

REVIEW ARTICLE

The gastric microbiome in carcinogenesis and therapy: From mechanisms to engineered microbial therapeutics

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Abstract

The tumor-associated microbiome has emerged as a novel hallmark of cancer. Gastric cancer (GC) serves as a paradigm for microbiome-associated carcinogenesis, with well-established roles for specific pathogens such as *Helicobacter pylori* and Epstein-Barr virus. However, the detailed molecular and cellular mechanisms by which microbial communities drive gastric tumorigenesis remain incompletely understood. Recent technological advancements have unveiled a broader spectrum of microorganisms implicated in GC, highlighting the emerging roles of the mycobiome (fungal microbiome) and bacterial-fungal interactions in shaping the tumor microenvironment. This review comprehensively summarizes recent progress in GC-associated pathogens, with a particular emphasis on how bacteria and fungi contribute to GC through direct carcinogenic effects, modulation of host immune responses, and influencing the efficacy of immune checkpoint inhibitors. We critically analyze the “double-edged sword” nature of the microbiome in GC and discuss the potential of multi-omics approaches to unravel complex microbe-host interactions. Finally, we explore the frontier of leveraging synthetic biology to develop engineered microbes (including bacteria and oncolytic viruses) as novel anticancer therapeutics, while addressing the challenges in translating these strategies into clinical practice. A deeper understanding of the gastric microbiome, particularly the multi-kingdom microbial network, is poised to open new avenues for microbiome-based precision diagnosis and innovative therapies for GC management.

Keywords: Microbiome; Gastric cancer; Mycobiome; Bacterial-fungal interactions; Tumor microenvironment; Immunotherapy; Engineered microbial therapeutics

1. Introduction

Gastric cancer (GC), the fifth most prevalent malignancy globally, accounted for approximately 770,000 deaths in 2020, with over one million new cases diagnosed, representing 5.6% of all cancer cases.¹ Due to its poor prognosis, GC ranks as the third leading cause of cancer-related death, accounting for approximately 7.7% of all cancer-related deaths. Notably, there are significant gender disparities in GC incidence, with males exhibiting nearly twice the rate observed in females.² The cumulative risk of GC-related death is estimated at 1.29% in males and 0.55% in females, with consistently higher mortality in males. Marked regional and socioeconomic differences also shape GC distribution. The highest incidence rates are reported in East Asia (particularly China and Japan), Southern Europe, and Central and South America, where the incidence is up to 40 times higher than in regions with the lowest rates (such as South Asia, Northern Europe, North America, Australia, and New Zealand).³ In East Asia, the age-standardized incidence rate in males is 32.5/100,000 individuals, with even higher rates observed in Central and Eastern Europe.² In China, GC ranks second in both incidence and mortality, accounting for nearly half of all new cases worldwide.³ Recent studies also suggest a rising incidence of GC among younger populations.⁴ Therefore, understanding the etiology of GC is critical.

Development of GC is driven by multiple factors, including genetic predisposition, smoking, alcohol consumption, obesity, unhealthy dietary patterns, and infections with specific microbiota. Rather than resulting from a single causative agent, GC typically arises from complex interactions among these factors, especially microbial infections.

1.1. Host factors and microbiota interactions in GC

As previously mentioned, sex plays a crucial role in influencing the carcinogenesis and mortality rates of GC. Numerous studies have demonstrated that gender differences affect various aspects, including disease susceptibility, life expectancy, and responsiveness to immunotherapy. Differences in gut microbiota composition between males and females may also contribute significantly. Studies have shown that adult females (20–45 years old) exhibit higher gut microbiota diversity than age-matched males and are more enriched in beneficial microbes. For example, the phyla *Firmicutes* and *Actinobacteria* contain numerous probiotic genera. Within *Firmicutes*, *Lactobacillus* promotes immune regulation, while *Lachnospiraceae* produce short-chain fatty acids that help maintain the intestinal barrier. Similarly, *Bifidobacterium*, a representative genus of *Actinobacteria*, is a classic example

of a probiotic. These differences may also help explain the higher prevalence of autoimmune diseases in females, such as autoimmune atrophic gastritis.⁵ The study by Peng *et al.*⁶ lends further support for the gender disparities, reporting distinct microbial distributions between male and female mice. Specifically, *Bifidobacterium* and *Lachnospiraceae* preferentially colonize in females, whereas *Escherichia shigella* and *Akkermansia* are more prevalent in males, potentially leading to greater inflammatory infiltration and more severe intestinal metaplasia in male mice.

Age is another critical factor in GC development. The incidence of GC increases with age, peaking between 55 and 80 years. It is strongly speculated that age-associated shifts in microbial composition play a vital role. The gut microbiome undergoes extensive changes across the lifespan: the abundance of *Enterococcus* spp. increases, while *Bacteroidaceae* and *Lachnospiraceae* decrease, and levels of *Lactobacilli* and *Bifidobacteria* remain relatively stable. *Streptococcus anginosus*, a newly identified pathogen implicated in GC carcinogenesis, peaks in the 35–54-year age group, coinciding with a rise in GC incidence.⁷ In contrast, *Helicobacter pylori*, as the earliest found pathogen in GC, seems not to correlate with age. There are still some other factors influencing GC.

Diet is also a major contributor to GC. High salt intake can stimulate the gastric mucosa, increase gastric acid secretion, alter mucus barrier viscosity, damage the gastric lining, and facilitate colonization by bacteria capable of reducing nitrate to nitrite – an important precursor to carcinogenic N-nitroso compounds.⁸ Similarly, hypochlorhydria secondary to atrophic gastritis may promote colonization by bacteria and yeasts that produce alcohol dehydrogenase, which converts ethanol or glucose into the highly toxic carcinogen acetaldehyde.⁹ This chronic inflammatory microenvironment, driven by microbial metabolites, facilitates the excessive colonization of non-native gastric microbes, ultimately promoting GC development. A recent study on GC tissues from 276 Asian patients revealed a reduced number of certain microorganisms, such as *Sphingobium yanoikuyae*, which is known for degrading pollutants from cigarette smoke.¹⁰

Apart from the host factors, the complex process of GC is also affected by environmental factors. In recent years, heavy metal exposure has been suggested as one of the severe environmental risk factors. These heavy metals, such as chromium, cadmium and nickel may contribute to the carcinogenesis of GC by destroying the gastric mucosa barrier and changing the distribution of gut microbiomes, causing further tissue damage. Wang *et al.*¹¹ reported that a higher concentration of stibium is positively correlated with the microsatellite instability

in GC. The long-term exposure of Cd caused a higher abundance of monoderm bacteria like *Bacillus cereus* and *Enterococcus* spp. in gut, but no such effect was found on diderm bacteria such as *Escherichia coli* and *Klebsiella* spp.¹² Exposure to lead (Pb) resulted in alterations in commensal bacteria responsible for producing short-chain fatty acids (SCFAs), as well as changes in intestinal bacterial amino acid profiles, particularly in alanine and glycine levels.¹³ Recent studies integrating metagenomic sequencing with metabolomic analysis have shown that certain SCFAs produced by the microbiome are significantly altered in GC patients.^{14,15} These SCFAs, such as butyrate, are known to affect the immune microenvironment and influence tumor progression. The mechanisms underlying the heavy metal exposure-mediated GC development remain to be elucidated. Nevertheless, at this point, we deduce that it shares the common traits in process, such as reactive oxygen species generation, antioxidant defense weakening, and enzyme inactivation.

1.2. Landscape of gastric microbiota during GC progression

The impacts of microbial dysbiosis on the carcinogenesis and progression of GC have been clearly deciphered. These findings raise several critical questions: (i) Which specific microorganisms influence the onset and progression of GC? (ii) Through what mechanisms do they drive gastric carcinogenesis?

1.2.1. Bacteria and GC

Gastric microbial dysbiosis has been reported to be closely associated with GC development. Distinct microbial signatures have been identified at different stages of GC progression. A markedly increased bacterial load in various precancerous gastric conditions, including hypochlorhydria and mucosal atrophy, suggests that microbes act as cancer-promoting factors. Using 16S ribosomal RNA (rRNA) sequencing, numerous population-based studies have shown that Gram-negative bacteria are predominantly associated with chronic gastritis and intestinal metaplasia, while Gram-positive and anaerobic bacteria increase in intraepithelial neoplasia and chronic gastritis.^{16,17} For instance, the abundance of certain phylum, such as *Armatimonadetes*, *Chloroflexi*, *Elusimicrobia*, and *Nitrospirae*, decreased progressively with the progression from chronic gastritis to intestinal metaplasia. Conversely, *Actinobacteria*, *Bacteroides*, *Firmicutes*, *Fusobacteria*, SR1, and TM7 were enriched in intraepithelial neoplasia and GC.¹⁸ *Rhizobiales* have been found to be more abundant in patients with intestinal metaplasia than in those with superficial gastritis.¹⁹ Sung *et al.*¹⁷ reported that *Granulicatella*, *Actinomyces*,

Rothia, *Peptostreptococcus*, *Streptococcus*, *Abiotrophia*, and *Parvimonas* are associated with atrophic gastritis or intestinal metaplasia in patients after successful *H. pylori* eradication. A recent study further revealed that *Sphingomonas* and *Aquicola tertiarycarbonis* are increased in intestinal metaplasia, while *Neisseriaceae*, *Streptococcus*, and *Haemophilus parainfluenzae* are significantly enriched in patients with intraepithelial neoplasia. In contrast, *Veillonella* and *Lactobacillus* are more abundant in GC.¹⁸ Overall, *Proteobacteria*, *Firmicutes*, *Bacteroidetes*, *Fusobacteria*, and *Actinobacteria* are consistently shown to be predominant in the gastric microbiota (Figure 1).

1.2.2. Mycobiome and GC

The impact of the fungal microbiome on GC has not been investigated as extensively or in as much detail as bacterial influences, mainly due to the low abundance of fungi in tumor tissues and limitations in sequencing depth. In recent years, with advancements in internal transcribed spacer (ITS) amplicon sequencing technology, research on the role of the fungal microbiome in cancer has garnered increasing attention.

The mycobiome in GC patients is characterized by decreased biodiversity and richness, with distinct community signatures compared to healthy individuals. Fungal dysbiosis during gastrointestinal cancer progression is marked by a distorted *Basidiomycota*-to-*Ascomycota* ratio, along with increased abundance of opportunistic fungi such as *Malassezia*, *Candida*, *Saccharomyces*, *Alternaria*, and *Aspergillus*, and decreased levels of *Pezizomycetes*, *Sordariales*, *Chaetomiaceae*, and *Rozellomycota*. This profile differs from that of normal gastric epithelial tissues, which are dominated by genera such as *Rhizopus*, *Rhodotorula*, *Apodus*, and *Cystobasidium* (Figure 1).²⁰ Moreover, a specific panel of GC-associated fungi, notably *Solicocozyma*, demonstrated promising diagnostic potential.²⁰ Zhang *et al.* reported that the high abundance of *Malassezia globosa* is associated with poorer prognosis in GC patients receiving immunotherapy and shorter overall survival. A summary of studies on mycobiome abundance in GC is presented in Table 1. Although host–pathogen interactions have been shown to contribute to tumor development in the gastric system, evidence for fungal involvement in earlier stages of GC development (such as chronic gastritis, atrophic gastritis, and intestinal metaplasia) remains limited. Further research is required to elucidate these strategies more efficiently.

1.2.3. Viruses and GC

Viruses are increasingly recognized as important contributors to the development and progression of GC. Beyond Epstein–Barr virus (EBV), which is among

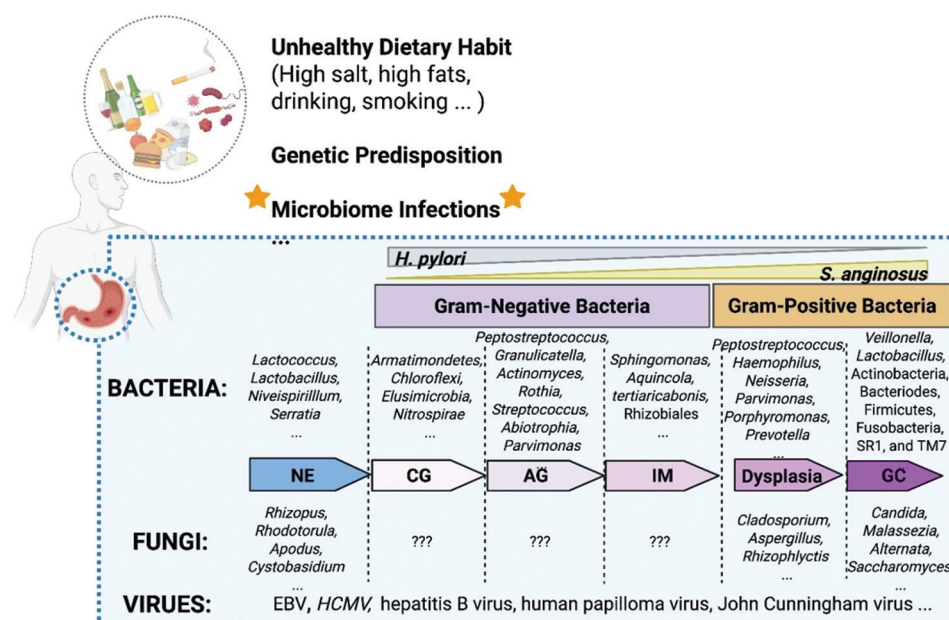


Figure 1. Schematic of the impact of the microbiome on gastric cancer (GC). Microbiota infection is one of the key factors of carcinogenesis. The main abundance of microorganisms in the different stages of GC development was marked, that is, the abundance of *Helicobacter pylori* gradually decreased with increasing severity of gastric disease, in contrast to that of *S. anginosus*. For fungi, the abundance of key fungi in chronic gastritis, atrophic gastritis, and intestinal metaplasia currently remains unknown. Figure created in BioRender. Han *et al.* (2025) <https://BioRender.com/r44w824>.

Abbreviations: AG: Atrophic gastritis; EBV: Epstein-Barr virus; CG: Chronic gastritis; HCMV: Human cytomegalovirus; IM: Intestinal metaplasia; NE: Normal epithelia.

Table 1. Summary of mycobiome abundance studies on patients with gastric disease on the basis of ITS sequencing

Genus (top 5)	Sample source	Sample type	Sample number	Ref.	Year
<i>Apiotrichum</i> , <i>Cutaneotrichosporon</i> , <i>Sarocladium</i> , <i>sarocladium</i> , <i>Malassezia</i>	Tissue	GC/para-GC/HC	22v22v11	Yang <i>et al.</i> ²¹	2022
<i>Kluyveromyces</i> , <i>Penicillium</i> , <i>Geotrichum</i> , <i>Cladosporium</i> , <i>Malassezia</i>	Tissue	GC/Dyspepsia	22v12	Hansen <i>et al.</i> ²²	2020
<i>Candida</i> , <i>Alternaria</i> , <i>Saccharomycetes</i> , <i>Dothideomycetes</i> , <i>Pleosporaceae</i>	Tissue	GC/NAT	45 pairs	Zhong <i>et al.</i> ²³	2021
<i>Candida</i> , <i>Saccharomyces</i>	Tissue and blood (TCGA database)	Stomach/STAD	321	Dohlman <i>et al.</i> ²⁴	2022
<i>Candida</i>	Tissue	Stomach/STAD	/	Narunsky-Haziza <i>et al.</i> ²⁵	2022

Abbreviations: GC: Gastric cancer; HC: Healthy controls; ITS: Internal transcribed spacer; NAT: Non-adjacent tissue; STAD: Stomach adenocarcinoma.

the 11 established carcinogenic microbes and has a well-documented role in gastric tumorigenesis, meta-analyses suggest that other viruses may also potentially contribute to gastric carcinogenesis. For instance, human cytomegalovirus has been identified in GC tissues through immunohistochemistry and quantitative polymerase chain reaction.²⁶ In addition, infections with hepatitis B virus, human papilloma virus, and John Cunningham virus have been reported to increase GC risk, although definitive evidence is still lacking.²⁷

1.3. Functional modes of microorganisms

Given the close association between microorganisms and

the development and progression of GC, an important question is how these microorganisms influence the host to promote tumorigenesis. Based on the context in which they act, the effects of microorganisms on the host can be categorized into macroenvironmental and microenvironmental levels.

1.3.1. Microbiome and macroenvironment

Four strategies have been proposed for bacteria-mediated GC development: (i) *Creation of a carcinogenic N-nitroso-enriched environment.*^{28,29} By promoting nitrite production, certain bacteria create an environment conducive to the formation of carcinogenic N-nitroso compounds.

Wang *et al.* reported that compared with chronic gastritis tissues, GC tissues uniquely harbor the phylum Nitrospirae, which metabolizes nitrates and nitrites into N-nitroso compounds.^{30,31} (ii) Established of an acid-decreased environment. *H. pylori* localization reduces acid production, facilitating colonization by other commensal microbes from the gut (e.g., *Lactobacillus*, *Enterococcus*, *Carnobacterium*, *Parvimonas*, *Citrobacter*, *Clostridium*, *Achromobacter*, *Rhodococcus*) and from the oral cavity (e.g., *Fusobacterium nucleatum* [Fn], *Veillonella*, *Leptotrichia*, *Haemophilus*, *Campylobacter*),³² which positively contribute to the progression of GC. (iii) Serving as an energy source for tumor growth and angiogenesis. Several studies have shown increased diversity of *Lachnospiraceae*, *Lactobacillus*, and *Lactococcus* genera in GC patients compared to those with functional dyspepsia. The lactic acid produced by these bacteria can be utilized by tumor cells to stimulate angiogenesis.^{33–36} (iv) Induction of a proinflammatory environment. Certain oral and skin bacteria, such as *Fusobacterium*, *Veillonella*, *Leptotrichia*, *Haemophilus*, *Streptococcus bovis*, *Campylobacter*, *Propionibacterium acnes*, *Peptostreptococcus stomatis*, *Parvimonas micra*, *Slackia exigua*, and *Dialister pneumosintes*, are enriched in GC tissues and promote chronic inflammation.^{31,34,37–43} Conversely, there is a decreased abundance of certain bacteria, such as *Sphingobium yanoikuvae*, which can degrade carcinogenic hydrocarbon compounds.⁴⁴ A summary of bacterial abundance studies in gastric diseases over the past 5 years is presented in Table 2.

1.4. Microbiome and tumor microenvironment (TME)

After colonization, microorganisms promote tumor initiation and progression by modulating the local microenvironment through direct interactions with host cells or indirectly via immune cell modulation.

1.4.1. Microbiome and non-immune cells

Microorganisms interact with tumor cells either through direct contact or through secreted factors. Surface adhesion molecules enable tight binding to host cells and activation of downstream responses. For instance, *H. pylori*, classified as a Group 1 carcinogen by the World Health Organization, expresses adhesion factors such as BabA, SabA, OipA, and AlpA/B, which induce inflammatory genes including interleukin (IL)-8, IL-6, and RANTES. In addition, pathogens could secrete several virulence factors to interact with host cells and regulate the molecular activities of host cells. For instance, *H. pylori* can produce a series of virulence factors such as cytotoxin-associated gene A (CagA), vacuolating cytotoxin A (VacA), and other outer membrane proteins. CagA is translocated

into gastric epithelial cells through a Type IV secretion system (T4SS), undergoes tyrosine phosphorylation, and activates oncogenic pathways, leading to abnormal proliferation.^{74,75} As a pore-forming toxin, VacA enters cells and the mitochondrial membrane through the formation of chloride channels to alter mitochondrial membrane permeability, leading to mitochondrial fragmentation, reactive oxygen species formation, and autophagy.⁷⁶ Outer membrane proteins (e.g., Hop, Hor, Hof, Hom, FecA/FrpB-like proteins, efflux pumps) further promote chronic inflammation and DNA damage, contributing to tumorigenesis (Figure 2).^{77,78} Furthermore, Hippo signaling could be induced in response to the *H. pylori* and EBV infection-associated GC initiation.⁷⁹

S. anginosus, a gram-positive, non-spore-forming, non-motile bacterium, has been identified as a new carcinogenic pathogen enriched in the gastric epithelial mucosa of GC patients. The virulence factor TMPC produced by *S. anginosus* binds to the membrane receptor ANXA2 on gastric epithelial cells, activating oncogenic MAPK signaling through the phosphorylation of ERK and JNK, thereby promoting gastric tumorigenesis.⁸⁰

Mycobial pathogen also exhibits a similar interaction pattern. The important roles of the fungal microbiome in carcinogenesis are related to microbial inflammation. During fungal invasion, pathogen-associated molecular patterns (PAMPs), such as Coley's toxins, lipopolysaccharide, monophosphoryl lipid A, glucans, and mannans in polysaccharides and aliphatic groups, *etc.*, are recognized by pattern recognition receptor (PRR) receptors such as Toll-like molecules. Interactions between fungal PAMPs and host PRRs trigger multiple signaling cascades leading to chronic inflammation. For instance, *Malassezia*, typically a skin pathogen, promotes cancer development by activating the lectin pathway through the production of PAMPs such as mannose-binding lectins, which drive the C3 complement cascade.⁸¹ This strategy of inducing protumor cytokines such as IL-4, IL-5, and IL-13 through PAMPs is dependent on fungi within the TME.⁸² To counteract this, oncogenic KrasG12D induces cancer cells to secrete IL-33, a chemoattractant for Type 2 immune cells. This strategy of inducing protumor cytokines such as IL-4, IL-5, and IL-13 via PAMPs is dependent on fungi within the TME⁸² (Figure 3, left side—non-specific pattern). As a prototypical pathogenic fungus, *Candida albicans* also possesses various PAMPs, which play different roles in host interactions, *that is*, lectin-like sequence (Als) proteins facilitate the binding of *C. albicans* to cadherins, which are critical for adhesion and epithelial disruption.^{83,84} Membrane-bound enzymes involved in hyphal growth, such as enolase and phytase,

Table 2. Summary of microbiota sequencing studies on patients with gastric disease from the past 5 years

Genus (top 5)	Sample source	Sample type	Sample number	Ref.	Year
<i>Streptococcus</i> , <i>Lactobacillus</i> , <i>Haemophilus</i> , <i>Neisseria</i> , <i>Vellonella</i>	GC/ChG	Feces	25v25	Zhou <i>et al.</i> ⁴⁵	2022
<i>Alloprevotella</i> , <i>Neisseria</i> , <i>Pasteurellaceae</i> , <i>Aggregatibacter</i> , <i>Porphyromonas</i>	GC/SG	Tissue	6v5	Hu <i>et al.</i> ⁴⁴	2018
<i>Lactobacillus</i> , <i>Streptococcus</i> , <i>Acinetobacter</i> , <i>Prevotella</i> , <i>Sphingomonas</i>	GC/NC	Tissue	37v37	Dai <i>et al.</i> ⁴⁶	2021
<i>Oceanobacter</i> , <i>Methylobacterium</i> , <i>Syntrophomonas</i> , <i>Prevotella</i> , <i>Comamonas</i>	GC/SG	Tissue	53v30	Peng <i>et al.</i> ⁴⁷	2022
<i>Lactobacillus</i> , <i>Streptococcus</i> , <i>Fusobacterium</i> , <i>Muribaculaceae</i> , <i>Methylobacterium</i> , <i>Methylobacterium</i>	GC/NC	Tissue	16v16	Yang <i>et al.</i> ⁴⁸	2022
<i>Kroppenstedtia</i> , <i>Lentibacillus</i> , <i>Oceanobacillus</i> , <i>Eikenella</i> , <i>Prevotella-2</i>	GC/SG	Tissue	15v17	Zhang <i>et al.</i> ⁴⁹	2021
<i>Corynebacterium</i>	GC/FD	Tissue	108v20	Oosterlinck <i>et al.</i> ⁵⁰	2023
<i>Peptostreptococcus</i> , <i>Neisseria</i> , <i>Aggregatibacter</i> , <i>Filifactor</i> , <i>Veillonella</i>	GC/NC	Antral brushing sample	144v144	Wu <i>et al.</i> ⁵¹	2022
<i>Haemophilus</i> , <i>Acinetobacter</i> , <i>Bacteroides</i> , <i>Haemophilus parainfluenzae</i>	GC/NC	Serum	108v50	Dong <i>et al.</i> ⁵²	2019
<i>Lactobacillus</i> , <i>Streptococcus</i> , <i>Fusobacterium</i>	GC/NC	Feces	49v49	Yu <i>et al.</i> ⁵³	2021
<i>Lactobacillus</i> , <i>Veillonella</i> , <i>Alloprevotella</i>	GC/ChG	Gastric juice	56v16	Park <i>et al.</i> ⁵⁴	2022
<i>Lactobacillus</i> , <i>Pseudomonas</i> , <i>Staphylococcus</i>	GC/NC	Tissue	76v29	Nikitina <i>et al.</i> ⁵⁵	2023
<i>Proteus</i> , <i>Phyllobacteriaceae</i> , <i>Enhydrobacter</i> , <i>Moryella</i> , <i>Vibro</i>	GC/NC	Tissue	4v17	Png <i>et al.</i> ⁵⁶	2022
<i>Lactobacillus</i> , <i>Parvimonas</i> , <i>Streptococcus</i> , <i>Fusobacterium</i> , <i>Glutamicibacter</i>	GC/Non-GC	Tissue	48v120	Gantuya <i>et al.</i> ³²	2020
<i>Brevundimonas</i> , <i>Lactacaseibacillus</i>	GC/Non-GC	Tissue	45v92	Kim <i>et al.</i> ⁵⁷	2022
<i>Paracoccus</i> , <i>Brevundimonas</i> , <i>Deinococcus</i> , <i>Roseburia</i> , <i>Pseudomonas</i>	NL/Non-NL	Tissue	27v36	Li <i>et al.</i> ⁵⁸	2021
<i>Bradyrhizobium</i> , <i>Sphingomonas</i> , <i>Sphingobium</i> , <i>Acinetobacter</i> , <i>Serratia</i>	PLGC/SG	Tissue	121v27	Liu <i>et al.</i> ⁵⁹	2021
<i>Bacillus</i> , <i>Acinetobacter</i> , <i>Sphingomonas</i> , <i>Peptostreptococcus</i> , <i>Streptococcus</i>	GC/NAT	Tissue	62v62	Chen <i>et al.</i> ⁶⁰	2019
<i>Lactobacillus</i> , <i>Fusobacterium</i> , <i>Veillonella</i> , <i>Neisseria</i> , <i>Brevundimonas</i>	GC/SG	Tissue	64v61	He <i>et al.</i> ⁶¹	2022
<i>Streptococcus</i> , <i>Bifidobacterium</i> , unclassified <i>Streptophyta</i>	GC/ChG	Saliva	99v194	Huang <i>et al.</i> ⁶²	2021
<i>Streptococcus</i> , <i>Lactobacillus</i> , <i>Bifidobacterium</i> , <i>Mobiluncus</i> , <i>Lautropia</i>	GC/Non-GC	Tissue	16v44	Peng <i>et al.</i> ⁶³	2023
<i>Escherichia shigella</i> , <i>Dialister</i> , <i>Streptococcus</i>	GC/NC	Feces	119v140	Zhang <i>et al.</i> ⁶⁴	2022
<i>Abiotrophia</i> , <i>Prochlorococcus</i> , <i>Peptococcus</i> , <i>Shewanella</i> , <i>Lachnoanaerobaculum</i>	IM/SG	Gastric juice	12v12	Li <i>et al.</i> ⁶⁵	2022
<i>Parabacteroides</i> , <i>Oscillibacter</i> , <i>Fusobacterium</i> , <i>Haemophilus</i> , <i>Veillonella</i>	GC/SG	Feces	32v33	Jeong <i>et al.</i> ⁶⁶	2024
<i>Cupriavidus</i> , <i>Sphingomonas</i> , <i>Sphingobium</i> , <i>Brevundimonas</i> , <i>Herbaspirillum</i>	GC/NAT	Tissue	20v20	Shi <i>et al.</i> ⁶⁷	2022
<i>Streptococcus</i> , <i>Ruminococcus gnavus</i> , <i>Candidatus Nitrotoga</i> , <i>hungatella</i> , <i>Erysipelatoclostridium</i>	GC/NC	Feces	20v30	Zhang <i>et al.</i> ⁶⁸	2021
<i>Streptococcus</i> , <i>Lactobacillus</i> , <i>Bifidobacterium</i>	GC/Non-GC	Tissue	15v168	Sun <i>et al.</i> ⁶⁹	2022
<i>Prevotella</i> , <i>Streptococcus</i> , <i>Troponoma</i> , <i>Lachnoanaerobaculum</i> , <i>Peptostreptococcus</i>	GC/NAT	Tissue	6v6	He <i>et al.</i> ⁷⁰	2023
<i>Streptococcus</i> , <i>Neisseria</i> , <i>Haemophilus</i> , <i>Veillonella</i>	GC/SG	Tissue	14v63	Wang <i>et al.</i> ⁷¹	2024
<i>Lactobacillus</i> , <i>Veillonella</i> , <i>Streptococcus</i> , <i>Rothia</i> , <i>Fusobacterium</i>	GC/Non-GC	Tissue	54v78	Wang <i>et al.</i> ¹⁸	2020
<i>Streptococcus</i> , <i>Selenomonas</i> , <i>Fusobacterium</i> , <i>Propionibacterium</i> , <i>Corynebacterium</i>	GC/NC	Tissue	229v230	Liu <i>et al.</i> ³⁸	2019
<i>Streptococcus</i> , <i>Parvimonas</i> , <i>Veillonella</i> , <i>Haemophilus</i> , <i>Neisseria</i>	GC/NAT	Tissue	36v36	Shao <i>et al.</i> ⁷²	2018
<i>Streptococcus</i> , <i>Veillonella</i> , <i>Neisseria</i> , <i>Haemophilus</i> , <i>Actinobacillus</i>	GC/NAT	Tissue	25v9	Liu <i>et al.</i> ⁷³	2019

Abbreviations: ChG: Chronic gastritis; FD: Functional dyspepsia; GC: Gastric cancer; IM: Intestinal metaplasia; NAT: Nonadjacent tumor; NC: Normal control; NL: Neoplasia lesions; PLGC: Precancerous lesions of GC; SG: Superficial gastritis.

enable binding with host fibronectin and laminin, destroy epithelial tissue, and promote nutrient acquisition.^{85,86} Other PAMPs, including candidalysin, aspartic protease, phospholipase, and lipase, drive tissue damage and immune cell recruitment.^{87,88} Notably, candidalysin, a recently discovered toxin peptide encoded by the

ece1 gene, has been shown to play a significant role in inflammasome activation through the activation of the EGFR and MAPK pathways, promoting cell proliferation and neutrophil recruitment during invasion.⁸⁸ In addition to this innate immunity triggered by nonspecific patterns, microbial pathogens can also promote tumor development

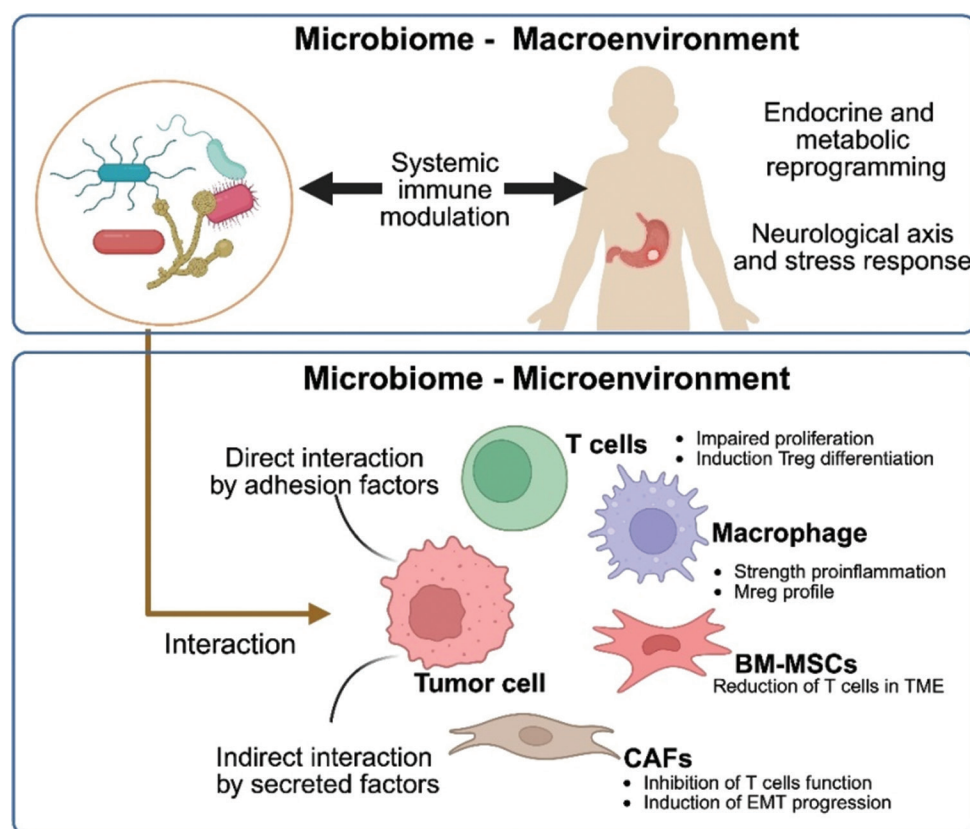


Figure 2. Multi-level interactions between microbiota, macroenvironment, and the tumor microenvironment in gastric cancer (GC). The human microbiota—including gastric, intestinal, and oral microbial communities—can influence GC development through both systemic (macroenvironmental) and local (microenvironmental) pathways. At the macroenvironmental level, alterations in the composition of microbiota can affect host immunity, metabolism, and inflammation. These systemic effects subsequently modulate tumor microenvironment, shaping immune cell infiltration, stromal remodeling, and tumor-immune interactions. Within the tumor microenvironment, microbial-derived signals influence various immune and non-immune cell populations, including T cells, macrophages, dendritic cells, fibroblasts, and myeloid-derived suppressor cells, thereby promoting or restraining tumor progression. Figure created in BioRender. Han *et al.* (2025) <https://BioRender.com/76rd6wm>.

Abbreviations: BM-MSCs: Bone marrow-derived mesenchymal stem cells; CAFs: Cancer-associated fibroblasts; EMT: Epithelial-mesenchymal transition; Mreg: Regulatory macrophages; TME: Tumor microenvironment; Treg: Regulatory T cell.

by secreting specific virulence factors to increase their virulence. Regarding fungal secreted effectors, to date, only one specific effector has been identified from *C. albicans*, namely Cmi1, which is secreted into the host cytosol and binds TBK1 to abrogate IRF3 phosphorylation and Type I interferon activation, thereby promoting the virulence and colonization of *C. albicans*⁸⁹ (Figure 3, left side—specific pattern). However, no other studies on fungus-derived virulence factors (with the exception of *C. albicans*) have been reported.

In addition to cancer and epithelial cells, immune-associated cells—such as cancer-associated fibroblasts (CAFs)—also play a key role in shaping the TME to defend against the infection of microorganisms. CAFs inhibit T cell function via fibroblast activation protein-mediated pathways. *H. pylori* also induces epithelial-mesenchymal transition in CAFs through nuclear factor

kappa B, signal transducer and activator of transcription 3, and transforming growth factor beta signaling pathways, thereby enhancing tumor progression.⁹⁰

1.4.2. Microbiome and immune cells

Besides the interaction with cancer cells, microorganisms shape the TME by modulating various immune cell populations, including tumor-associated macrophages, T cells, and myeloid-derived suppressor cells (MDSCs).

Microbial regulation of macrophages mainly involves altering the expression of immune response-related genes or preventing M1 polarization while promoting a greater regulatory macrophage (Mreg) profile. For example, macrophages in the TME are controlled by *H. pylori* through the regulation of specific microRNAs, such as decreasing the expression of miR-4270 to increase the proinflammatory effect of macrophages and upregulating

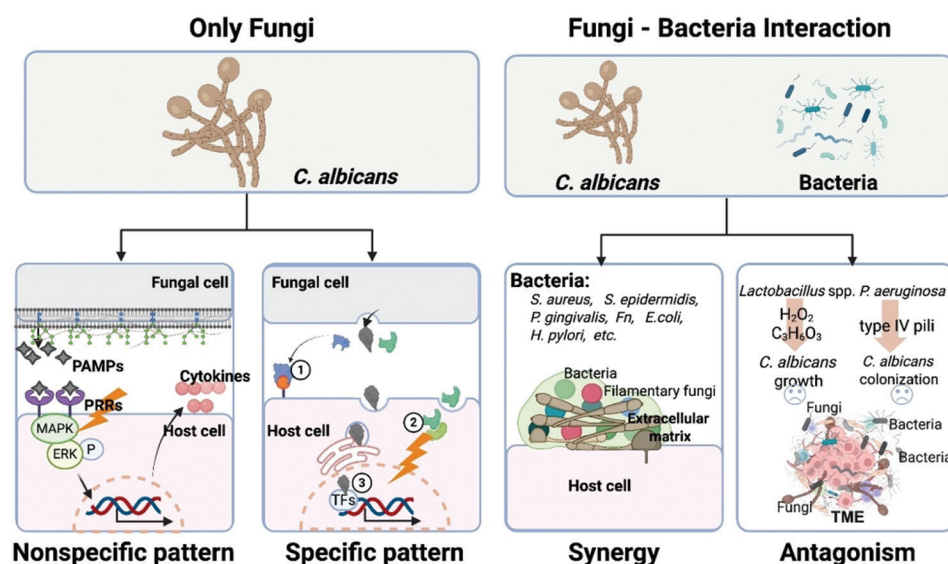


Figure 3. Schematic of two strategies of the interaction of fungi with host cell. The left side shows that fungi can interact with host cells by PAMPs-PRRs and the secretion of virulence factors. Some nonspecific small molecules, such as cell wall components, lipopolysaccharide, can be recognized by some membrane-bound receptor, thereby activating innate immune response. On the other hand, fungi could secrete some specific small virulence proteins to activate adaptive immune response. These proteins either remain in the extracellular space (①) or enter the cytosol (②), or enter the nucleus (③) of the host. They can be recognized by designated receptor, resulting in activation of a particular pathway. The right side of the schematic shows the interaction of fungi with host cell by synergy or antagonism with another microbiota. On the one hand, some bacteria, such as *Streptococcal* spp., *Fusobacterium nucleatum*, *Escherichia coli*, and *Helicobacter pylori*, can coexist with *Candida albicans* to enhance adhesion and biofilm formation. On the other hand, the existence of some bacteria like *Pseudomonas aeruginosa* and *Lactobacillus* spp. can inhibit the growth and colonization of *C. albicans* by producing toxic compounds such as hydrogen peroxide and lactic acid, as well as secreting type IV pili to prevent biofilm formation. Figure created in BioRender. Han *et al.* (2025) <https://BioRender.com/y96q680>.

Abbreviations: PAMPs: Pathogen-associated molecular patterns; PRP: Pattern recognition receptor.

the expression of miR-146b-5p, miR-185-5p, and miR146b to compromise bacterial antigen presentation to Th lymphocytes and impair immune responses.^{91,92} The upregulation expression of *arg2* results in cell apoptosis and reduced proinflammatory cytokine responses.⁹³ Matrix metalloproteinase 7 facilitates *H. pylori* escape from immune surveillance.⁹⁴ The production of heme oxygenase-1 results in less M1 polarization and a greater Mreg profile.

T cells play a crucial role in immune responses. Microorganisms can upregulate programmed death-ligand 1 (PD-L1) expression to inhibit T-cell proliferation and induce regulatory T cell (Treg) differentiation from naïve T cells, leading to immune escape. *H. pylori* components, such as T4SS elements, activate p38 MAPK signaling to induce PD-L1, weakening cytotoxic T cell activity.

Bone marrow-derived mesenchymal stem cells (BM-MSCs) further contribute to local and systemic immunosuppression by reducing T cell proportions.⁹⁵ During *H. pylori* infection, BM-MSCs upregulate thrombospondin 4, activating the integrin $\alpha 2$ /PI3K/AKT pathway, which promotes angiogenesis and facilitates differentiation into CAFs.^{96,97}

MDSCs are central mediators of immunosuppression in GC. A high abundance of MDSCs indicates more advanced GC and a poor prognosis. For example, *H. pylori* induces SLFN4⁺ MDSCs through miR-130b, promoting gastric metaplasia.⁹⁸ In addition, several markers play important roles in *H. pylori*-associated GC via effects on MDSCs, such as IL-22, which is secreted by polarized TH22 cells and stimulates CXCL2 production from gastric epithelial cells and causes CXCR2⁺ MDSC migration, contributing to the development of gastritis;⁹⁹ PD-1, which promotes tumor infiltration of MDSCs, leads to resistance to anti-PD-1/PD-1 treatment;¹⁰⁰ and Krüppel-like factor 4, which downregulates CXCL8, promoting MDSC recruitment to tumors and creating an immunosuppressive TME.^{101,102} Reduced expression of apoptosis signal-regulating kinase 1 has also been linked to the recruitment of immature MDSCs, facilitating gastric atrophy and metaplasia.¹⁰³

Compared to *H. pylori*, studies on the interactions between other bacteria or fungi and immune cells remain limited. Nonetheless, evidence suggests that microbial modulation of cytokine secretion contributes to an immunosuppressive TME. For instance, *Staphylococcus epidermidis* can significantly downregulate the expression

of proinflammatory cytokine genes, such as *IL-1B* and *IL-22* in *H. pylori*-infected mice.¹⁰⁴ Increased *IL-10* messenger RNA levels have been positively correlated with fungi such as *Apiotrichum*, *Cutaneotrichosporon*, *Simplicillium*, and *Sarocladium*,²¹ creating an immune-evasive microenvironment, thereby leading to poor prognosis.¹⁰⁵ *Candida*-dominated tumors exhibit activation of the IL-1 proinflammatory pathway, increased neutrophil infiltration, impaired cell adhesion, and a higher frequency of advanced-stage (stage IV) metastasis.^{24,106}

1.5. Microbiome and immunotherapy in GC

Immunotherapy has played a pivotal role and has remained a challenging issue for antitumor treatment in the last decade. The main strategy of immunotherapy lies in the activation of the innate immune system, particularly T-cell-mediated immunity, by targeting immune checkpoint inhibitors (ICIs), including cytotoxic T-lymphocyte-associated antigen 4 (CTLA4), PD-1, and its ligand PD-L1 (or B7-H1). Kang *et al.*¹⁰⁷ evaluated PD-1/PD-L1 blockade therapy and reported long-lasting responses ranging from 30% to 50% in advanced GC.

However, the efficacy of ICIs is often inconsistent, which can be attributed to multiple factors, including host-related and tumor-intrinsic characteristics. Emerging evidence suggests that the microbiome may play a role in modulating responses to immunotherapy. Certain microbial signatures have been identified as potential predictors of treatment outcomes. For instance, the phylum *Firmicutes*, family *Ruminococcaceae* and *Lachnospiraceae*, and genera *Bacteroides*, and *Catenibacterium* harbor the most predictive features, and they might play a role in the response to anti-PD-1/PD-L1 therapy in patients with gastrointestinal cancer.^{108–110} The absence of *Faecalibacterium prausnitzii*, *Akkermansia muciniphila*, *Prevotella*, *Bacteroides*, and *Bifidobacterium* dampens the efficacy of anti-PD-1 treatment.¹⁰⁹ Several studies have suggested that microbiota, mainly from the gastrointestinal tract, such as *Burkholderiales*, *Bacteroides fragilis*, and *Bacteroides Thetaiotaomicron*, can inhibit the antitumor effects inspired by CTLA4 in mice by promoting the maturation of dendritic cells. Based on these findings, combining microbiome modulation with ICIs represents a promising therapeutic strategy, although the underlying mechanisms remain largely unclear.

Transplantation or supplementation of specific microbiota has shown potential to enhance ICI responses. For instance, transplantation of *Haldermania*, *Enterococcus faecalis*, and *Bacteroides polyformis* improved responses to nivolumab, while *Doloides* enhanced responses to pembrolizumab.¹¹¹ Tanoue *et al.*¹¹² reported that oral

administration of a defined consortium of 11 bacterial strains enhanced the efficacy of ICIs in murine models. Sivan *et al.*¹¹³ demonstrated that oral administration of *Bifidobacterium* alone has the same degree of therapeutic effect as PD-L1 immunotherapy. In advanced GC patients, *Odoribacter* and *Veillonella* could enhance nivolumab monotherapy.¹¹⁴ To date, however, no related literature has definitively demonstrated a direct causal relationship between specific microbiota and ICIs efficacy in GC patients.

1.6. Bacteria-fungi interactions with tumorigenesis

A vast array of microorganisms colonizes the human body, and the intricate interactions among these microbial communities—including mutualistic, commensal, and competitive relationships—exert profound and multifaceted effects on the TME. Recent studies have revealed that the microbial diversity within GC tissues is significantly increased, indicating a more complex microbial network shaping the TME.^{32,115} In *H. pylori*-positive patients, there is an enrichment of phyla such as *Proteobacteria*, *Spirochetes*, *Akkermansia*, and *Acidobacteria*, alongside a depletion of *Actinobacteria*, *Bacteroidetes*, and *Firmicutes*.^{116,117} Coker *et al.*⁴³ suggested that *Methylobacillus* and *Arthrobacter*, together with *H. pylori*, are among the primary pathogens contributing to gastritis in China. Beyond bacterial interactions, the certain fungi, notably *C. albicans*, play pivotal roles in tumorigenesis. *C. albicans* can promote GC progression by reducing the diversity and abundance of gastric bacterial communities.²³ Its infection disrupts mucosal bacterial homeostasis, resulting in a marked enrichment of *Streptococcus* and *Enterococcus* species. Moreover, synergistic interactions between *C. albicans* and various oral *Streptococcus* species enhance adhesion, biofilm formation, and inflammatory cytokine production, collectively fostering a pro-tumorigenic environment^{118–121} (Figure 3, right side—synergy). Several bacterial species, such as *Porphyromonas gingivalis*, *F. nucleatum*, and *E. coli*, have been reported to interact synergistically with *C. albicans* by the formation of polymicrobial biofilms to strengthen systemic bloodstream infections.¹²² More interestingly, In GC, *H. pylori* has been observed to gain protection against environmental stress through co-colonization with *C. albicans*.¹²³ *C. albicans*, *Actinomyces naeslundii*, and *Streptococcus mutans* produce biofilms that trigger the malignant transformation of oral keratinocytes, modulate the adhesion of oral squamous cell carcinoma cells to the extracellular matrix, and induce the production of proinflammatory cytokines such as IL-6 and IL-8.¹²⁴ Conversely, certain bacterial species have an antagonistic relationship with *C. albicans* (Figure 3, right side—antagonistic). For instance, *Lactobacillus* spp. produced

hydrogen peroxide and lactic acid to inhibit the growth of *C. albicans*.¹²⁵ Similarly, *Pseudomonas aeruginosa* can impede *C. albicans* biofilm formation through secretion of type IV pili effectors and modulate IL-22-mediated host responses to suppress fungal colonization.¹²⁶ Besides this, *P. aeruginosa* could inhibit the colonization of *C. albicans* by regulating the transcription of IL-22 to inhibit the inflammatory response by macrophages.

Functional analysis of colorectal cancer (CRC) metagenomes suggested that bacterial-fungal interactions may contribute to carcinogenesis by increasing D-arginine and D-ornithine levels and stimulating butyrate metabolism pathway.¹²⁷ Studies have demonstrated a strong positive correlation between mycobiome and bacterial communities within the TME, regardless of their diversity, abundance, or co-occurrence patterns. It indicates the possibility of cooperative or non-competitive intratumoral microbial survival, in stark contrast to the gut microbiome, where fungal and bacterial populations often exhibit antagonistic dynamics, especially under anticancer or antibiotic treatments.¹²⁸⁻¹³¹ For instance, Shiao *et al.*¹²⁹ demonstrated that antibiotic-mediated depletion of intestinal fungi enhanced responses to radiotherapy, whereas bacterial depletion had the opposite effect. These findings suggest that the TME may autonomously select or passively accommodate diverse microbial communities, highlighting the need to consider cancer clonal evolution as a multispecies process involving coordinated interactions among the mycobiome, bacterial microbiota, and the host immune system. A multi-kingdom microbial analysis of a CRC metagenomic dataset revealed that 16 microbial biomarkers (including 11 bacterial, 4 fungal, and 1 archaeal signature) were more effective in identifying CRC patients than single boundary markers were.¹²⁷ Zhu *et al.*¹³² reported that, for CRC patients with excess body weight (EBW-CRC), a multi-kingdom microbial analysis including 12 bacterial and 3 fungal species may contribute to the precise diagnosis and treatment of EBW-CRC. Among them, *Fn*, *Porphyromonas asaccharolytica*, *G. morbillorum*, and *C. difficile* have been reported as important biomarkers for CRC.^{127,133,134} There is still a lack of evidence concerning multi-kingdom microbial analysis in GC.

Collectively, these insights underscore the potential of multi-kingdom microbial profiling in improving diagnostic accuracy and therapeutic stratification in GC and CRC patients, offering advantages over analysis limited to single microbial domains.

1.7. Double-edged sword effect of the microbiome on GC

The role of microorganisms in cancer is highly context-dependent and does not follow a simple “beneficial” or

“harmful” dichotomy. For instance, although *H. pylori* is a well-established carcinogen that actively promotes gastric carcinogenesis, emerging evidence indicates that *H. pylori*-infected GC share molecular features with immunotherapy-responsive subtypes, with higher expression levels of genes involved in proliferation-related pathways as well as immune response pathways, including *PDCD1* (encoding PD-1) and *CD274* (encoding PD-L1), while concurrently showing reduced expression of stromal-related genes. These findings suggest that *H. pylori* infection might paradoxically act as a “probiotic-like” factor in certain GC contexts, potentially enhancing responsiveness to immune checkpoint blockade.^{135,136} Supporting this notion, *H. pylori*-positive patients receiving anti-PD-1 therapy (e.g., pembrolizumab) demonstrated higher combined positive scores ≥ 10 , improved overall survival, and enhanced treatment efficacy compared to *H. pylori*-negative patients.¹³⁷ These observations suggest that microorganisms themselves may not be inherently “good” or “bad;” rather, their effects largely depend on the surrounding microenvironment, host responses, and specific cancer subtypes. A similar dual role is seen in other microbes. *Fn*, for example, has been reported to confer resistance to anti-PD-1 therapy in microsatellite-stable (MSS) CRC, yet it may sensitize microsatellite instability-high colorectal tumors to immunotherapy, highlighting subtype-specific effects. Moreover, patients with EBV-positive GC tend to exhibit better prognoses than those with other GC subtypes, further emphasizing the subtype-dependent nature of microbe-tumor interactions.¹³⁸

Whether a microorganism functions as a “probiotic” or a “pathogen” may also depend on the broader microbial components that coexist within the same niche. For example, *H. pylori*-positive but EBV-negative MSS GC patients treated with anti-PD-1/PD-L1 antibodies displayed significantly longer immune-related progression-free survival and median immune-related overall survival compared to *H. pylori*-negative counterparts.¹³⁵ In preclinical models, *H. pylori* infection combined with a decrease in *Lachnospiraceae* and *Erysipelotrichaceae* abundance and an increase in *Bifidobacterium* has been shown to enhance the efficacy of anti-CTLA4 therapy in B16-OVA melanoma-bearing mice.¹³⁹ Collectively, these findings illustrate the “double-edged sword” nature of the microbiome in GC, whereby its impact on tumor progression and therapy responsiveness is dictated by complex interplays among microbial composition, host factors, and tumor molecular characteristics. This nuanced understanding highlights the potential of microbiome-based stratification and modulation strategies to optimize cancer immunotherapy.

1.8. Epstein–Barr virus and GC

The mechanisms by which viruses contribute to gastric carcinogenesis are entirely different from those of bacteria and fungi. EBV has two distinct phases in its life cycle: latency and lytic replication. During latency, the chromatin of EBV, as a circular episome, travels through the host nucleus and is tethered to host chromatin. In this process, the majority of EBV genes, except for those encoding EBV nuclear antigens (EBNA1, EBNA2, EBNA3A, 3B, and 3C) and EBNA leader protein (EBNA-LP) and latent membrane protein 1 (LMP1), LMP2A, and LMP2B, are silenced to escape host defense immune surveillance.¹⁴⁰ Once a human is infected by EBV, it establishes a lifelong state of carrying the virus, which is called latent infection. According to the gene expression pattern, this period can be categorized as latency I, II, and III.¹⁴¹ Half of Nasopharyngeal carcinoma (NPC) and Epstein–Barr virus-associated gastric carcinoma (EBVaGC) cases are latency I; many EBV nucleus antigen genes, such as *EBNA1*, *EBER1*, and *EBER2*, as well as *BamHI*-A rightward transcripts are expressed. Latent Phase II tumors, including the remaining NPC and Hodgkin lymphoma types, are characterized by the expression of LMP1 in addition to latency I transcripts. Latent Phase III tumors are typified by lymphomas observed in immunosuppressed patients and additionally express EBNA2, 3A, 3B, 3C, and LP.¹⁴² During the viral lytic replication cycle, epigenetic suppression is triggered, and all EBV lytic genes are expressed simultaneously. This results in more than 100-fold genome amplification and subsequent cell death.¹⁴³ In 2023, Wen *et al.*¹⁴⁴ reported that EBV can secrete olfactomedin 4 (OLFM4) to promote GC tumor progression through Hippo signaling.

1.9. Application of multi-omics in GC

Recently, the technique of multi-omics has been applied into various diseases such as inflammatory bowel disease, COVID-19, and CRC.^{145–149} The occurrence of GC is multifactorial. Multi-omic approaches provide a comprehensive view of the connection between the microbiome and host gene expression in gastric carcinogenesis. For instance, canonical correlation analysis showed that *Helicobacteraceae* and *Veillonellaceae* were related with various genes, including FAM3 metabolism-regulating signaling molecule D, serine/threonine kinase 17b, and complement factor I in GC patients, which is distinct from upregulation of *CKM* and *CA9* genes in the healthy stomach group with various probiotics such as *Comamonadaceae*, *Lachnospiraceae*, and *Bacteroidales*.¹⁵⁰ The application of multi-omics analysis in GC has revealed distinct microbial and metabolic signatures that correlate with GC progression. By integrating microbiome profiling with transcriptomic and metabolomic data, studies have

demonstrated that specific microbial communities, such as *E. shigella*, *Bacteroides*, *Enterococcus*, and *Lactobacillus*, through 16S rRNA sequencing in the *H. pylori*-positive group, interact with host genetic pathways, influencing key oncogenic processes. Transcriptome sequencing showed three genes (*GCG*, *APOA1*, and *IGFBP1*) are good predictors of overall survival. This multi-layered approach uncovers new biomarkers and therapeutic targets.¹⁵¹ While multi-omics approaches hold great promise in identifying biomarkers and unraveling the complexities of GC, several challenges remain, including the integration of heterogeneous data types and the need for standardized protocols across platforms. These challenges can complicate the reproducibility of findings and the translation of multi-omics results into clinical practice. Collectively, by identifying specific microbial signatures associated with GC, multi-omics analyses could pave the way for microbiome-based therapies or microbiota modulation as an adjunct to conventional treatments like chemotherapy or immunotherapy.

1.10. Engineered microbes: A new therapeutic approach

As mentioned above, specific gut microbiota can serve as biomarkers for the occurrence, development, and prognosis of cancer. In turn, specific gut microbiota can also be used as a means of preventing or treating cancer. Certain gut microbiota has been reported to exhibit antitumor properties. For example, *Clostridium butyricum* induces cancer cell apoptosis by stimulating the release of TNF-related apoptosis-inducing ligand (TRAIL) from polymorphonuclear neutrophils through the toll-like receptor 2/4 signaling pathway.¹⁵² Pre-operative treatment with *Streptococcus pyogenes* has been shown to improve the 5-year survival rate of Stage III GC patients and prevent cancer recurrence by inducing direct tumor cell lysis and stimulating humoral immunity.^{153–156} Gut microbiota transplantation is one of the mainstream practices for using microorganisms to treat cancer. It can be done by preparing the donor's gut microbiome into capsules or by feeding it to the recipient through capsule. Numerous studies found that germ-free or antibiotic-treated mice showed the improvement of antitumor effect via the transplantation the fecal microbiota of PD-1 responders. At present, this method has been widely applied to various diseases, such as digestive diseases (inflammatory bowel disease,¹⁵⁷ irritable bowel syndrome¹⁵⁸), neurological disorders (multiple sclerosis, hepatic encephalopathy), and metastatic melanoma.^{159–161} Evenly, fecal microbiota transplantation achieved high cure rates of patients with inflammatory bowel disease¹⁶² (Figure 4A).

The microbiota plays a pivotal role in maintaining host health and homeostasis, influencing not only metabolic

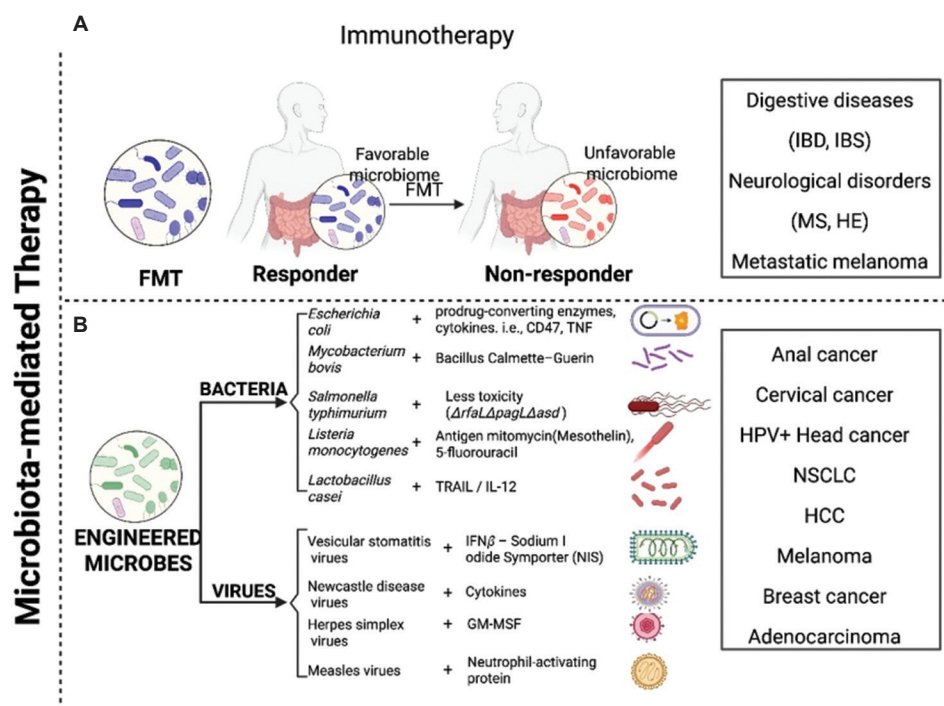


Figure 4. Summary of therapeutic strategies based on the microbiome. (A) Fecal microbiota transplantation strategy. The fecal microbiome originating from patients who responded to immunotherapy treatment was transplanted into nonresponsive patients. Fecal microbiota transplantation strategy has been applied to digestive diseases, neurological disorders, and metastatic melanoma. (B) Engineered-microbiota strategy. There are three strategies based on microbiota engineering techniques: (1). Microbiomes with antitumor functions via the expression of cytokines, secondary metabolites, and inflammatory activators. (2) Functional microbiome with less toxicity caused by the mutagenesis of key virulence genes. The engineered-microbiota strategy has been widely applied in various cancers, such as anal cancer, cervical cancer, and head cancer. Figure created in BioRender. Han *et al.* (2025) <https://BioRender.com/3z9b25u>.

Abbreviations: FMT: Fecal microbiota transplantation; HCC: Hepatocellular carcinoma; HE: Hepatic encephalopathy; HPV: Human papillomavirus; IBD: Inflammatory bowel disease; IBS: Irritable bowel syndrome; MS: Multiple sclerosis; NSCLC: Non-small cell lung cancer; TNF: Tumor necrosis factor; TRAIL: TNF-related apoptosis-inducing ligand.

and immunological functions but also the initiation, progression, and dissemination of cancer.^{163,164} Although the identification of beneficial gut microbes for therapeutic use holds significant promise, challenges such as undefined microbiota toxicity and the “great plate count anomaly” (the discrepancy between observed microbes and those that can be cultured) remain major hurdles.¹⁶⁵ Beyond the conventional approach of microbiota supplementation combined with immunotherapy, recent advances have focused on exploiting the intrinsic tumor-targeting properties of microbes through synthetic biology. Three main strategies have emerged for engineering microbes for cancer biotherapy (Figure 4B):

(i) *Genetically attenuated strains.* These bacteria are genetically modified to reduce pathogenicity while retaining tumor-targeting capacity and immunostimulatory potential. They can enhance intratumoral immune cell infiltration and mediate potent antitumor effects. One notable example is *Bacillus Calmette–Guerin*, derived from

Mycobacterium bovis, which remains the only Food and Drug Administration (FDA)-approved bacterial therapy, used clinically for non-muscle-invasive bladder cancer.¹⁶⁶ *Salmonella spp.* are gram-negative and facultative anaerobic bacteria. Similarly, VNP20009, an attenuated strain of *Salmonella Typhimurium*, has demonstrated therapeutic potential in models of renal cell carcinoma and treatment-resistant metastatic melanoma.^{167,168}

(ii) *Drug chassis with tumor-homing bacteria.* This strategy programs tumor-targeting bacteria to deliver cytotoxic agents, prodrug-converting enzymes, or immunomodulatory molecules (e.g., cytokines) directly into TME. A wide range of bacterial genera, including *Escherichia*, *Bifidobacterium*, *Listeria*, *Shigella*, *Clostridium*, *Lactococcus*, *Vibrio*, and *Salmonella*, have been explored as delivery vehicles.¹⁶⁹ Among these, *E. coli* is the most extensively engineered. For instance, engineered *E. coli* DH5 α expressing TRAIL can induce apoptosis in solid tumors. Other

E. coli strains engineered to produce β -glucuronidase impair cancer cell replication through DNA damage; TNF-producing *E. coli* suppress angiogenesis and promote direct tumor cell death; *E. coli* secreting azurin inhibit tumor metastasis by disrupting key signaling pathways.¹⁷⁰⁻¹⁷² Engineered *Salmonella choleraesuis* carrying an endostatin-expressing plasmid has shown to significantly reduce tumor burden and elicit robust antitumor immune responses through targeted gene therapy.¹⁷³

- (iii) *Smart control of microbial therapeutics.* An emerging innovation in microbial engineering involves quorum-sensing systems that enable therapeutic proteins to be expressed only when bacterial populations reach a defined threshold within the tumor. This approach minimizes systemic toxicity while enhancing therapeutic specificity.^{174,175} Both non-pathogenic *E. coli* and *Salmonella* have been designed to lyse at high densities, releasing chemokines, hemolysins, or pro-apoptotic agents directly into the tumor niche.¹⁷⁶ In 2019, non-pathogenic *E. coli* was further engineered to express a CD47 nanobody antagonist, thereby enhancing the phagocytic clearance of tumor cells and increasing T cell infiltration, effectively blocking tumor metastasis.¹⁷⁷

Beyond model organisms such as *E. coli* and *Salmonella*, other bacterial species with distinct biological characteristics have also been harnessed for tumor-targeted applications. *Listeria monocytogenes*, a Gram-positive facultative intracellular bacterium, thrives within the host cytoplasm and can directly stimulate cellular immunity. Engineered *L. monocytogenes* strains with attenuated toxicity and integrated antigen-adjuvant systems represent promising platforms for cancer immunotherapy. For instance, ADXS11-001, a live attenuated listeria-based vaccine with the antigens mitomycin and 5-fluorouracil, has shown favorable therapeutics outcomes in several cancers, including anal cancer, cervical cancer, and HPV⁺ head cancer, attributed to enhance T cell infiltration and reduce local immunosuppression.¹⁷⁸ Another strain, CRS-207, expresses the tumor-associated antigen mesothelin, effectively activating cytotoxic immune responses against mesothelin-overexpressing tumors.¹⁷⁹ Beyond *listeria*, *Lactobacillus casei* ATCC393 has also been engineered for anticancer applications. It promotes the expression of TRAIL and decreases cancer cell viability, offering therapeutic potential in CRC models.¹⁸⁰ To overcome limitations such as rapid clearance and immune-mediated toxicity, a novel biomimetic strategy (Lmo@RBC) has been developed. This approach involves encapsulating *L. monocytogenes* in red blood cell membranes and selectively deleting key virulence genes, allowing the

bacteria to evade immune detection and prolong systemic circulation. The resulting platform enhances tumor accumulation and preferential colonization due to the hypoxic, anaerobic nature of the TME.¹⁸¹

In parallel with bacterial platforms, oncolytic virotherapy has emerged as another innovative modality in cancer treatment. Oncolytic viruses can selectively infect, replicate within, and lyse tumor cells while simultaneously stimulating systemic antitumor immunity. Commonly studied oncolytic viruses include adenovirus, vesicular stomatitis virus, Newcastle disease virus (NDV), herpes simplex virus (HSV), and measles virus. Reovirus, a naturally nonpathogenic virus, exploits Ras pathway activation in tumor cells to exert oncolytic effects.¹⁸² NDV preferentially infects tumor cells with impaired Type I interferon signaling, leading to immunogenic cell death.¹⁸³ NDV preferentially infects tumor cells with impaired Type I interferon signaling, leading to immunogenic cell death.¹⁸⁴ *Talimogene laherparepvec* (T-VEC), the first FDA-approved oncolytic HSV, is engineered to express granulocyte-macrophage colony-stimulating factor (GM-CSF), which promotes antigen presentation and enhances immune cell recruitment.¹⁸⁵ T-VEC, the first FDA-approved oncolytic HSV, is engineered to express GM-CSF, which promotes antigen presentation and enhances immune cell recruitment.¹⁸⁶

Together, advances in engineered bacteria and oncolytic virotherapy represent a new frontier in precision cancer therapeutics. By harnessing the natural tumor-targeting properties and immune-modulatory capacities of microbial agents, these strategies offer highly customizable platforms for safe, localized, and synergistic antitumor interventions. As synthetic biology and microbiome engineering continue to evolve, integrating microbial therapies into multimodal cancer treatment regimens holds great promise for improving patient outcomes.

Translating microbiome-based therapies into clinical trials for GC presents several significant challenges. First, the complexity and diversity of the gastric microbiome make it difficult to identify universally applicable therapeutic targets. Unlike simple pharmacological agents, microbiome-based treatments involve modulating entire microbial communities, which can have unpredictable effects on both the host and other microorganisms. Another major hurdle is the potential for off-target effects and safety concerns. While certain microbiota has demonstrated therapeutic potential, such as promoting the efficacy of immunotherapies or reducing cancer cell proliferation, introducing new microbial strains or altering existing microbiota may have unintended consequences. These could include disrupting the delicate balance of the

gastric ecosystem, leading to adverse effects like dysbiosis or immune system perturbations. In addition, conducting large-scale, longitudinal clinical trials to evaluate the long-term effects and safety of microbiome-based therapies in GC patients is resource-intensive and requires careful design to account for confounding factors such as diet, geography, and comorbid conditions. The lack of established biomarkers to monitor microbiome intervention success further complicates patient stratification and treatment response evaluation.

In summary, continued research into the mechanisms by which the microbiome influences GC and careful clinical trial design are essential for the successful translation of microbiome interventions into effective therapies for GC patients.

2. Limitations and future challenges

Despite significant advances in understanding the complex interplay between the microbiome and GC, several critical limitations continue to hinder the translation of research findings into clinical practice: (i) Technological and methodological inconsistencies: Variability in sample collection protocols, DNA extraction methods, sequencing platforms, and bioinformatics pipelines can significantly influence microbial composition profiling. These discrepancies not only affect taxonomic resolution and functional inference but may also underlie the inconsistencies in species diversity and abundance reported across different studies. Standardized methodologies and cross-platform validation are essential to ensure data reproducibility and comparability. (ii) Ethnic and geographic variability: The composition and function of the gastric microbiome, particularly the mycobiome, are heavily influenced by host ethnicity, regional diet, and environmental exposures. Current studies are often limited to specific geographic or ethnic populations, restricting the generalizability of findings. Broadening the demographic scope of microbiome research through multinational, multiethnic cohorts is critical for defining universally relevant microbial signatures associated with GC. (iii) Lack of longitudinal data: GC develops over decades through a multistep cascade from chronic inflammation to metaplasia and dysplasia. However, most microbiome studies are cross-sectional in nature, capturing microbial profiles at a single time point and often in late-stage disease. Longitudinal studies with repeated sampling in high-risk individuals or during precancerous stages are urgently needed to elucidate causal relationships and dynamic microbial changes during tumor evolution. (iv) Translational and clinical integration barriers: Despite increasing evidence supporting the role of the microbiome in GC pathogenesis and therapy response, translating

these insights into effective diagnostic tools or microbial therapeutics remains challenging. Obstacles include small sample sizes, insufficient functional validation, lack of “gold-standard” microbial reference databases, and limited regulatory frameworks for live microbial products. Moreover, the integration of advanced tools such as spatial transcriptomics, metabolomics, and multi-omics-based microbial mapping remains in its infancy. Enhancing translational potential will require not only methodological innovation but also collaboration among microbiologists, oncologists, bioinformaticians, and regulatory experts. Addressing these limitations is not merely a matter of technical refinement; it represents a paradigm shift in how we conceptualize cancer biology. The stomach is not a sterile organ but a dynamic ecosystem, and understanding its microbial ecology over space and time is key to unlocking novel preventative, diagnostic, and therapeutic avenues. Future studies must embrace interdisciplinary, longitudinal, and population-scale approaches while simultaneously advancing the precision and functional interpretation of microbial data.

3. Conclusions and perspectives

Microorganisms accompany the human host throughout life, playing key roles in immune regulation, metabolic homeostasis, and, increasingly recognized, cancer biology. A growing body of evidence highlights the indispensable contributions of the microbiome to the initiation, progression, and therapeutic responsiveness of GC. This review summarizes current insights into how microbial communities—particularly bacteria and fungi—modulate the tumor immune microenvironment and influence responses to immunotherapy in GC.

Dominant bacterial phyla associated with GC include *Proteobacteria*, *Firmicutes*, *Actinobacteria*, and *Fusobacteria*.¹⁸⁷ However, investigations into the gastric mycobiome remain nascent. Several technical and conceptual challenges have hindered fungal research in this field. The stomach's acidic environment, low fungal biomass, and limited sensitivity of fungal detection methods (e.g., ITS sequencing with incomplete reference databases) all contribute to under-characterization. Moreover, most existing studies are correlative and lack functional validation through *in vitro* or *in vivo* models. Small, regional-specific cohorts also limit the generalizability of findings. Historically, the research landscape has been dominated by *H. pylori*, leading to underfunding and insufficient methodological development in fungal microbiome research.

To overcome these barriers, future efforts should prioritize integrative, multi-omics approaches, such

as deep ITS2 sequencing, metagenomics, and meta-transcriptomics, to enhance taxonomic resolution and functional annotation. Mechanistic studies using co-culture systems, humanized mice, and GC organoids are essential to dissect causal relationships. Furthermore, large-scale, multi-center cohort studies incorporating clinical metadata and immune profiling will be crucial to evaluate the diagnostic and therapeutic potential of fungal communities in GC. Given the structural complexity and rich secondary metabolite biosynthetic capacity of fungal genomes, understanding their contributions may unveil novel immunomodulatory or oncogenic mechanisms.

To date, only specific bacteria and viruses, such as *H. pylori*, EBV, and *S. anginosus*, have been demonstrated to directly cause GC carcinogenesis. However, emerging evidence implicates others, such as the fungus *C. albicans*, as potential microbial cofactors. Fungal dysbiosis in GC is often characterized by reduced diversity, abundance, and community evenness, with *C. albicans* being explored as a potential biomarker.²³ Nevertheless, relying on single-species assessments is insufficient in capturing the complexity of host-microbiome-tumor interactions. The emergence of core microbiota panels—defined by combinatorial microbial signatures—has improved diagnostic accuracy and prognostic prediction in other cancers. For instance, a panel of sputum bacterial biomarkers, including *Acidovorax* and *Veillonella*, could be used for the detection of lung adenocarcinoma.¹⁸⁸ Derosa *et al.*¹⁸⁹ demonstrated that a 21-bacteria probe could be applied for the prediction of non-small cell lung cancer patients as well as colorectal and melanoma cancer patients.

In the past, antimicrobial interventions aimed to eliminate all microbes indiscriminately. However, it is now evident that not all microorganisms exert detrimental effects on cancer. On the contrary, several commensals may enhance therapeutic efficacy. For example, *Enterococcus hirae* and *Barnesiella intestinihominis* have a positive regulatory relationship with the efficacy of chemotherapy when treated with the alkylating agent cyclophosphamide. Similarly, *Akkermansia* and *Bifidobacterium* species are associated with improved responses to immunotherapies, particularly checkpoint inhibitors targeting PD-1/PD-L1 and CTLA4.^{190,191} Despite these advances, such microbiota-therapy interactions remain underexplored in GC, especially with respect to fungal species and their influence on treatment response and long-term prognosis.

In summary, this paper provides a comprehensive overview of the intricate and dynamic relationship between the microbiome and GC. Unraveling the mechanisms by which microbial communities influence GC development and therapy response is essential for advancing precision

oncology. Moving beyond correlative observations toward mechanistic and translational studies will enable the discovery of microbial biomarkers, immunomodulatory metabolites, and engineered therapeutic consortia. Understanding these interactions at a deeper level will not only enhance our knowledge of GC pathogenesis but also open new avenues for more targeted and effective interventions, ultimately improving patient outcomes in GC management.

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Conflict of interest

The authors declare that they have no competing interests.

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