



Reprogramming Gastric Cancer Therapy: A Microbiome-Guided Approach to Precision Oncology

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Abstract

Gastric cancer (GC) remains a leading cause of cancer-related mortality worldwide, with limited therapeutic success in advanced stages. Emerging evidence suggests that the gut microbiota plays a pivotal role in modulating tumor progression, immune responses, and treatment efficacy. This review explores the multifaceted interactions between the gut microbiome and GC therapies, including surgery, chemotherapy, radiotherapy, immunotherapy, and viroimmunotherapy. We highlight how microbial dysbiosis influences treatment outcomes and discuss the potential of microbiota-targeted interventions such as probiotics, prebiotics, fecal microbiota transplantation (FMT), and microbial metabolites to enhance therapeutic efficacy and reduce adverse effects. Furthermore, we examine clinical and preclinical studies that support the integration of microbiome modulation into personalized cancer care. Harnessing the gut microbiota as a therapeutic offers a promising avenue for improving GC management. Future strategies should focus on microbiome-informed treatment design to optimize clinical outcomes and pave the way for precision oncology.

Keywords Gastric cancer · Gut microbiota · Immunotherapy · Probiotics · Fecal microbiota transplantation · Viroimmunotherapy · Personalized medicine

Introduction

Gastric cancer (GC) is one of the most common causes of death related to cancer globally. Increasing evidence highlights the pivotal role of the gastrointestinal microbiota in gastric carcinogenesis and therapeutic response, positioning the microbiome as a central theme in precision oncology. The treatment of GC often involves gastrectomy with lymph node dissection [1]. The widely utilized Lauren classification system delineates macroscopic and microscopic variances, dividing GC into two major subtypes: intestinal

type associated with chronic atrophic gastritis and intestinal metaplasia, and diffuse type originating from normal gastric mucosa [2]. Beyond microbial influences, several non-microbial risk factors such as dietary habits, medication use, smoking, and family history also contribute to GC development; however, microbial dysbiosis, particularly *H. pylori* infection, represents the most critical axis linking environmental exposures to tumorigenesis [3, 4]. The development of atrophic gastritis and intestinal metaplasia is attributed to chronic *H. pylori* infection, often presenting asymptomatically in infected individuals. Factors such as environmental influences, host genetic polymorphisms and bacterial virulence contribute to *H. pylori*-induced GC. Notably, the presence of a cytotoxin-associated gene A (CagA), known for its oncogenic potential, and its pathogenicity island is associated with GC development through modulation of cellular signaling proteins [5]. Treatment of *H. pylori* can mitigate the risk of GC, with the extent of risk reduction contingent upon the eradication efficacy and the extent of preexisting damage at the time of treatment [4, 6].

Recent studies have highlighted an escalation in microbial diversity and abundance within the gastric microbiota of GC patients [7, 8]. Liu et al. [9] demonstrated an elevated

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bacterial diversity and richness in non-tumor tissues compared to peritumoral and tumoral tissues, employing advanced sequencing techniques. In addition, there are differentiations between different stomach microhabitats and the composition of gastric microbiota. This review aims to synthesize current evidence on the role of gastrointestinal microbiota in GC therapy, investigate the effects of microbiota changes on postoperative outcomes, and identify potential therapeutic strategies involving microbiota modulation.

Gastrointestinal Microbiota in GC

Gastric microbiota plays a critical role in the progression of GC. Interactions between the host's immune system and the gastric microbiota have implications for tumorigenesis in the stomach. Dysbiosis in the gut microbiota has been associated with a higher risk of GC. Microbiota dysbiosis is observed in various stages of gastric carcinogenesis from superficial gastritis (SG) to GC. Studies have shown that gastric bacterial diversity is significantly shaped by *H. pylori* infection status, gastric pH, immunosuppression, and antibiotic use [10–13]. In *H. pylori*-negative individuals, the gastric microbiota is more diverse and includes phyla such as *Fusobacteria*, *Bacteroidetes*, *Actinobacteria*, *Firmicutes*, and *Proteobacteria*. In contrast, when *H. pylori* is present, it dominates the gastric niche, comprising up to 97% of sequence reads, which in turn influences the abundance of other taxa like *Lactobacillus*, *Prevotella*, and *Fusobacterium* [10–13]. Temporal dynamics of gastric microbiota shifts are heterogeneous. Short-term changes may occur within days to weeks after antibiotic exposure, dietary modulation, or proton pump inhibitor therapy, whereas long-term restructuring linked to carcinogenesis can evolve over months to years. Several studies demonstrate the partial reversibility of dysbiosis following *H. pylori* eradication or probiotic supplementation, though recovery is often incomplete and influenced by host immune status and mucosal integrity. Dicksved et al. [14] demonstrated that the species of *Prevotella*, *Veillonella*, *Streptococcus*, and *Lactobacillus* are dominant in patients, with reduced presence of *H. pylori* advanced premalignant lesions. Similarly, Wang et al. [15] demonstrated that the abundance of *Escherichia-Shigella*, *Lachnospiraceae*, *Lactobacillus*, *Burkholderia*, and *Nitrospirae* was higher in patients with GC in comparison to controls in the gastric biopsy. These findings support previous studies that suggested a higher abundance of *Lachnospiraceae* and *Lactobacillus* is associated with GC [8, 14, 16] and that patients with colorectal cancer are enriched with *Escherichia-Shigella* [17]. Conflicting findings regarding the role of *Lactobacillus* in GC highlight the complexity of host-microbiome interactions. Although *Lactobacillus* spp. are widely promoted for their probiotic and immunomodulatory

potential. These observations highlight the need for careful patient selection and monitoring when considering *Lactobacillus*-based interventions in GC therapy. Therefore, the role of *Lactobacillus* in GC appears complex and context-dependent, necessitating strain-specific investigations and cautious interpretation when considering probiotic interventions [8, 14, 18–20]. A higher abundance of certain bacteria has been linked to GC, supporting the idea that non-*H. pylori* bacteria in the stomach could influence the risk of GC. In addition, recent research has shown that microbial diversity is increased in cancerous tissues, with oral bacteria potentially playing a pathogenic role in GC. Chen et al. [21] demonstrated that oral bacteria, including *Fusobacterium*, *Streptococcus*, and *Peptostreptococcus*, increased microbial diversity and richness in cancerous tissues. The co-occurrence network in these tissues displayed greater complexity than in adjacent non-tumor tissues, which were predominantly composed of lactic acid-producing bacteria such as *Lactobacillus brevis* and *Lactococcus lactis*. The modified acidic conditions present in the gastrointestinal tract could potentially facilitate the colonization of oral bacteria. Geographic and ethnic variations, driven by diet, genetics, and environmental factors, shape distinct gastric microbiome profiles. For instance, Asian populations typically show higher *H. pylori* prevalence and *Lactobacillus* enrichment, whereas Western cohorts harbor more *Streptococcus* and *Prevotella*. These differences may underlie regional disparities in GC incidence and therapy response, highlighting the need for geographically tailored microbiome-informed strategies [10, 14, 21–23]. Individuals harboring specific oral pathogens are at an elevated risk of developing pancreatic cancer [24]. *Lactobacillus* and *Lactococcus* species are generally recognized as beneficial probiotics. Recent studies have demonstrated that the production of lactic acid possesses properties that are anti-cancer, anti-inflammatory, and immunomodulatory, supporting the eradication therapy of *H. pylori* [18–20]. Additionally, *Serratia marcescens*, a genus commonly found in non-cancerous tissues, has not previously been associated with cancer-related microbiota. Prodigiosin, a secondary metabolite derived from *S. marcescens*, has exhibited inhibitory effects on the proliferation of human oral squamous carcinoma cells and has been shown to induce apoptosis in GC cells in vitro [25].

In the gastric mucosa of many cancer patients without *H. pylori*, Enterococci and Lactobacilli dominate. Other bacterial species, including *Parvimonas*, *Fusobacterium Pae-niglutamibacter*, *Glutamibacter*, and *Carnobacterium* have been identified irrespective of *H. pylori* infection [26]. Noteworthy enrichments of *Streptococcus anginosus*, *Dialister pneumosintes*, *Slackia exigua*, *Parvimonas micra*, and *Peptostreptococcus stomatis* have been observed during GC progression [27]. Prolonged colonization by *H. pylori* and

the administration of proton pump inhibitors, which act as acid-suppressive agents, could lead to the neutralization of the gastric environment, resulting in an increase in non-*H. pylori* bacteria. This shift could facilitate GC progression by elevating non-*H. pylori* bacteria levels and inflammatory responses, potentially contributing to inflammation in an acid-deficient stomach [28]. Furthermore, the differential effects of anastomosis techniques following gastrectomy should be considered. Reconstructions such as Billroth I, Billroth II, and Roux-en-Y modify bile reflux and gastric acid exposure, thereby reshaping the microbial landscape of the gastric remnant. These alterations can promote colonization by oral and intestinal bacteria, increase microbial diversity, and potentially influence postoperative outcomes and cancer recurrence [13, 29].

Collectively, multiple studies indicate that the gastric microbiota in GC patients shifts from a *Helicobacter*-dominant state to a more diverse community enriched with oral and intestinal commensals such as *Streptococcus*, *Prevotella*, *Veillonella*, *Fusobacterium*, and *Lactobacillus* [14, 27, 30]. This microbial restructuring is observed across different stomach microhabitats and may originate from the upper respiratory and intestinal tracts. Dai et al. [31] demonstrated an increase in the abundance of genera such as *Prevotella*, *Bacteroides*, *Streptococcus*, and *Lactobacillus* in tumor tissues, whereas *Helicobacter* was more prevalent in non-tumor tissues. Various studies have indicated that the development of tumors is influenced by both microbiota and their metabolites [21, 32]. Yang et al. [30] reported no significant differences in microbial richness and diversity between proximal and distal GC tissues. However, they noted a significantly higher abundance of *Moraxella*, *Oribacterium*, *Proteus*, *Catonella*, *Porphyromonas*, and *Rikenellaceae* RC9 gut group in proximal tissues, while *Methylobacterium* *Methylobacterium* was significantly more abundant in distal tissues. These findings suggest that microbiota other than *H. pylori* may play a role in GC development.

These mechanistic insights complement clinical studies showing improved immune and metabolic indices after probiotic supplementation and strengthen the rationale for probiotic adjuvants in perioperative care of GC patients. Consistently, in vitro experiments have demonstrated that probiotic intervention can directly inhibit GC cell proliferation and promote apoptosis, further supporting their therapeutic potential in GC management [33]. Despite these encouraging findings, safety considerations must be acknowledged. Probiotics are generally considered safe in healthy populations and have shown promising immunomodulatory and anti-inflammatory effects in GC therapy. However, rare but clinically significant adverse events, including bacteremia, fungemia, and gastrointestinal disturbances, have been reported in immunocompromised

or severely ill patients. Safety therefore depends on strain specificity, dosing regimen, and host immune status. Careful patient selection, standardized monitoring, and further clinical trials are required to ensure both efficacy and safety of probiotic interventions in GC management [18–20, 33]. Despite encouraging results, dose–response relationships for probiotics and Fecal microbiota transplant (FMT) remain unclear. Probiotic efficacy varies by strain, concentration, and duration, and standardized regimens have not yet been established. Similarly, FMT outcomes depend on donor selection and dosing frequency, with long-term durability of microbiome restoration still under investigation. Future clinical trials are required to define optimal dosing and treatment duration to maximize therapeutic benefit. To better understand gastric carcinogenesis, further research is needed to explore the functional variations of microbes in the GC microenvironment.

Alterations of the Gastric Microbiota Metabolism in GC

The metabolites produced by the gut microbiota can disrupt the equilibrium between anti-inflammatory and pro-inflammatory signaling pathways, consequently influencing inflammation and the development of cancer [34]. Chen et al. [21] demonstrated that microbial communities linked to cancer support various metabolic activities such as bacterial carbohydrate metabolism, energy metabolism, purine and pyrimidine metabolism, and denitrification functions, aligning with the metabolic characteristics of the tumor microenvironment. Conversely, non-cancerous samples exhibited an increase in signal transduction (two-component system), lipopolysaccharide biosynthesis, bacterial motility, and membrane transport. Metabolomic studies have identified distinct biomarkers in GC tumors, such as 1-methyl nicotinamide and N-acetyl-D-glucosamine-6-phosphate, alongside elevated purine metabolism and denitrification pathways mediated by nitrate reductase, a known contributor to carcinogenesis [27, 31]. The correlation analysis showed that various metabolites were positively and negatively correlated with *Lactobacillus* and *Helicobacter*, respectively, suggesting their role in metabolite turnover. Moreover, metabolites spanning glycerophospholipids, nucleotides, carbohydrates, amino acids, and pathways like fatty acid and amino sugar biosynthesis were significantly associated with several bacterial genera, including *Streptococcus*, *Sphingomonas*, *Acinetobacter*, *Faecalibacterium*, and *Comamonas* [31]. Additionally, elevated levels of amino acids and carbohydrates in tumor tissues were linked to energy production and biosynthetic demands [35]. Kaji et al. [35] demonstrated that adenosine is a prognostic indicator and a predictor of peritoneal recurrence for GC. Several studies have explored

metabolite differences between non-tumor and cancerous tissues in GC patients, which have been associated with the energy metabolite levels in both normal and cancerous gastric tissues, influencing amino acid, cholesterol, fatty acid β -oxidation, and glycolysis pathways [36, 37]. Increased levels of metabolites in cysteine, glutathione, and methionine metabolism pathways could enhance the antioxidative capacity of GC tumor tissues [35, 38]. The metabolites such as S-methyl-5'-thioadenosine, L-cystathionine, S-adenosyl-methionine, and S-adenosylhomocysteine were found to be elevated in GC tumors, participating in methionine, cysteine and glutathione metabolism pathways. Metabolomic profiling has also revealed numerous potential biomarkers associated with abdominal metastasis in GC, spanning lipid species, amino acids, organic acids, and bile acid derivatives [39, 40]. The microbial composition and metabolome of the stomach have been correlated with cancer-promoting metabolites [30]. Yang et al. [30] demonstrated the presence of distinct microbial metabolites in distal and proximal GCs. Proximal GC exhibits variations in hormone metabolisms related to microbial metabolites, whereas distal GC is characterized by variances in metabolites related to glutamate, alanine, and aspartate metabolism, protein absorption and digestion, sphingolipid signaling pathway, and arginine biosynthesis.

The progression of tumors can be influenced positively or negatively by metabolites derived from commensal bacteria [41]. *Clostridium scindens* can generate secondary bile acids and butyrate in the digestive tract, impacting carcinogenesis and exerting antitumor effects, respectively [42]. In addition, gallic acid produced by *Lactobacillus plantarum* and *Bacillus subtilis* has been shown to inhibit oncogenesis by suppressing mutant p53 [43]. Furthermore, the levels of some bacterial metabolites such as lactate, galactosamine PTS system EIIB component (agaB, agaC, and agaD) [44] N-nitroso compounds [45], nitrate, nitrite [46], arginine [44], 1-methyl nicotinamide, N-acetyl-D-glucosamine-6-phosphate, glycerophospholipids, adenosine [44], and LPS (lipopolysaccharide) [44] play critical roles in the progression and development of GC. Lactate, mainly produced by lactic acid bacteria like *Lactobacillus* spp., is a significant metabolite influencing the progression of GC. Increased levels of reactive oxygen species and exogenous lactate can promote GC cell growth and epithelial-mesenchymal transition, provide energy to tumor cells, and facilitate metastasis [45]. Conversely, branched amino acids and short-chain fatty acids (SCFAs), such as butyrate, are metabolites associated with superficial gastritis and colorectal cancer development, rather than GC [44]. Nevertheless, Marques et al. [47] demonstrated that sodium acetate could trigger mitochondria-mediated apoptosis or necrosis in CRC. Sodium acetate could prompt apoptosis in

gastric adenocarcinoma cells through Fas receptor (FasR)/Fas ligand (FasL) via activation and Caspase-3 induction [48]. Furthermore, there is a weakening of nitrate reductase function from non-atrophic chronic gastritis to GC, which correlates with shifts in the dominant gut microbiota in the gastric mucosa as GC advances [46].

In summary, distinct metabolomic profiles in GC tissues arise from complex interactions between gastric bacteria (e.g., *Lactobacillus*, *Helicobacter*) and their metabolic outputs, particularly involving nitrogen and nucleotide metabolism. However, broader metabolomic screens are needed to fully characterize these associations [21]. In addition to microbial metabolites, drug-microbe interactions represent a critical axis influencing therapeutic efficacy. Gut bacteria can directly metabolize chemotherapeutic agents, alter drug availability and modulate host toxicity profiles. Chemotherapy itself induces profound dysbiosis, characterized by reduced microbial diversity and expansion of opportunistic pathogens, which may exacerbate mucosal injury and systemic inflammation [26, 31, 32]. Emerging evidence suggests that baseline microbiome composition can predict susceptibility to treatment-related toxicities, including gastrointestinal and hematologic adverse events. Specific microbial signatures, such as enrichment of lactic acid-producing bacteria or depletion of commensal *Firmicutes*, have been associated with heightened risk of chemotherapy-induced complications [33, 44, 45]. These findings underscore the potential of microbiome-based predictors as tools for stratifying patients and guiding personalized supportive care in GC therapy.

Immunoregulatory Effects of the Gastrointestinal Microbiota on GC

Gut microbiota can either promote or inhibit anti-tumor immune responses through various mechanisms (Fig. 1) such as receptor recognition that mediates anti-inflammatory and immunogenic effects, cross-reactivity of bacterial and tumor antigens, and the influence of small metabolites on tumor-specific antigens [13]. *H. pylori* infection, for instance, can enhance the activation of CD80 and CD86 in gastric epithelial cells, thereby initiating T-cell responses [49]. Moreover, *H. pylori* has also been shown to upregulate PD-L1 (programmed cell death-ligand 1) expression on gastric epithelial cells, subsequently reducing the production of IL-2 and IFN- γ and inhibiting the proliferation of CD4 + T cells. In turn, IFN- γ activates the cytotoxicity of NK cells and tumor-specific T cells by promoting the release of granzyme and perforin [50]. Furthermore, it is suggested that *H. pylori* infection may stimulate group 2 innate lymphoid cells (ILC2s) to encourage B cells to produce IgA [51]. The chemically diverse compounds derived

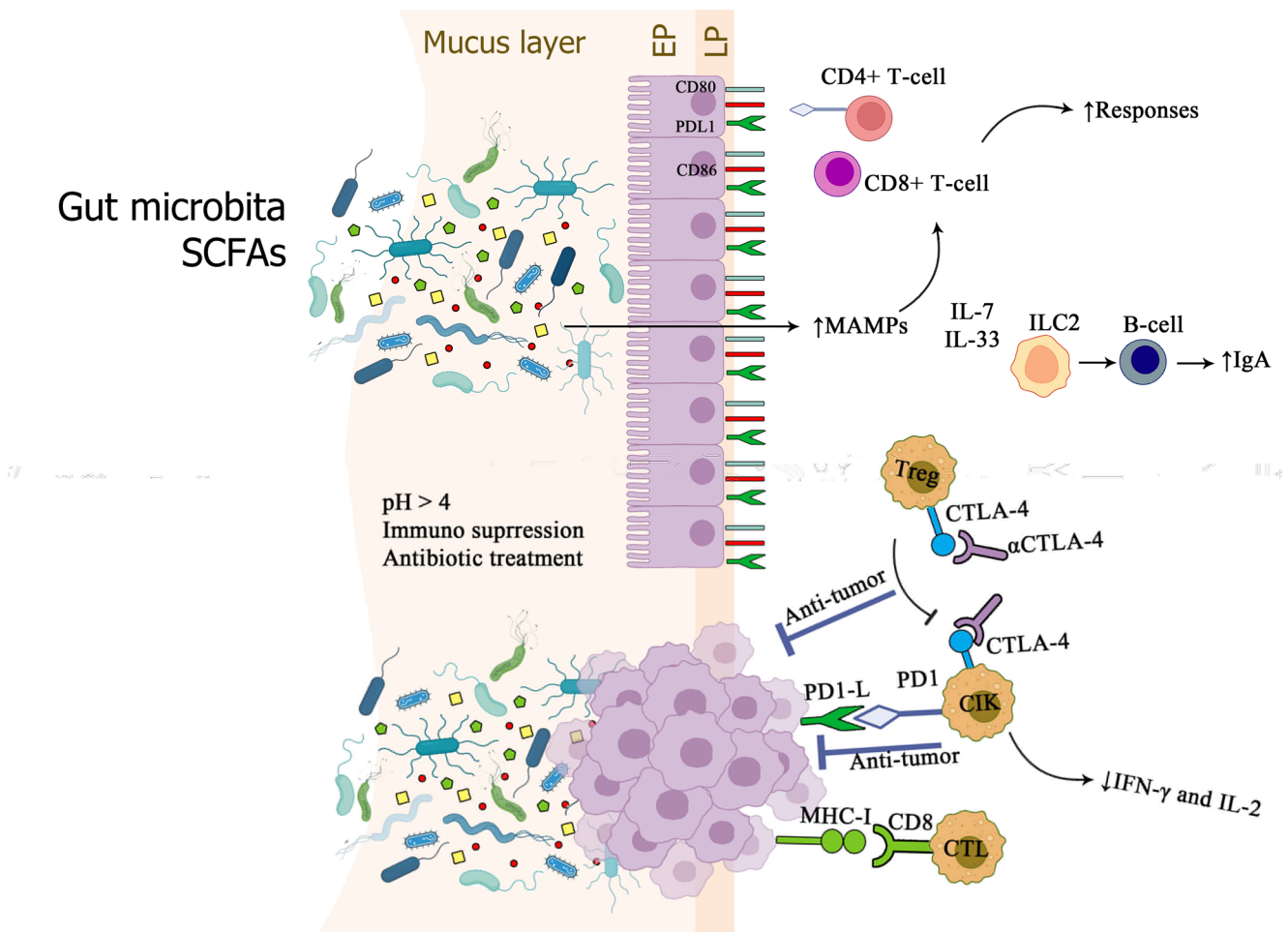


Fig. 1 Association of gastrointestinal microbiota and GC. Alterations in pH, immune suppression, and antibiotic treatment could cause gastrointestinal dysbiosis, which can lead to GC development. The gut microbiota may either strengthen or weaken anti-tumor immune response through various mechanisms. These include the recognition of receptors that mediate anti-inflammatory effects and immunogenicity, the cross-reactivity of bacterial antigens with tumor antigens, and the identification of tumor-specific antigens through the influence of small metabolites on the host. The binding bacteria to CD80/CD86 on gastric epithelial cells could initialize the T-cell responses. In addition,

from the microbiome activate pro-inflammatory pathways by interacting with MAMPs (microbe-associated molecular patterns) via NLRs (nucleotide oligomerization domain (NOD)-like receptors), RLRs (retinoic acid-inducible gene (RIG)-I-like receptors), and TLRs (Toll-like receptors), which are categorized as PRRs (pattern recognition receptors). The Gut microbiota can engage with specific PRRs such as TLRs and nuclear receptors on various gut cells to trigger T or B cell responses [52, 53]. Regulatory T (Treg) cells are crucial for resolving inflammation and maintaining immune tolerance. The balance between regulatory and effector T cells is vital for preserving homeostasis in healthy conditions. Moreover, the gut microbiome has an impact on how the host reacts to microbial molecules, thereby

tion, bacteria could enhance PD-L1 on the epithelial cells and inhibit the proliferation of CD4+T-cells or reduce the production of IFN- γ and IL-2. Stimulation of ILC-2 cells could promote B-cells to generate IgA. Furthermore, metabolites like SCFAs could activate MAMPs and GPR41/GPR43 to trigger T-cells and B-cells and to stimulate the production of IL-10 and IL-22 from Th1-cells and CD4+T-cells, respectively. Using antibodies against CTLA-4, PD-1, and PD-L1 released from tumor cells could regulate immune response against GC. Therefore, there are complex interactions between immunoregulation and the gut microbiota in the context of GC

stabilizing its environment through the regulation of mucosal homeostasis and the stimulation of antimicrobial peptide production [54]. Importantly, antibiotic exposure has been consistently associated with reduced efficacy of immune checkpoint inhibitors. Broad-spectrum antibiotics can disrupt gut microbial diversity, deplete commensal species that promote antitumor immunity, and impair T-cell mediated responses. Clinical studies have demonstrated that patients receiving antibiotics prior to or during ICI therapy exhibit poorer progression-free and overall survival compared to those without antibiotic exposure. These findings underscore the critical role of preserving microbiome integrity to optimize immunotherapy outcomes [13, 53, 54]. Dysbiosis of gut microbiota has the potential to disrupt the immune

environment of the gut, ultimately leading to inflammation and the development of cancer. Moreover, *Methylobacterium* has been observed to suppress CD8 + tissue-resident memory T cells in the gastric tumors microenvironment, consequently reducing the expression of TGF- β [55]. In addition, Ling et al. [56] demonstrated a significant positive correlation between *Selenomonas* and *Stenotrophomonas* with Foxp3 + Regulatory T cells (Tregs) and BDCA2 + plasmacytoid dendritic cells (pDCs). Conversely, *Comamonas* exhibited a negative correlation with BDCA2 + pDCs, which are implicated in the evasion of the immune system by GC cells. In addition, host microbiota could be modulated to improve the host immune responses or decrease the side effects of immunotherapy. Marie Vétizou et al. [57] demonstrated that T cell responses specific for *Bacteroides fragilis* or *Bacteroides thetaiotaomicron* are linked to the effectiveness of cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) blockade in mice and patients. Peng et al. [58] found that the abundance of *Bacteroides* was lower in patients with gastrointestinal cancer treated with anti-PD1/PD-L1 compared to non-responders, while the diversity of gastrointestinal microbiota did not critically differ between the two groups. Other studies also demonstrated that the composition of intestinal microbiota, especially *A. muciniphila* could decrease PD-1 [59, 60]. These findings highlight actionable microbiome-immune interactions relevant to GC. In vitro data suggest probiotics and their metabolites may also “prime” anti-tumor immunity by enhancing dendritic cell maturation, increasing IL-12 and IFN- γ signaling, and reducing immunosuppressive mediators, thereby potentially improving cytotoxic CD8 + T-cell responses in the tumor microenvironment. While human evidence in GC remains nascent, these mechanistic findings align with observational data linking specific taxa (e.g., *Lactobacillus*, *Akkermansia*) with improved responses to PD-1/PD-L1 blockade, indicating an opportunity to test strain-specific probiotic or postbiotic adjuncts with ICIs in GC [33]. These findings establish a foundational basis for comprehending the complex interactions between immunoregulation and gut microbiota in the context of GC.

The gut microbiota could influence immune responses during tumorigenesis and play a critical role in cancer immunity and development through their metabolites. Legoux et al. [61] identified that the proliferation of MAIT (mucosal-associated invariant T) cells is stimulated by the metabolite 5-(2-oxopropylideneamino)-6-d-ribitylaminouracil, which was transmitted from mucosal surfaces to the thymus, potentially boosting the protective immune response. Additionally, gut microbial metabolites such as lipopolysaccharides, SCFAs, and gallic acid influence tumors by repressing histone deacetylase expression, modulating immunosuppressive cytokine release, and enhancing immune cell functions

by interacting with receptors on immune cells such as GPR41 and GPR43 [41, 62, 63]. SCFAs can preserve gut homeostasis by stimulating IL-10 production in Th1 cells [63] and promoting IL-22 production in CD4 + T cells [64]. Yao et al. [65] revealed that Roux-en-Y reconstruction following radical gastrectomy in GC patients increased butyrate levels, suppressing macrophage activation by downregulating the NLRP3 inflammasome and inhibiting the release of pro-inflammatory mediators. Furthermore, the production of hydroxycitrate during starvation can enhance the effectiveness of mitoxantrone in a T cell-dependent manner [66]. In addition, SCFAs also regulate immune responses through histone methylation and phosphorylation, DNA methylation, inhibition of histone deacetylases (HDACs), modulation of cell proliferation, and apoptosis via transcription factors (NF- κ B) and signaling pathways (Akt/mTOR and MEK/ERK) [67]. He et al. [68] demonstrated that butyrate from gut microbiota regulates the function of CD8 + T-cells in the tumor microenvironment (TME) and enhances chemotherapy efficacy through ID2-dependent IL-12 signaling. Collectively, these mechanisms illustrate how the gastric microbiome fundamentally shapes the tumor-immune microenvironment, offering actionable targets to enhance the efficacy of immunotherapies in GC.

Interaction of Gastrointestinal Microbiota with GC Therapies

In order to integrate microbiome-based insights into clinical practice, Table 1 illustrates the main therapeutic modalities and their microbial associations.

Gastrectomy

Recent evidence shows that the gut microbiome plays a role in GC initiation, progression, and postoperative outcome [69, 70]. After gastrectomy, which is the main treatment for GC, numerous studies have indicated alterations in gut microbiota. Tseng et al. [71] showed that the community composition, diversity, and predicted gene functions of the gastric microbiota change significantly after subtotal gastrectomy, closely linked to the alterations in the gastric environment following the procedure. *Helicobacter* and *Ralstonia* were the most abundant genera in cancerous stomachs before procedure, while *Prevotella* and *Streptococcus* dominated after tumor resection [71]. The findings were supported by Lin et al. [72], who analyzed the long-term fecal microbiome following gastrectomy. After subtotal gastrectomy with Roux-en-Y gastrojejunum (RYGJ), there was a significant increase in the diversity and richness of gut microbiota. In contrast, subtotal gastrectomy with Billroth

Table 1 Interactions between gut microbiota and GC therapies

Therapy Type	Microbial Shifts/Taxa Involved	Mechanisms/Effects	Clinical Implication	References
<i>H. pylori</i> eradication therapy	↓ <i>H. pylori</i> , ↑ <i>Lactobacillus</i> , ↑ microbial diversity	Reduces inflammation and premalignant lesions	Decreases GC risk	[6, 96]
Probiotics (e.g., <i>Lactobacillus</i> , <i>Bifidobacterium</i>)	↑ SCFA producers (e.g., <i>Faecalibacterium</i> , <i>Akkermansia</i>), ↓ <i>Streptococcus</i>	SCFA synthesis; immune modulation; epithelial repair	Improved surgical recovery; reduced complications	[75, 76]
Neoadjuvant chemotherapy	Altered gut composition; ↑ <i>Ruminococcaceae</i> , ↓ beneficial taxa	Changes in drug metabolism; inflammation; microbiota-related toxicity	Post-op infections, delayed recovery	[69, 81]
ICIs (PD-1/PD-L1, CTLA-4 inhibitors)	↑ <i>Akkermansia</i> , ↑ <i>Bacteroides fragilis</i> , ↑ <i>Lactobacillus</i>	T-cell activation; IFN-γ & IL-12 upregulation; modulation of checkpoint blockade efficacy	Improved response rate; microbiome-based biomarkers	[58, 82]
Surgery (Gastrectomy)	↑ oral-type species (<i>Veillonella</i> , <i>Prevotella</i>); ↑ butyrate producers	Anatomical shift in pH and nutrient flow; gut recolonization patterns	CRC risk ↑ post-surgery; potential metabolic benefit (RYGJ)	[71, 72, 74]
Viroimmunotherapy (Delta-24-RGDOX)	↑ <i>Clostridium sensu stricto</i> , ↑ <i>Ruminococcaceae</i> , ↓ <i>Actinobacteria</i>	Butyrate-mediated apoptosis; immune homeostasis restoration	Enhanced viral efficacy via microbial synergy	[87, 88]

II (BII) anastomosis and RYGJ showed notable differences in the frequency of bacterial genera in comparison to the control group, as indicated by principal component analysis. Both RYGJ and BII reconstructions led to a significant shift in gut microbial composition, characterized by an increased abundance of genera such as *Prevotella*, *Clostridium*, and *Veillonella*, among others. Patients with primary GC who underwent subtotal gastrectomy with RYGJ experienced a lower incidence of type II diabetes mellitus and metabolic syndrome in comparison to the control group during extended follow-up. Overall, subtotal gastrectomy with RYGJ was associated with significant improvements in gut microbial diversity and richness, as well as metabolic outcomes [72].

There is growing evidence indicating a potential link between post-gastrectomy outcomes and gut microbiota. For instance, GC patients may face a heightened risk of developing metachronous cancers, such as colorectal cancer (CRC), following gastrectomy [73]. Erawijantari et al. [74] demonstrated that the intestinal microbiota in patients with a gastrectomy for GC displayed greater species richness and diversity, along with higher levels of aerobic, facultative anaerobic, and oral microbes, likely due to the reconstruction of the digestive system in GC patients. Notably, certain bacteria associated with CRC, including *Fusobacterium nucleatum*, were significantly more abundant in post-gastrectomy patients compared to controls. Metabolite analysis indicated increased levels of branched-chain amino acids and deoxycholic acid in these patients.

Effect of Probiotics on Postoperative Outcomes

The combination of probiotics such as *Bifidobacterium infantis*, *Enterococcus faecalis*, *Lactobacillus acidophilus*, and *Bacillus cereus* could significantly reduce inflammation indicators (leukocyte) and increase immunity indicators (lymphocyte) and nutrition indicators (albumin and total protein) [75]. Although partial gastrectomy significantly alters gut microbial diversity, administration of the probiotic combination significantly reduced the *Firmicutes/Bacteroidetes* ratio compared to patients who did not consume probiotics. The probiotic mixture led to a significant rise in the populations of the probiotic bacteria types *Bacteroides*, *Faecalibacterium*, and *Akkermansia*, while reducing the abundance of *Streptococcus* [75]. As a result, the consumption of probiotic combinations significantly increases patients' immune response and alleviates inflammation severity by altering the composition of intestinal microbiota. In light of recent discoveries linking microbial composition to immunologic, metabolic, and clinical pathways in GC, Table 2 outlines key bacterial taxa associated with therapeutic responses and mechanisms, supported by recent clinical and molecular findings.

Neo-adjuvant chemotherapy may result in postoperative problems. The potential of probiotics is to diminish complications and infections after surgery. Liu et al. [76] found that patients in the probiotic group who underwent minimally invasive surgery following neo-adjuvant chemotherapy had significantly fewer postoperative infections compared to the control group. Additionally, these patients experienced a faster return of first flatus and bowel movements, and their

Table 2 Specific bacterial roles in treatment modulation

Microbial Taxa	Related Therapies	Functional Mechanisms/Molecules	Impact on GC Progression/Immunity	Clinical Utility	Translational Opportunities	Key References
<i>Helicobacter pylori</i>	Antibiotic eradication; chemo-immunotherapy	CagA, VacA, Urease, Nitrate reductase, N-nitroso formation	Initiates gastritis, promotes carcinogenesis, immune evasion	Gold standard target for early GC prevention	Vaccination strategies; virulence-based risk profiling	[96, 97]
<i>Lactobacillus spp.</i>	Probiotic therapy; immunomodulation; ICI	SCFAs (butyrate, acetate), gallic acid, IL-10 induction, HDAC inhibition	Anti-inflammatory; barrier enhancement; PD-L1 modulation	Support in surgical recovery and ICI response	Live biotherapeutic products; strain-specific formulations	[18, 19, 82]
<i>Fusobacterium nucleatum</i>	Chemotherapy resistance; CRC risk	LPS; modulation of autophagy and TLR pathways; EMT promotion	Inflammation-induced proliferation; drug resistance; metastatic potential	Prognostic biomarker for therapy response	Target in microbiome modulation therapies	[27, 81]
<i>Akkermansia muciniphila</i>	PD-1 checkpoint modulation; probiotics	Mucin degradation; SCFA synthesis; ↑ CD8+ T-cell activation; gut barrier stabilization	Boosts ICI efficacy; enhances mucosal immune surveillance	Microbiome-based predictor of immunotherapy success	Engineered live biotherapeutics	[59, 60]
<i>Clostridium scindens</i>	Viroimmunotherapy; metabolic reprogramming	Butyrate; secondary bile acids; oxidative stress modulation	Induces apoptosis; regulates bile acid metabolism	Adjuvant in viral immunotherapy protocols	Butyrate-based microbial combinatorial therapies	[41, 87]
<i>Streptococcus spp.</i>	Post-gastrectomy dysbiosis; inflammation	Lactic acid; EPS production; biofilm formation	Tumorigenic potential post-surgery; associated with immune evasion	Dysbiosis marker; target for post-op probiotic modulation	Microbiota-reset strategies	[98]
<i>Bacteroides fragilis</i>	CTLA-4 immunotherapy synergy	Polysaccharide A; dendritic cell activation; Th1 priming	Enhances anti-CTLA4 response; boosts effector T-cell functions	Positive modulator of ICIs	Microbiome adjuvant for personalized immunotherapy	[57, 58]
<i>Veillonella spp.</i>	Post-surgical microbial remodeling	Propionate synthesis; nitrate metabolism	Promotes inflammatory shifts; metabolic compensation after anatomical reconstruction	Microbial signature of gastric reconstruction	Diagnostic marker for post-gastrectomy microbiome	[72, 83]
<i>Methylobacterium spp.</i>	Tumor immune microenvironment	Suppresses CD8+ TRM cells; ↓ TGF-β signaling	Promotes immune evasion; immunosuppressive microbe enriched in GC tumors	Potential resistance indicator to immunotherapy	Target in tumor microbiota engineering	[98]
<i>Selemonas, Stenotrophomonas spp.</i>	Tumor-associated immune dysregulation	↑ Tregs; ↑ BDCA2+ pDCs; cytokine modulation	Facilitates tolerogenic immunity; contributes to GC immune escape	Biomarker for immune-suppressive tumor niches	Therapeutic immune checkpoint balancing	[56]

Table 2 (continued)

Microbial Taxa	Related Therapies	Functional Mechanisms/Molecules	Impact on GC Progression/Immunity	Clinical Utility	Translational Opportunities	Key References
<i>Rumino-coccaceae</i> family	Surgery, viro-therapy, metabolic health	Butyrate synthesis; ROS reduction; bile acid metabolism	Maintains gut homeostasis; supports anti-inflammatory environment	Microbially in surgery recovery	Foundation for SCFA-targeted probiotic development	[87, 88]
<i>Escherichia-Shigella</i> group	Tumor enrichment; CRC link post-gastrectomy	Endotoxins; nitrate/nitrite metabolism; oxidative DNA damage	Promotes inflammation; linked to GC and CRC progression	Risk marker post-surgery	Screening in metachronous cancer monitoring	[15, 17]
<i>Peptostreptococcus</i> spp.	Advanced GC microbiome	SCFA imbalance; oral–gastric transfer patterns	Enriched in cancer mucosa; links oral microbiota to GC development	Non-invasive biomarker for GC detection	Integration in metagenomic diagnostic platforms	[21, 49]
<i>Parvimonas micra</i> , <i>Slackia exigua</i>	Immune escape and invasion	Anaerobic metabolism; correlation with Tregs and tumor microbiota diversity	May promote tumor-associated microbiota complexity	Investigational markers in microbiota–tumor interaction studies	Candidate for network-level interventions	[27, 49]

inflammatory markers were lower. The probiotic group also had a shorter hospital stay after surgery. As a result of fewer infections and quicker recovery, adjuvant chemotherapy could begin earlier for patients in the probiotic group. Thus, probiotic supplementation before surgery may improve short-term clinical outcomes, lower common inflammatory markers, and reduce the risk of postoperative infections in GC patients receiving neo-adjuvant chemotherapy [76].

Chemotherapy

The gut microbiome has emerged as a key modulator of chemotherapy efficacy and toxicity in gastrointestinal cancers. Zheng et al. [69] suggest that gut microbes may predict the effectiveness of cancer treatments. While these initial findings are promising, further large-scale, prospective studies are needed to validate the predictive value of specific microbial signatures and to elucidate the precise mechanisms by which the gut microbiome modulates chemotherapy response in GC. Li et al. [77] found that the gut microbiomes of patients with esophageal, stomach, and CRC differ from those of healthy individuals. The intestinal microbiota characteristics in patients with esophageal cancer and GC were similar to those in CRC patients. Notably, changes in the frequency of *R. faecis* in gastrointestinal cancer patients may indicate chemotherapy effectiveness. These findings suggest that microbial features in individuals with esophageal cancer, GC, and/or CRC could serve as potential diagnostic biomarkers for future research. In summary, while preliminary data suggest associations between

specific gut microbial features (e.g., *R. faecis* abundance) and chemotherapy outcomes in GC, rigorous validation in larger cohorts is essential. Future research should focus on elucidating the causal mechanisms and translating these microbial signatures into clinically useful predictive tools.

Immunotherapy

The introduction of immune checkpoint inhibitors (ICIs) has provided novel treatment options, but the overall response rate (ORR) remains low at 11%–15% [73, 78]. Only patients with rare subtypes, such as Epstein-Barr virus-associated GCs (EBVaGCs) and microsatellite instability-high/deficient mismatch repair (MSI-H/dMMR1), may benefit from this therapy [79]. Most patients do not experience significant improvements from ICI monotherapy, making it essential to find strategies to overcome ICI resistance. Combining chemotherapy with ICIs may effectively tackle this resistance, but the factors influencing the success of this combination therapy are not well understood. The gut microbiome significantly impacts the immune system and can influence cancer patients' responses to chemotherapy and immunotherapy. Gopalakrishnan et al. [80] have shown that the gut microbiome affects the tumor microenvironment in melanoma by modulating CD8 + T-cell infiltration and directly influencing responses to anti-PD-1/PD-L1 immunotherapy. Additionally, studies suggest that the presence of *Fusobacterium nucleatum* and other gut microbiome components can affect the body's response to chemotherapy [81, 82]. Peng et al. [58] showed an association between

the *Prevotella/Bacteroides* ratio and resistance to ICIs in gastrointestinal cancer, although this correlation was not deemed significant in cases of GC or GEJ cancer. Han et al. [82] conducted a prospective cohort study involving 170 patients with metastatic or unresectable HER2-negative GC/GEJ adenocarcinoma, who were treated with standard chemotherapy, ICI monotherapy, or chemotherapy combined with ICI. They utilized metagenomic sequencing to analyze the gut microbiome profiles of patients at the beginning and throughout treatment. The findings revealed that microbiome signatures associated with clinical responses differed among the three treatment groups. Patients with higher *Lactobacillus* levels exhibited greater microbiome diversity and a significantly improved response to anti-PD-1/PD-L1 immunotherapy, suggesting potential for better progression-free survival. *Lactobacillus* may emerge as a promising adjunct to enhance immunotherapy efficacy in GC.

Nivolumab monotherapy has shown survival benefits in previously treated GC patients. However, approximately 60% of subjects did not respond to nivolumab in later lines of treatment, highlighting the need for predictive markers in GC [78]. Sunakawa et al. [83] recruited 501 individuals with advanced GC receiving nivolumab monotherapy. Their exploratory analysis identified that the genera *Veillonella* and *Odoribacter* were linked to tumor responses to nivolumab. This translational study was the first to demonstrate that gut bacteria invading the epithelial cell pathway could serve as a new potential indicator for nivolumab treatment in advanced GC. Additionally, a GC-specific gut microbiome has been shown to predict responses to ICIs [83]. In addition, the fatty acid metabolism pathway and the *Arthrobacter* genus in the gut microbiome predict skin toxicities in nivolumab-treated advanced GC. Some single-nucleotide polymorphisms (SNPs) have the potential to serve as indicators for both skin toxicities and diarrhea in nivolumab treatment [84].

Zhang et al. [85] have shown the relationship between the effectiveness of ICIs and the use of probiotics in lung and renal cancers. However, knowledge regarding their impact on other cancers, including gastrointestinal cancer, remains limited. Arai et al. [86] conducted a multicenter retrospective cohort study to investigate the impact of probiotics on the duration of nivolumab treatment across various cancers. The study included 488 patients undergoing nivolumab therapy. Overall, there was no significant difference in treatment duration between probiotic users and nonusers across all cancer types. However, in patients with GC, the use of probiotics was critically related to a longer duration of nivolumab treatment compared to nonusers. In summary, probiotics potentially extend progression-free survival and may enhance the response to nivolumab in GC patients.

Viroimmunotherapy

Oncolytic virotherapy represents an emerging immunotherapeutic strategy for gastric cancer. Beyond their direct cytotoxic effects, oncolytic viruses can stimulate systemic antitumor immunity. Emerging preclinical evidence suggests that the gut microbiome may be a critical modulator of virotherapy efficacy, influencing host immune responses and treatment outcomes. The treatment of solid tumors has progressed with the development of the oncolytic adenovirus Delta-24-RGDOX, which includes the T-cell activator OX40L [87]. It is hypothesized that gut microbiota significantly modulates the virus-based antitumor response [88]. Much of the current evidence for viroimmunotherapy in GC is derived from preclinical mouse models, which provide valuable mechanistic insights but may not fully translate to human physiology. Human data remain limited to early-phase clinical trials and case reports, underscoring the need for caution when extrapolating preclinical findings to clinical practice. Melendez-Vazquez et al. [87] found notable differences in the gut microbiome structure of mice treated with viral immunotherapy compared to a control group. To explore this hypothesis, immunocompetent C57BL/6 mice were implanted with GC cells and received intratumoral injections of either Delta-24-RGDOX or PBS (control). Although gut diversity showed no significant differences in fecal samples collected before tumor implantation, after tumor establishment, and 14 days post-initial treatment, control animals exhibited greater richness. Notably, responders to viroimmunotherapy demonstrated an increase in *Patescibacteria* and a decrease in *Actinobacteria*. Additionally, responders had higher levels of butyrate-producing bacteria, such as *Clostridium sensu stricto* and *Ruminococcaceae*. These findings indicate that butyrate producers may significantly contribute to maintaining intestinal homeostasis, which correlates with the clinical efficacy of Delta-24-RGDOX, suggesting that modulating the microbiota could enhance patient survival. Preclinical studies have explored oncolytic viruses, such as engineered herpes simplex virus (HSV), as potential agents for GC treatment, with ongoing efforts to enhance their tumor selectivity and oncolytic potency [78, 89, 90]. Even in late-stage disease, third-generation HSV-1 G47Δ (a third-generation oncolytic HSV-1) has shown promising activity. This virus can replicate in GC cell lines, including scirrhous subtypes, and induce marked cytopathic effects. In vivo, G47Δ significantly suppressed tumor growth in subcutaneous xenograft models, and intratumoral administration produced robust antitumor responses across different dosing schedules. In peritoneal dissemination models, intraperitoneal delivery of G47Δ was also effective, likely due to its ability to rapidly

infiltrate disseminated lesions and selectively replicate within tumor nodules [91].

Oncolytic virotherapy (e.g., using engineered adenoviruses or herpes simplex viruses) represents an emerging modality for GC treatment [87, 89, 90, 92]. Preclinical evidence suggests that the gut microbiome may modulate its efficacy; for instance, in murine GC models, responders to an oncolytic adenovirus (Delta-24-RGDOX) exhibited a distinct microbial signature enriched in butyrate producers [87]. However, most evidence remains preclinical, and human data are sparse, highlighting the need for translational studies. Ultimately, the dual role of oncolytic viruses, as direct cytotoxic agents and as in situ immune modulators, creates a compelling rationale for combining them with microbiome-targeting strategies to enhance therapeutic outcomes [93, 94]. Recent advances in viroimmunotherapy highlight the dual role of oncolytic viruses as direct cytolytic agents and as modulators of antitumor immunity. Oncolytic viruses not only induce immunogenic cell death but also reshape the tumor microenvironment by enhancing antigen presentation and stimulating T-cell infiltration. Importantly, accumulating evidence suggests that the gut microbiota may influence the efficacy of viroimmunotherapy, with commensal bacteria contributing to systemic immune activation and modulation of cytokine responses [94, 95]. In GC, integrating microbiome-informed strategies with viroimmunotherapy could optimize therapeutic outcomes, reduce toxicity, and provide a novel avenue for precision oncology GC [93].

Challenges and Future Perspectives

Despite the growing interest in microbiome-guided strategies for GC therapy, several challenges remain unresolved. A major obstacle is the considerable heterogeneity of the gastric and intestinal microbiota across individuals, which complicates the development of standardized therapeutic protocols. Current interventions such as probiotics, prebiotics, and FMT lack uniform guidelines regarding dosage, duration, and patient selection, limiting their reproducibility and clinical translation. Many investigations are limited by small cohorts, heterogeneous patient populations, or reliance on preclinical models, which restricts the generalizability of their findings. Furthermore, interpreting reported associations requires caution due to risks of bias (e.g., selection, publication) and a general lack of standardized microbiome profiling methods. Mitigating these issues will require future studies to prioritize transparent reporting, including negative findings. Concerns regarding the potential transmission of opportunistic pathogens and unforeseen adverse effects further highlight the importance of rigorous safety assessments.

Looking ahead, future research should prioritize the integration of multi-omics approaches, including metagenomics, metabolomics, and transcriptomics, to achieve a comprehensive understanding of host-microbiome interactions in GC. Personalized therapeutic strategies informed by individual microbiome profiles may enhance treatment precision and minimize adverse effects. In addition, microbial metabolites with demonstrated anti-cancer or immunomodulatory properties represent promising candidates for adjunctive therapies. Combining microbiome modulation with established modalities such as chemotherapy, immunotherapy, and targeted agents may further improve therapeutic efficacy. To ensure clinical applicability, large-scale, longitudinal studies are required to establish robust evidence and inform regulatory frameworks. Ultimately, advancing microbiome-informed interventions holds the potential to transform GC management and pave the way toward precision oncology.

Conclusion

Mounting evidence underscores the significant role of non-*H. pylori* bacteria in gastric carcinogenesis, progression, and response to various therapies. Although specific microbial taxa or metabolites definitively predictive of treatment outcomes or disease development have yet to be established, the collective data strongly suggest that modulating the gastric microbiome through strategies like targeted probiotics, prebiotics, or FMT holds considerable promise as an adjunctive therapeutic approach. Such interventions may enhance the efficacy of existing treatments, particularly immunotherapy, and potentially mitigate treatment-related complications. To translate this potential into clinical reality, future research must prioritize elucidating the precise mechanistic pathways linking the microbiome to GC biology and treatment response.

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