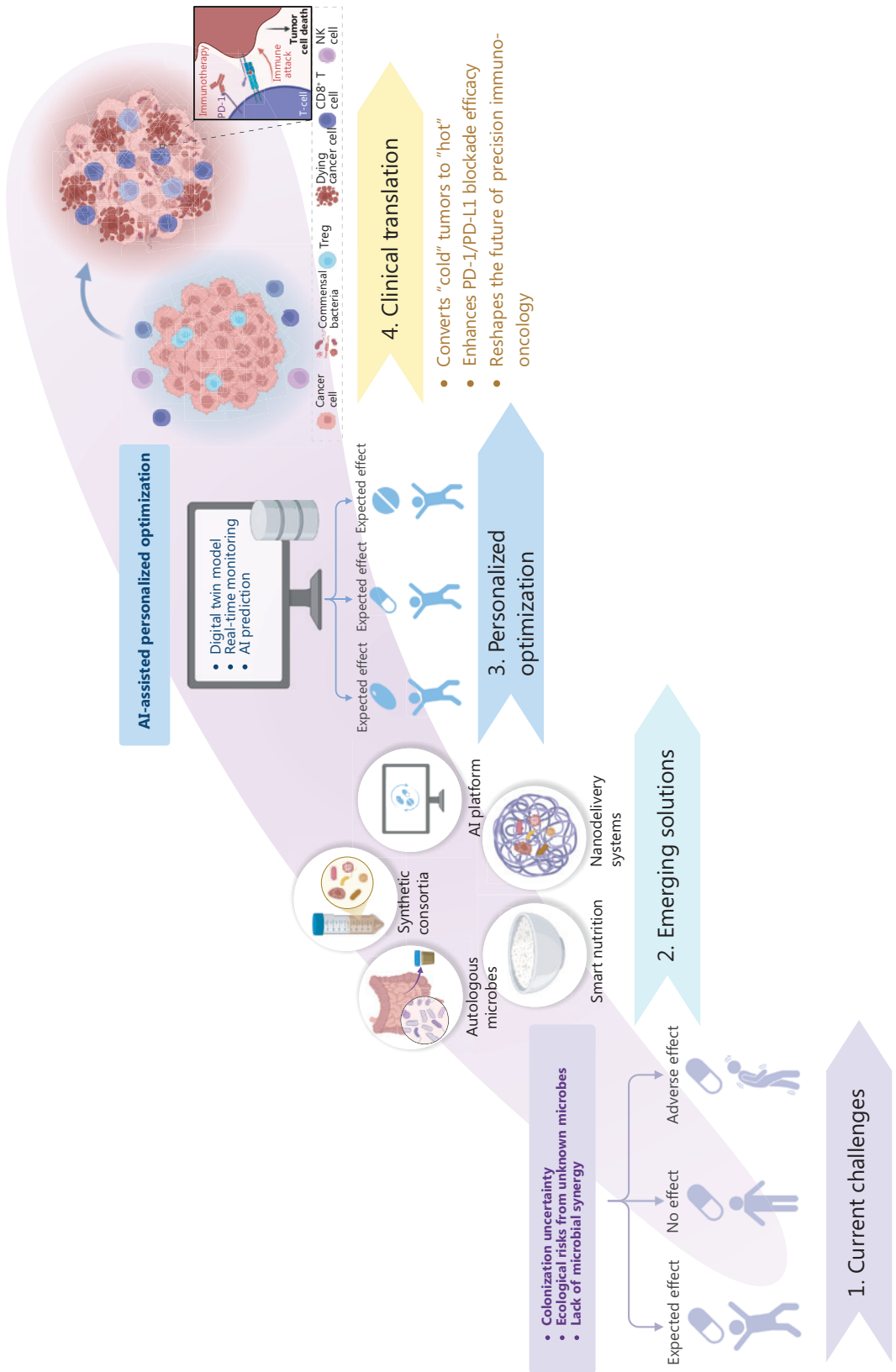

1. Current challenges
Expected effect
No effect
Adverse effect
Colonization uncertainty
Ecological risks from unknown microbes
Lack of microbial synergy
2. Emerging solutions
Autologous microbes
Smart nutrition
Synthetic consortia
Nanodelivery systems
AI platform
3. Personalized optimization
Expected effect
Expected effect
Expected effect
Digital twin model
Real-time monitoring
AI prediction
AI-assisted personalized optimization
4. Clinical translation
Converts "cold" tumors to "hot"
Enhances PD-1/PD-L1 blockade efficacy
Reshapes the future of precision immuno-oncology
Cancer cell
Commensal bacteria
Treg
Dying cancer cell
CD8+ T cell
NK cell
Immunotherapy
PD-1
Immune attack
Tumor cell death
T cell

Figure 4 Future roadmap for enhancing gut microbiota-driven PD-1 therapy. AI-assisted personalized optimization strategy framework for microbiota-based cancer immunotherapy, illustrating the transition from current challenges to clinical solutions, aiming to overcome the limitations of microbiota modulation therapies, such as FMT, and enhance the efficacy of PD-1/PD-L1 blockade: (1) Current challenges: highlights three core challenges associated with the use of FMT: (a) Colonization uncertainty: transplanted microbes struggle to stably colonize the gut or tumor microenvironment. (b) Ecologic risks from unknown microbes: introducing poorly characterized, unculturable species into the host ecosystem may pose potential adverse effects. (c) Lack of microbial synergy: the absence of key metabolic interactions (e.g., cross-feeding) among microbial communities limits their stability and efficacy. (2) Emerging solutions: proposes two key strategies to address the above challenges: (a) Synthetic consortia: utilizes rationally designed, engineered microbial communities to ensure stable colonization and functional synergy. (b) AI platform: A core artificial intelligence system that enables: Smart nutrition: dynamic dietary interventions tailored to individual metabolic profiles to support microbial colonization; Nanodelivery systems: precision-targeted delivery technologies (e.g., oral nanoparticles) to direct therapeutic agents to the tumor microenvironment. (3) Personalized optimization: integrates emerging solutions through an AI-assisted personalized optimization framework, which includes: (a) Digital twin model: a computational model that simulates patient-specific "microbiota–immune–metabolism" interactions. (b) Real-time monitoring: continuous data streams from biosensors and wearable devices to track host and microbial states. (c) AI prediction: machine learning algorithms that utilize digital twin and real-time data to predict outcomes and optimize treatments within a feedback loop. (4) Clinical translation: the ultimate outcomes of implementing this personalized approach include: (a) Converting "cold" tumors to "hot" tumors, making them responsive to immunotherapy. (b) Enhancing the efficacy of PD-1/PD-L1 blockade. (c) Reshaping the future of precision immuno-oncology. This future clinical translation emphasizes a paradigm shift: moving from empirical, one-size-fits-all approaches, such as FMT, toward a dynamic, closed-loop, and programmable precision medicine strategy. Created in BioRender. https://BioRender.com/xewsbgx.

The engineered *Salmonella* vector, DB1, which was developed by Liu et al.[89] at the Shenzhen Institute of Advanced Technology (Chinese Academy of Sciences, Shenzhen, China), to address the challenges of intratumoral colonization, achieved tumor-specific proliferation but carried the risk of bacteremia due to intravenous administration. Alternative approaches, such as hypoxia-activated *Bacteroides*, can be considered to mitigate this issue. The innate anaerobic characteristics significantly reduce systemic infection risks, while genetic engineering enables specific activation and therapeutic protein expression within the hypoxic TME. Future breakthroughs may focus on autologous commensal-based delivery systems. Engineered gut commensals equipped with a "hypoxia-activated immune escape" dual-circuit system could proliferate exclusively in hypoxic TMEs to secrete immunomodulators while undergoing self-lysis in normal tissues. This design could be optimized for personalized autologous strain engineering to mitigate safety risks from heterologous strains. Oral nanodelivery systems (LR-S-CD/CpG@LNP) offer another avenue. Nanocarrier surface-modified with microbiota-specific adhesion molecules (e.g., glycan-binding proteins) can direct commensals to tumors expressing specific surface markers[85]. Coupled with GlycoCaging technology, future systems may enable TME-specific drug release *via* activation by distinct microbial metabolic enzymes, avoiding interference with the native microbiota[90]. By integrating photoacoustic imaging for real-time monitoring, such systems could achieve closed-loop control over therapeutic dosing and spatiotemporal distribution, maximizing intratumoral microbial efficacy while minimizing systemic exposure.

Personalized treatment response prediction remains another critical challenge. Rozera et al.[87] developed a multiomics AI model that identifies 12 core microbial signatures that are quantitatively linked to PD-1 antibody efficacy by integrating metagenomic, metabolomic, and tumor immune microenvironment data from 3000 patients (89% prediction accuracy). The next steps involve dynamic prediction systems. Benjamin et al.[91] reported that single-cell spatial transcriptomics can resolve real-time 3D distribution gradients of microbial metabolites in tumors, whereas the Kennedy[86] dynamic metabolic network models quantify microbiota–host nutrient competition and T-cell metabolic reprogramming interactions. Cutting-edge approaches include integrating wearable device data (e.g., gut pH and oxygen tension) with engineered bacterial biosensor outputs into AI systems[92], creating a "microbiota–immune–metabolism" digital twin to enable minute-level therapeutic optimization. This technologic convergence could revolutionize clinical practice by transitioning from static FMT to real-time feedback-controlled "living therapeutic ecosystems."

The gut microbiota, through multidimensional metabolic–immune–barrier regulation, serves as an "ecologic lever" to optimize PD-1/PD-L1 efficacy. Despite lingering challenges in clinical standardization and safety, synthetic biology-driven engineering of autologous commensals, AI-powered personalized microbiota prediction models, and spatiotemporally precise delivery technologies are synergistically advancing microbiota-directed therapies from empirical interventions towards programmable, predictable precision medicine. This interdisciplinary integration not only offers new hope for "cold tumor" patients but also may reshape the entire landscape of cancer immunotherapy (**Figure 4**).

Conclusions

The commensal gut microbiota has been proven to be a key "ecologic lever" regulating the efficacy of PD-1/PD-L1 ICIs. Despite transforming cancer therapy, ICI effectiveness is often limited by low response rates, drug resistance, and adverse reactions. This review has clarified how specific gut microbiota reshape the TME *via* multidimensional metabolic, immune, and barrier mechanisms, enhancing immunotherapy responses and reducing toxicity. Preclinical and clinical studies have confirmed the synergistic effects of key commensal species and the translational potential of FMT and probiotic interventions. Although microbiota-based strategies face challenges, such as standardization, safety, and individual heterogeneity, the integration of synthetic biology, AI, and multiomics technologies promises to enable precise interventions targeting the gut microbiota. This could be used to overcome current hurdles and optimize immunotherapy.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Daiming Fan, Xue Bai, Yuanyuan Lu, Xiaodi Zhao.
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