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REVIEW

Role of the Microbiome in the Diagnosis and Management of Gastroesophageal Cancers

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Abstract

Purpose Stomach and esophageal cancers are among the highest mortality from cancers worldwide. Microbiota has an interplaying role within the human gastrointestinal (GI) tract. Dysbiosis occurs when a disruption of the balance between the microbiota and the host happens. With this narrative review, we discuss the main alterations in the microbiome of gastroesophageal cancer, revealing its potential role in the pathogenesis, early detection, and treatment.

Results *Helicobacter pylori* plays a major role the development of a cascade of preneoplastic conditions ranging from atrophic gastritis to metaplasia and dysplasia, ultimately culminating in gastric cancer, while other pathogenic agents are *Fusobacterium nucleatum*, *Bacteroides fragilis*, *Escherichia coli*, and *Lactobacillus*. *Campylobacter* species (spp.)'s role in the progression of esophageal adenocarcinoma may parallel that of *Helicobacter pylori* in the context of gastric cancer, with other esophageal carcinogenic agents being *Escherichia coli*, *Bacteroides fragilis*, and *Fusobacterium nucleatum*. Moreover, gut microbiome could significantly alter the outcomes of chemotherapy and immunotherapy. The gut microbiome can be modulated through interventions such as antibiotics, probiotics, or prebiotics intake. Fecal microbiota transplantation has emerged as a therapeutic strategy as well.

Conclusions Nowadays, it is widely accepted that changes in the normal gut microbiome causing dysbiosis and immune dysregulation play a role gastroesophageal cancer. Different interventions, including probiotics and prebiotics intake are being developed to improve therapeutic outcomes and mitigate toxicities associated with anticancer treatment. Further studies are required in order to introduce the microbiome among the available tools of precision medicine in the field of anticancer treatment.

Keywords Microbiome · Esophageal cancer · Gastric cancer · Gut · Helicobacter pylori

Introduction

Stomach and esophageal cancers are among the highest mortality from cancers worldwide, ranking third and sixth, respectively [1]. Esophageal cancer can develop as a result of uncontrolled gastroesophageal reflux disease (GERD). Approximately 7% of patients with reflux experience a change in the esophageal epithelium from squamous to columnar, leading to Barrett's esophagus (BE). BE is a premalignant condition which carries a risk of progression to esophageal adenocarcinoma (EAC). EAC and squamous cell carcinoma (ESCC) are the two most common forms of esophageal cancers [2–4].

Other identified risk factors that may cause the development of BE and EAC include male sex, advanced age, obesity, and cigarette smoking [5]. The gut microbiota has been shown as an independent factor that contributes

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to the development of GERD, BE, and EAC. Microbiota plays a mutualistic role within the human GI tract, influencing numerous physiological mechanisms such as digestion, regulating metabolism, drug metabolism, vitamin synthesis, and immune system development and helps maintain the integrity of the esophageal mucosal barrier.

Dysbiosis occurs when there is a balance disruption between the microbiota and the host. Dysbiosis, through a complex series of mechanisms, can lead to inflammation, genomic instability, mutations, proliferative signaling, and immune system evasion [2, 6–8]. Dysbiosis can be attributed to a variety of factors, including inadequate nutrition, stress, environmental factors (e.g., smoking and physical inactivity), or specific diseases like inflammatory, autoimmune, and chronic conditions. Additionally, drug usage (e.g., antibiotics and anticancer drugs) and various medical and surgical procedures may also play a role in the development of dysbiosis [9, 10].

Dysbiosis has been implicated in other GI tract cancers, including gastric cancers. One of the most common risk factors for developing gastric cancer (GC) is infection with *Helicobacter pylori* (*H. pylori*). In many cases, *H. pylori* sets off an inflammatory process which goes from atrophic gastritis to intestinal metaplasia and, finally, gastric cancer [11–13]. Other risk factors include older age, male gender, environmental factors such as smoking, alcohol, and consumption of salty and smoked foods [11, 14]. In addition to the role of *H. pylori*, it has been shown that the oral and stomach microbiome also has an important function in the pathogenesis of GC [15]. In fact, several studies demonstrate a reduction in diversity and an alteration of microbial composition in patients with GC compared to healthy patients [16].

How the Microbiome Can Predispose to Tumor Formation

The gut microbiome has been recognized not only as a critical player in maintaining homeostasis but also as a potential contributor to different diseases, including cancer. The mechanisms by which the microbiome can influence tumorigenesis are multifaceted and intricate, ranging from immune modulation to direct genotoxic effects. Despite ongoing explorations, the direct influence of the gut microbiota on the pathogenesis of cancers remains less definitively established. Within the scope of this review, our objective is to dissect and scrutinize the array of mechanisms through which the gut microbiota may influence the predisposition to gastroesophageal neoplasms.

Key Pathways and Mechanisms of Carcinogenesis Mediated by Gut Microbes

Alteration in the microbiota's diversity and composition is often viewed to be a key factor in the etiology of cancer [17]. Preclinical studies performed using germ-free mice models showed how the gut microbiome may cause cancer development and progression through different mechanisms [18, 19]. Three primary mechanisms by which dysbiosis contributes to carcinogenesis are chronic inflammation, immune dysregulation, and the effects of microbial metabolites.

Chronic Inflammation as a Carcinogenic Driver

Chronic inflammation is recognized as a catalyst for cancer, promoting tumor progression, invasion, and metastasis. It can directly cause DNA damage in epithelial cells through aberrant DNA methylation [20]. Gut dysbiosis can drive cancer formation; it causes epithelial reprogramming and induces local inflammation. In turn, it leads to local induction of interleukin (IL)-6 secretion and proliferation of intestinal epithelial cells, ultimately leading to tumor formation [21]. Elevations in cytokines such as IL-1, IL-6, IL-10, and tumor necrosis factor-alpha (TNF-α) contribute to cancer development through a tripartite process: (I) activation of pathways like nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), Wnt signaling, and mitogen-activated protein kinases (MAPK); (II) inhibition of apoptosis; and (III) an increase in oxidative stress [22]. Inflammatory mediators may also downregulate oncosuppressor genes, such as by inducing P53 mutations, and activate oncogenes, including KRAS mutations [23, 24].

Dysbiosis and Immune Dysregulation in Tumor Formation

The innate and adaptive immune systems play an important role in managing the colonization niche of the intestinal microbiota, employing mechanisms that include the production of antimicrobial peptides and IgA antibodies [25]. Within the gut mucosa, the T and B cells adapted to specific microflora-affected locales, which are pivotal in maintaining immune homeostasis. They achieve this by suppressing responses to benign antigens and protecting the integrity of the intestinal mucosal barrier [25]. The intestinal mucosal surface barrier not only permits microbial symbiosis but also serves as a critical line of defense against environmental

insults to the gut microbiota. The prompt restoration and ongoing maintenance of the intestinal barrier are crucial for re-establishing and preserving homeostatic balance.

While the immune system's mechanisms are vital in preventing dysbiosis, the establishment of a dysbiotic microbial community can profoundly affect both the local mucosal and systemic immune responses. This dysbiosis can lead to the movement of bacterial products into the systemic circulation, further exacerbating immune dysregulation. Such disturbances in immune homeostasis and barrier integrity are increasingly recognized as significant contributors to the process of tumorigenesis, highlighting the interplay between the gut microbiota, immune function, and cancer development [25–28].

Role of Microbial Metabolites in Carcinogenesis

Microbial metabolites such as lipoteichoic acid (LTA), secondary bile acids, and short-chain fatty acids (SCFAs) have been shown to play ambivalent roles in cancer development [29]. LTA interacts with cluster of differentiation 14 (CD14) or Toll-like receptor 2 (TLR), provoking an overproduction of pro-inflammatory factors [30, 31]. Secondary bile acids, via the activation of G protein-coupled bile acid receptor 1 (GPBAR1), can promote intestinal cell proliferation, induce DNA damage, and lead to cellular senescence and a pro-inflammatory secretory phenotype [32–34]. These metabolites collectively contribute to the malignant transformation process. Conversely, SCFAs can exert anti-inflammatory and anticarcinogenic effects by promoting immunoregulation through regulatory T cells (Tregs) [35–37].

The microbiome's role in the diagnosis and management of gastroesophageal cancers is a rapidly developing field of research due to its association with reduced patient prognosis. We next review alterations in the microbiome among both healthy individuals and those with gastroesophageal cancer, revealing its potential role in the pathogenesis, early detection, and treatment of this disease.

Gastroesophageal Microbiome and Differences Between Healthy Individuals and Cancer Patients

Esophageal Microbiome

It has been estimated that the GI tract contains 10^{14} microorganisms [38]. Studies have suggested that the majority of the gut microbiota is represented by the following phyla: Firmicutes (*Clostridium*, *Ruminococcus*, *Eubacterium*, *Peptostreptococcus*, *Peptococcus*, *Lactobacillus*-L.), Bacteroidetes, Proteobacteria (Enterobacteriaceae), and Actinobacteria (*Bifidobacterium*-BF) [5]. In the esophagus, there is a complex microbial community, and it has been estimated that there are 140–166 bacterial species of resident microbes [39, 40]. Pei et al. found that six phyla represent the esophageal microbiota: Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria, and TM7 (Saccharibacteria). The predominant genus is *Streptococcus* (39%), then there are *Prevotella* (17%), and *Veilonella* (14%) [41]. Yang et al. confirmed the predominance of Firmicutes and *Streptococcus* genus in the esophageal tract [40].

Chronic reflux can cause esophageal mucosal damage, leading to the formation of an inflammatory background that facilitates dysplasia and carcinogenesis. This phenomenon may indirectly influence the microbial composition of the esophagus because different bacteria belong to specific niches [42]. In fact, the microbiota of the normal esophagus undergoes changes in patients with reflux-related disorders, as well as in response to proton-pump inhibitor therapy [43]. These findings have supported the concept of categorizing the microbiome composition into two groups, labeled as "type I and type II." Type I, representing the normal esophagus, was found to be predominantly populated with high quantities of *Streptococcus*, in contrast to patients with excessive esophageal acid exposure (type II), which exhibited a higher proportion of Gram-negative, anaerobic, and microaerophilic organisms [42]. This suggests that Gram-positive bacteria are more present in the healthy esophageal microbiome, while GERD leads to a shift towards an increased presence of Gram-negative and anaerobic bacteria [42, 44]. Their data revealed that the phylum Planctomycetes was significantly reduced across the disease groups, particularly in cases of high-grade dysplasia (HGD) and EAC, when compared to control subjects. Additionally, the phylum Crenarchaeota exhibited a similar reduction [42].

A case–control study conducted by Snider et al. revealed changes in microbial communities associated with esophageal carcinogenesis, including increases in Proteobacteria presence and reductions in Firmicutes. Additionally, two families, Verrucomicrobiaceae and Enterobacteriaceae, exhibited increased presence in cases of HGD and EAC [45]. EAC, compared to healthy subjects, shows a decrease in microbial diversity, and community composition is modified; in particular, there is a reduction in Gram-negative (*Veillonella*, *Megasphaera*, and *Campylobacter)* and Gram-positive taxa (*Granulicatella*, *Atopobium*, *Actinomyces*, and *Solobacterium*) and increased *Lactobacillus fermentum* [39].

In 2016, Yamamura et al. analyzed esophageal cancer tissues from 325 patients who had undergone esophageal cancer resection. They discovered the presence of *Fusobacterium nucleatum* (*F. nucleatum*) in esophageal cancer tissues, and this was linked to shorter survival, indicating a role as a prognostic biomarker [46].

Gastric Microbiome

The human stomach has always been considered an inhospitable organ for microorganisms because of acidic conditions and other antimicrobial factors. However, with the discovery of *H. pylori* and the development of new molecular techniques and metagenomics analyses, bacterial communities have been found in the stomach.

H. pylori is part of the gastric biota in a considerable portion of the human population. It is the strongest risk factor for GC development and is reported as a type I carcinogen by the International Agency for Research on Cancer [14]. *H. pylori* is an acidotolerant bacterium that can survive at pH 5, so its favorite location is in the gastric mucus near the epithelial cells of the mucosa [12]. Several factors influence the survival and function of the gastric microbiota. The typical gastric environment, full of antibacterial enzymes, defensins, immunoglobulins, and high gastric acid levels, poses a significant challenge to gastric microbiota [47].

The most represented phyla in gastric mucosa are Proteobacteria, Firmicutes, Bacteroidetes, Actinobacteria, and Fusobacteria [14, 48, 49]. Zilberstein et al. found a predominance of *Lactobacillus* sp., *Veillonella* sp., and *Clostridium* sp., which are all acid-resistant [50]. Coker et al. studied the microbiome in patients with GC and noted changes in the microbial composition in different stages of the tumor. In particular, they found a significantly higher abundance of taxa that are members of the oral microbiome including *P. micra*, *P. stomatis*, *Fusobacterium nucleatum*, and *Gemella*. They had previously been associated with GI cancers [51]. In particular, *F. nucleatum* has been positively correlated with a worse prognosis in patients with Lauren's diffuse-type gastric cancer [52].

Ferreira et al. compared the gastric microbiota of patients with gastric cancer and patients with chronic gastritis revealing significant differences. They found that in gastric carcinoma, there is an abundance of Proteobacteria, including the genera *Phyllobacterium* and *Achromobacter*, as well as the families Xanthomonadaceae and Enterobacteriaceae. Additionally, Firmicutes and Actinobacteria were also more abundant in gastric carcinoma, particularly *Lactobacillus*, *Clostridium*, and *Rhodococcus* [49]. As supported by the literature, they found a decreased alpha diversity in carcinoma compared to gastritis. In fact, microbial diversity has been identified as a characteristic of disease states, including inflammatory diseases and cancer [49].

Changes occur in the microbiome when there is a positive *H. pylori* status. Specifically, it is characterized by an increased number of non-*Helicobacter* bacteria from the Proteobacteria, Spirochetes, and Acidobacteria phyla, while there was a decreased abundance of Actinobacteria, Bacteroidetes, and Firmicutes [53]. Liu et al. worked to characterize the differences in the gastric microbiota associated with the development of GC. Their findings revealed an enrichment of *Prevotella melanogenic*, *Streptococcus anginosus*, and *Propionibacterium acnes* in cancerous tissues compared to normal and paracancerous tissues. In contrast, they noted a significant reduction in the abundance of *H. pylori*, *Prevotella copri*, and *Bacteroides uniformis* in cancerous tissue [54].

Specific Gut Microbes and Pathways of Carcinogenesis

Helicobacter pylori and Gastric Carcinogenesis

Within the intricate ecosystem of the gut microbiota, certain bacterial strains have been implicated in the oncogenic processes affecting the GI tract. A paradigm of this association is embodied by *Helicobacter pylori*, a bacterium with a well-established link to the development of a cascade of preneoplastic conditions ranging from atrophic gastritis to metaplasia and dysplasia, ultimately culminating in gastric cancer [55, 56]. The connection between *H. pylori* and oncogenesis is not merely associative; interventional studies have demonstrated that the eradication of this bacterium significantly diminishes the risk of gastric cancer, particularly noting a decreased onset of metachronous cancer following the endoscopic resection of early-stage gastric neoplasms [51, 57].

The mechanisms by which *H. pylori* facilitates oncogenesis are diverse, but many revolve oncoprotein cytotoxin-associated gene A (CagA) and vacuolating toxin A (VacA) [58]. Infections with CagA-positive *Helicobacter pylori* strains significantly escalate the risk of developing gastric cancers [59, 60]. Research has demonstrated that individuals infected with CagA-positive *H. pylori* exhibit increased levels of pro-inflammatory cytokines in the gastric mucosa, including interferon-γ, TNF-α, and interleukins such as IL-1, IL-1β, IL-6, IL-7, IL-8, IL-10, and IL-18. This cytokine accumulation prompts the recruitment and activation of lymphocytes, peripheral mononuclear cells, eosinophils, macrophages, neutrophils, mast cells, and dendritic cells. Correspondingly, the infection by CagA-positive *H. pylori* strains leads to the activation of several oncogenic signaling pathways, such as ERK/MAPK, PI3K/Akt, NF-κB, Wnt/β-catenin, Ras, sonic hedgehog, and STAT3. These strains also contribute to the suppression of tumor suppressor pathways, which is evidenced by the induction of mutations in the P53 gene, further contributing to the malignancy risk [61–63].

VacA, a multimeric pore-forming protein, is present in all *H. pylori* strains, and its presence in the human stomach is facilitated through pore formation in the epithelial membrane and subsequent exit of urea, enabling *H. pylori* to catalyze urea hydrolysis as a means of protecting against

gastric acidity [64]. VacA is known to induce vacuolation in cells and has been demonstrated to trigger autophagy in gastric epithelial cells of human origin [65–67] This effect is mediated through a direct interaction with the mitochondria, which is substantiated by several studies [68–72]. Furthermore, VacA has been implicated in the modulation of cellular signaling pathways; it upregulates the expression of MAP kinase and ERK1/2 [73]. It also activates vascular endothelial growth factor, which is crucial for angiogenesis [74, 75]. Additionally, VacA is involved in enhancing the Wnt/β-catenin signaling pathway, pivotal for cell proliferation and differentiation [76]. It further exerts its influence by inhibiting glycogen synthase kinase 3 (GSK3) via the PI3K/Akt signaling pathway, thereby potentially contributing to cellular processes that favor oncogenic transformation [77].

Infection with *H. pylori* has been associated with epigenetic alterations, particularly the methylation of CpG islands in critical genomic regions [78]. This includes the promoter regions of E-cadherin—a crucial molecule involved in cell adhesion—and genes that serve tumor suppressor functions, such as those coding for trefoil factor 2 (TFF2) and the forkhead box transcriptional regulator (FOXD3). These methylation events can lead to the silencing of these genes and thereby play a substantial role in the heightened risk of developing adenocarcinoma in the gastric tissues [74].

Other Microbes and Gastric Carcinogenesis

The prevailing dogma that the gastric environment was devoid of microbial life due to its acidic nature was challenged and refuted by the identification of *H. pylori* [79]. Initially, *H. pylori* was considered the solitary microbe resilient enough to inhabit the gastric niche. However, recent advancements in microbial research have now established that the gastric microbiota is far more varied, housing multiple bacterial species that can endure the acidic milieu of the stomach [79].

Although *H. pylori* stands out as a significant risk factor for the development of gastric cancer, the incidence of cancer development among those colonized by the bacterium is relatively low, affecting merely 1–2% of those infected [80–82]. With the enhancement of high-throughput sequencing capabilities, a wider array of gastric microbial communities has been implicated, suggesting a more complex interaction between the host's microenvironment and the potential for gastric carcinogenesis beyond the role of *H. pylori* alone. For instance, investigations employing quantitative PCR techniques have uncovered significant variations in the microbial profiles of individuals with gastric cancer. Notably, there has been a reported decrease in bacterial populations including *Porphyromonas*, *Neisseria*, the TM7 group, *Prevotella pallens*, and *Streptococcus sinensis*, with a concomitant increase in species such as *Lactobacillus coleohominis*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and members of the Lachnospiraceae family [83–85]. These shifts in the gastric microbiota may have profound implications for the development of gastric malignancies.

The pathogenic components from these non-*H. pylori Helicobacter* species, particularly outer membrane proteins like phospholipase C-gamma 2, BAK protein, and nickel-binding proteins, have been shown to facilitate the colonization of these microbes in the gastric mucosa. This colonization is a precursor to gastritis, which may escalate the risk of gastric tumorigenesis [86].

It is also possible that gastric microbiota may link *H. pylori* and gastric carcinogenesis, when other bacteria colonize the stomach in case of decreased acidity (such as chronic atrophic gastritis), creating reactive oxygen and nitrogen species and modulating inflammatory responses [87, 88].

Fusobacterium nucleatum and *Bacteroides fragilis*

Gut bacteria possess the capability to influence various cellular proliferation and pro-survival pathways in the host, thereby playing a contributory role in cancer development. Notable examples include the effector adhesin A (FadA) of *Fusobacterium nucleatum* and the metalloproteinase toxin (MP toxin) of *Bacteroides fragilis*. These bacterial factors are known to interact, either directly or indirectly, with E-cadherin in the host's epithelial cells. This interaction disrupts intercellular junctions and activates β-catenin signaling, which can lead to increased cell proliferation and potentially induce oncogenic transformation in the affected host cells [89, 90].

Another mechanism of tumorigenesis involves the induction of oxidative stress, which can lead to autonomous genomic mutations in host cells. For instance, *Bacteroides fragilis* have been shown to activate host spermine oxidase. This activation results in the production of hydrogen peroxide and reactive oxygen species (ROS), leading to increased DNA damage, a critical factor in the development of cancer [91].

Fusobacterium nucleatum can also promote carcinogenesis by impairing immune effectors that typically serve to inhibit tumor development. It inhibits the host's Natural Killer (NK) cells for its own benefit. This inhibition facilitates the recruitment of myeloid suppressor cells to the infection site, indirectly aiding in cancer initiation. This process is orchestrated by the bacterial virulence factor Fap2, which can bind to and inhibit the NK cell's inhibitory receptor, TIGIT. This interaction effectively hampers the NK cells' ability to attack tumor cells, thereby contributing to the progression of cancer [92].

Lactobacillus

Lactobacillus, a common gut microbe, produces lactate, which can potentially fuel the accelerated growth of tumor cells [93]. Tumor cells, especially those in rapid growth phases, primarily rely on anaerobic glycolysis over oxidative phosphorylation [94, 95]. This metabolic shift leads to increased lactic acid production, with lactate concentrations in glycolytic tumors being approximately tenfold higher than basal lactate levels in an average human. This elevation in lactic acid production by *Lactobacillus* is hypothesized to promote tumor cell growth [96–99].

Moreover, *Lactobacillus* has been observed to convert nitrate to nitrite, resulting in the formation of substantial quantities of N-nitroso compounds [100, 101]. These compounds are known to facilitate gene mutations, angiogenesis, and the expression of proto-oncogenes by epithelial cells, thereby contributing to the development of gastric cancer (GC). *Lactobacillus* and other lactic acid bacteria are also potent inducers of reactive oxygen species (ROS) in both cultured cells and in vivo, which can cause significant DNA damage [102]. Furthermore, lactic acid bacteria have been shown to upregulate the expression of NANOG, a marker of multipotency, transforming adult fibroblasts into multipotent cells [93, 103]. This finding lends support to the notion of a direct cancer-promoting activity of *Lactobacillus* and its metabolic byproducts.

Atopobium species

Atopobium spp. belongs to the *Coriobacterium* family and is an anaerobic microorganism that can produce large amounts of lactic acid [104]. Its pathogenic mechanism may be similar to *Lactobacillus* spp.

Clostridium species

Clostridium spp. produces toxic factor adhesion A on the cell surface, which binds to E-cadherin on endothelial cells and regulates either the cadherin or b-catenin pathway. This process brings the release of transcription factors, oncogenes, and inflammatory genes. Moreover, it can regulate the growth and cell proliferation of epithelial cells [105].

E. coli

In instances of pathogenic infections that lead to dysbiosis in the gut microbiome, bacterial pathogens can proliferate and produce substantial quantities of toxins. These toxins are capable of inducing DNA damage in the host, thereby causing genomic instability and the initiation and progression of tumors in susceptible cells [106–108]. A prime example is the production of colibactin and cytolethal distending toxin (CDT) by certain strains of *Escherichia coli*, both of which exhibit DNAse activity. When these toxins are liberated near the GI epithelium, they cause DNA double-strand breaks within the epithelial cells of the host. This damage initiates a transient cell cycle arrest, creating an environment conducive to genomic mutations, which can ultimately lead to tumor development [109].

Helicobacter pylori and Esophageal Carcinogenesis

Emerging data from population studies suggest that *Helicobacter pylori* infection may lower the risk of esophageal adenocarcinoma (EAC) [110–114]. The underlying hypothesis posits that chronic *H. pylori* infections, by impeding parietal cell function or promoting the development of atrophic gastritis, may limit the secretion of hydrochloric acid by these cells. This reduction in acid secretion leads to a higher pH in the gastric tract. Considering that Gastroesophageal Reflux Disease (GERD) is a primary contributor to Barrett's esophagus—a known precursor to EAC—an increase in gastric pH and a consequent reduction in acidity could result in a diminished incidence of reflux disease. This chain of events may ultimately contribute to a lower occurrence of EAC [115, 116].

Other Microbes and Esophageal Carcinogenesis

The esophageal microbiome in its normal state is predominantly composed of oral flora. Among its major constituents are members of the phylum Firmicutes, particularly represented by *Streptococcus viridans*. However, the esophageal microbiota is diverse, encompassing a range of other phyla such as Bacteroides (e.g., *Prevotella*), Actinobacteria (e.g., *Rothia*), Proteobacteria (e.g., *Haemophilus*), and Fusobacteria (e.g., *Fusobacterium*). In the normal esophagus, Gram-positive bacteria, particularly from the Firmicutes phylum and the *Streptococcus* genus, are prevalent. Conversely, Gram-negative anaerobes and microaerophiles, including those from the Bacteroidetes, Proteobacteria, Fusobacteria, and Spirochaetes phyla, are more commonly associated with esophageal pathologies such as esophagitis and Barrett's esophagus [40]. Lipopolysaccharide (LPS), an important component of the cell wall of gram-negative bacteria, is implicated in the oncogenic process through various mechanisms. These mechanisms encompass the activation of innate immune responses leading to NF-κB activation, the promotion of inflammatory mediators like IL1β, IL6, IL8, and TNFα, and the elevation of inducible nitric oxide synthase (iNOS) and nitric oxide (NO) levels. Furthermore, LPS contributes to gastroesophageal reflux by reducing the activity the lower esophageal sphincter and impeding gastric emptying, thereby exacerbating the risk factors associated with esophageal cancer [117–119].

Blackett and colleagues observed a notable enrichment of *Campylobacter* species in cases of GERD and Barrett's esophagus compared to control groups and those with esophageal adenocarcinoma [44]. Furthermore, they identified a higher expression of cytokines linked to carcinogenesis, such as IL-18, in tissues colonized by *Campylobacter* [44]. Considering the recently acknowledged pathogenic potential of *Campylobacter* species in humans, its role in the progression of esophageal adenocarcinoma may parallel that of *Helicobacter pylori* in the context of gastric cancer. This suggests a possible significant role for *Campylobacter* in the etiology and progression of esophageal adenocarcinoma [120].

In a study involving a rat model with esophagojejunal anastomosis, Zaidi et al. found a notable presence of *Escherichia coli* in both Barrett's esophagus and esophageal adenocarcinoma [121]. Additionally, they observed a significant upregulation of Toll-like receptors (TLRs) 1–3, 6, 7, and 9 in esophageal adenocarcinoma tissues compared to normal epithelium. These findings suggest a link between the TLR signaling pathway and the presence of *E. coli*, indicating that microbial activity may mediate early molecular alterations in the carcinogenesis of esophageal adenocarcinoma in this rat model. This points to the potential role of microbes in the initiation and progression of esophageal cancer [121].

Bacteroides fragilis has been implicated in compromising the integrity of tight junctions and increasing the permeability of the digestive tract through its toxin production, ultimately leading to inflammation and tumorigenesis. Cheng et al. highlighted this pathogenic process, indicating the bacteria's role in disrupting the gut barrier and promoting carcinogenic pathways [122]. Further supporting the link between *B. fragilis* and cancer, Li et al. reported a markedly higher expression of *B. fragilis* in fecal samples from patients with esophageal carcinoma compared to those from healthy individuals, suggesting a potential association between this bacterium and the development of esophageal cancer [123].

In a report of *Fusobacterium nucleatum*–positive tissue samples, the most prominent feature was "cytokine-cytokine receptor interaction." A more detailed examination of this data indicated an upsurge in specific chemokine genes, notably CCL20. This suggests that *Fusobacterium nucleatum* may play a role in worsening tumor behavior through the activation of chemokines like CCL20, highlighting a potential mechanistic link between this bacterium and enhanced tumor aggressiveness [46].

These multifaceted interactions between gut microbiome and host pathways underscore the complexity of carcinogenesis and highlight potential targets for therapeutic intervention.

Role of the Microbiome in GI Cancer Diagnosis

The microbiome has obtained increasing attention in recent years for its potential role in the diagnosis and development of GI cancers. Several evidence has shown that the gut microbiota exerts both pro-tumorigenic and anti-oncogenic effects; thus, specific microbial signature could be an important diagnostic biomarkers and screening tools for GI cancers [15, 124]. However, the identification of a biomarker with excellent sensitivity and specificity is challenging (Table 1).

H. pylori is a well-known risk factor for the development of GC and is considered a class I carcinogen by the International Agency for Research on Cancer [14]. A test launched by BIOHIT HealthCare Ltd promotes the early detection of gastric cancer and precancerous lesions with a blood sample through the detection of *H. pylori* infection and three stomach-specific biomarkers such as pepsinogen I, pepsinogen II, and gastrin-17 [125]. However, despite several studies confirming the potential of GastroPanel for improving patient outcomes through early identification of high-risk individuals, Sivandzadeh and colleagues concluded that this kit lacked the sufficient accuracy to diagnose gastric atrophy [126–128].

Patients with *H. pylori* infection have increased the expression of NADPH oxidase (NOX) and inducible nitric oxide synthase (iNOS), enzymes that cause reactive oxygen (ROS) and nitrogen (RNS) species production [129]. A recent study showed that levels of circulating nitrosative stress markers were increased in patients with gastric cancer. However, levels of NO, kynurenine, and *N*-formylkynurenine change significantly between gastric cancer patients with and without *H. pylori* infection. Therefore, more research is needed to identify the causal

Table 1 Gut microbes associated with gastroesophageal carcinogenesis

Gastric cancer	Esophageal cancer
Helicobacter pylori [51, 55–88]	*Campylobacter* spp. [44, 120]
Lactobacillus coleohominis [93–103]	*Escherichia coli* [121]
Klebsiella pneumoniae [83–85]	*Bacteroides fragilis* [122, 123]
Acinetobacter baumannii [83–85]	*Fusobacterium nucleatum* [46]
Fusobacterium nucleatum [89–92]	
Lachnospiraceae spp. [83–85]	
Bacteroides fragilis [89–92]	
Lactobacillus spp. [93–103]	
Atopobium spp. [104]	
Clostridium spp. [105]	
Escherichia coli [106–109]	

spp. species

relationship between *H. pylori* and nitrosative stress in the development of gastric cancer [130].

Several *H. pylori* virulence genes also affect gastric carcinogenesis [131]. However, the role of individual single nucleotide polymorphisms in bacterial genes in cancer development is unknown. Sharafutdinov and colleagues showed that a single-nucleotide polymorphism in *H. pylori*, the 171S/L HtrA mutation, facilitates gastric cancer development, making this single-nucleotide polymorphism a potential biomarker for gastric cancer risk predictions [132]. In addition, the International Immunopharmacology published a Chinese work in which investigated the potential role of a *H. pylori* infection–related gene, SOCS1, in stomach adenocarcinoma. The SOCS1 expression was increased in both *H. pylori*-infected and stomach adenocarcinoma patients but a higher SOCS1 expression indicated poor prognosis in stomach adenocarcinoma, indicating that SOCS1 may act as a potential biomarker for gastric cancer [133]. Kamarhei and colleagues exposed differentially expressed miRNAs between *H. pylori*–induced gastric cancerous tissue and non-tumor tissue collected from H. pylori–positive patients. Five microRNAs changed among the two groups, and gene functional analysis revealed that the ubiquitination system and ciliary process were primarily involved in *H. pylori*–induced GC. They concluded that DOCK4, GNAS, CTGF, TGF-b1, ESR1, SELE, TIMP3, SMARCE1, TXNIP, and MRPS5 may be considered prognostic biomarkers for *H. pylori*–induced GC [134].

Finally, a recent study revealed that also the protein tyrosine phosphatase non-receptor type 20 (PTPN20) could be a significant prognostic marker in *H. pylori*–related GC. Indeed, by measuring PTPN20 levels, it is possible to predict the survival of *H. pylori*–related GC, suggesting that PTPN20 targeting may be a promising way to treat *H. pylori*–related GC [135].

It is important to note that while there is a growing body of research on the microbiome's role in GI cancer diagnosis, this field is still in its early stages. More research is needed to establish specific diagnostic markers and clinical applications. Nevertheless, the microbiome's potential impact on GI cancer diagnosis is an exciting area of research that may lead to improved early detection, risk assessment, and treatment strategies for GI cancers in the future.

Interaction Between Gastroesophageal Microbiome and Therapy

The dynamic interplay between microbiota and cancer has been a subject of fascination in the scientific community for over a century, dating back to William Coley's pioneering work in the 1890s. Coley introduced the concept of bacterial therapy for cancer, using heat-inactivated *Streptococci*, later known as "Coley's toxins," for intratumoral injection in sarcoma patients [136, 137]. This concept was further advanced with the successful intravesical administration of *Mycobacterium bovis* post-resection in bladder cancer patients, significantly reducing tumor recurrence [138].

This historical groundwork has set the stage for numerous published and ongoing clinical trials exploring the use of attenuated gut bacterial strains in anticancer therapy. Understanding how the microbiome contributes to the progression of cancer holds promise for novel therapeutic approaches, especially in the context of gastric and esophageal cancer prevention and treatment.

Modulation of the gut microbiome could significantly alter the outcomes of anticancer therapies. Treatments such as radiotherapy, chemotherapy, and immunotherapy are known to alter the patient's microbiome. Conversely, the composition of the microbiome can profoundly affect the patient's response to these therapies [139]. Therefore, identifying the factors that influence the gut microbiome and developing strategies to manipulate it are critical for enhancing therapeutic outcomes in patients. Specifically, modulating the microbiome may play a crucial role in reducing toxicity associated with anticancer therapies and enhancing their efficacy [140, 141]. This underscores the importance of integrating microbiome-focused interventions into comprehensive cancer treatment strategies.

Influence of Gut Microbiota on Chemotherapy and Immunotherapy Outcomes in Gastric and Esophageal Cancers

The interplay between gut microbiota dysbiosis and both cancer pathogenesis and therapeutic outcomes is increasingly acknowledged. Specifically, the gut microbiota's ability to metabolize anti-tumor agents and modulate host immune responses and inflammation pathways plays a critical role in the regulation of therapeutic outcomes [142]. This dual impact of the microbiota is key to understanding its significant role in influencing the effectiveness of chemotherapy and immunotherapy.

Microbiota and Chemotherapy

Research has shown that the gut microbiota is crucial for the effectiveness of certain chemotherapy drugs. In tumor-bearing mice, the absence of a healthy gut microbiota (either germ-free or depleted following antibiotic therapy) results in a diminished response to oxaliplatin treatment. The gut microbiome produces Toll-like receptor (TLR) agonists, fostering an oxidative stress environment conducive to tumor cell death. Reactive oxygen species (ROS) produced by the microbiota enhance the DNA damage inflicted by oxaliplatin, leading to cell death [143].

Cyclophosphamide reduced regulatory T cells and increases the number of T helper (Th1) and Th17 cells [144, 145]. Mice with reduced gut microbiota demonstrate a decrease in Th17 cells and resistance to cyclophosphamide treatment [146]. Administering specific oral bacteria like *Lactobacillus johonsoni* and *Enterococcus hiraecan* can convert T cells to pro-inflammatory TH17 cells, enhancing the drug's efficacy [146, 147].

The chemotherapy agent irinotecan is activated into SN-38 by carboxylesterase in plasma, intestinal mucosa, liver, and tumor cells. The gut microbiota's β-glucuronidase reactivates the detoxified SN-38G in the intestine, leading to GI toxicity. Targeted inhibition of these gut bacterial enzymes has shown promise in reducing chemotherapy-induced toxicity [148].

Microbiota and Immunotherapy

The last decade has witnessed immunotherapy emerge as a cornerstone in modern cancer treatment paradigms. The intricate correlation between gut microbiota and the immune system is now recognized as a critical determinant in modulating a host's response to immunotherapy. Pioneering clinical studies have substantiated that variations in gut microbiome composition significantly impact the efficacy of immune checkpoint inhibitor (ICI) therapy across various tumor types, even those distant from the GI tract.

Recent research has established a strong link between the composition of a patient's microbiome and the intrinsic efficacy of ICI-based immunotherapy for various solid tumors [149–151]. Immune checkpoint inhibition modulates T cell activation against tumor cells. The prevalent checkpoint inhibitors in the market are monoclonal antibodies targeting either the cytotoxic T lymphocyte-associated protein 4 (CTLA4) or the programmed death 1 (PD1) and its ligand PD-L1, which are expressed on the surface of T cells and antigen-presenting cells (APCs), respectively [152].

In murine models, the gut microbiome composition has been demonstrated to significantly influence the host response to ICIs. Notably, two studies have highlighted the potential role of gut microbiota in enhancing the efficacy of anti-CTLA4 and anti-PD1 therapies [153, 154]. Vetizou et al. revealed that the effectiveness of anti-CTLA4 antibodies in reducing sarcoma tumor growth is significantly enhanced in the presence of a gut microbiome enriched with *Bacteroides fragilis* and *Burkholderia cepacia* [153]. Similarly, Sivan et al. observed that the efficacy of PD-L1 targeting antibodies in treating melanoma is improved with a gut microbiome enriched in *Bifidobacterium* species [154]. They further demonstrated that oral administration of a *Bifidobacterium* cocktail together with anti-PD-L1 antibodies notably augmented T cell responses and impeded melanoma growth [154].

Research by Shi et al. has focused on two critical aspects of the interaction between *H. pylori* and cancer immunotherapies. Elements of *H. pylori*, such as HP-NAP, CagA, VacA, BabA, and HspA, can act as enhancing tumor responses to ICIs. Moreover, *H. pylori* infection may modulate the efficacy of antitumor immunity elicited by ICIs by altering host immune responses [155]. Che et al.'s study found a correlation between *H. pylori* infection and efficacy of gastric cancer patients' immunotherapy, where *H. pylori*–positive patients had a higher risk of nonclinical response to anti-PD-1 antibodies compared to *H. pylori*–negative patients [156]. This raises the possibility of incorporating microbial elements such as *H. pylori* into vaccine strategies for treating upper GI malignancies.

The microbiome is increasingly viewed as a potential source of biomarkers for predicting ICI response. Sunakawa et al. investigated the role of gut microbiome gene expression as a predictor of ICI efficacy in advanced GC treated with nivolumab monotherapy. Upregulation of the bacterial invasion of epithelial cell pathway was associated with disease progression, and certain bacterial genera, namely *Odoribacter* and *Veillonella*, correlated with tumor response to nivolumab [157].

While immune checkpoint inhibitors have succeeded in treating various malignancies, their use is limited in some patients due to severe toxic side effects, such as gut inflammation and immune dysregulation [158]. The microbiome's influence extends to modulating or predicting the toxicity of immunotherapy. Oral administration of *Bacteroides fragilis* and *Burkholderia cepacia* in animal models has been shown to mitigate immunotherapy-associated toxic side effects [154]. Similarly, in patients treated with anti-CTLA4 antibodies, toxic side effects were associated with an increased abundance of Firmicutes, such as *Faecalisbacterium*, and a decreased abundance of *Bacteroides* [159, 160].

In an observational study encompassing 95 patients with advanced GI malignancies treated with immunotherapy, the correlation between the gut microbiome and the incidence of immune-related adverse events (irAEs) was examined through metagenomic sequencing of baseline fecal samples. This analysis identified specific bacterial species and metabolic pathways potentially implicated in the genesis of irAEs among patients with gastric, esophageal, and colon cancers. The study found a higher prevalence of *Ruminococcus callidus* and *Bacteroides xylanisolvens* in patients who did not manifest severe irAEs [161]. These findings collectively reinforce the hypothesis that gut microbiota plays a crucial role in modulating not only the response to immunotherapy but also its associated toxicities.

Modulation of the Gut Microbiome with Probiotics: Implications for Cancer Therapeutics

The gut microbiome can be modulated through interventions such as antibiotics, probiotics, or prebiotics. The utilization of probiotics, in particular, offers a method to introduce beneficial microbial components absent in the human host. These probiotics, mainly consisting of lactic acid bacteria (LAB) from genera like *Lactobacillus* and *Bifidobacterium*, have shown promise in cancer prevention, especially among high-risk populations. Such probiotic strains, predominantly Gram-positive, are increasingly recognized for their role in treating GI disorders [162, 163].

GI cancers have been linked to certain bacterial strains, including *Streptococcus bovis*, *Bacteroides*, *Clostridia*, *and Helicobacter pylori* [164–166]. Conversely, strains like *L. acidophilus* and *B. longum* have shown the potential to inhibit carcinogenic tumor growth. Thus, maintaining a balance between damaging and beneficial bacteria is crucial in modulating cancer risk. Shifting the proportion of microbes with the use of probiotics influences carcinogen bioactivation and, thus cancer risk [167, 168].

Studies on probiotics and gastric cancer are mainly focused on *H. pylori* infection as the major risk factors of gastric cancer [169]. Notably, probiotic strains such as *B. bifidum*, *L. acidophilus*, *L. rhamnosus*, and *L. salivarius* have demonstrated inhibitory effects on *H. pylori* in diverse animal models [170]. Recent meta-analyses underscore the utility of incorporating probiotics alongside antibiotic therapy in enhancing the efficacy of *H. pylori* eradication protocols [171–173]. Such probiotic supplementation during antibiotic treatment for *H. pylori* has been observed to reduce adverse side effects, leading to improved patient compliance and, in some instances, heightened eradication rates. Additionally, the successful eradication of *H. pylori* has been correlated with the regression of gastric tumor–promoting lymphoid tissue proliferation [174, 175] The implications of these findings suggest that modulating gut microbiome with probiotic supplementation could represent a pivotal adjunct in the management of gastric cancer, particularly in strategies aimed at targeting *H. pylori* infection.

The efficacy of probiotics in mitigating the toxicities associated with anticancer treatments, such as diarrhea and mucositis, is a subject of ongoing preclinical studies and clinical trials [176, 177]. The administration of probiotics, particularly *Lactobacillli*, aims to repopulate the compromised gut microbiota of cancer patients, restoring the levels and functionality of commensal bacteria depleted post-treatment [178]. In animal models, *Lactobacillus* administration alongside food has shown to attenuate fluorouracil (5-FU)- mediated and radiation-mediated gut epithelial injuries, thus helping in the preservation of gut microbiota balance and intestinal epithelial barrier maintenance [179–181]. While generally safe, concerns remain about the potential risks of opportunistic infections and antibiotic resistance transfer in immunocompromised cancer patients [182, 183]. Nonetheless, probiotics have demonstrated beneficial effects in improving GI symptoms following anticancer therapy, thereby contributing to the re-establishment of a healthy gut microbiota (Fig. 1) [184].

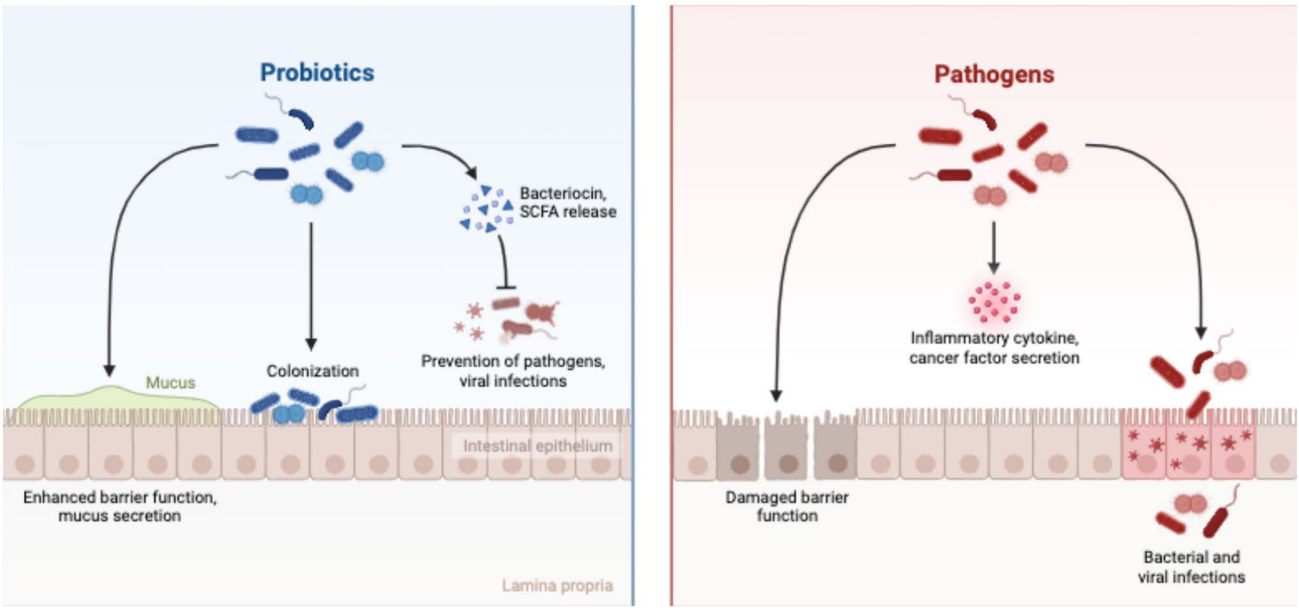

Fig. 1 Effects of probiotic vs. pathogenic gut microbiota. Bacteriocins are ribosomal synthesized antimicrobial peptides produced by bacteria able to inhibit bacterial strains. Probiotics may modulate bacteriocins and short chain fatty acid (SCFA) production, contributing to protect gut mucosal barrier. Figure created with Biorender app

In summary, the strategic use of probiotics to modulate the gut microbiome presents a promising avenue for improving therapeutic outcomes in cancer treatments, highlighting the potential for microbiome-targeted interventions in oncology.

Fecal Microbiota Transplantation: A Novel Approach in Cancer Therapy

The transplantation of gut microbiota between individuals, known as fecal microbiota transplantation (FMT), has emerged as a therapeutic strategy for treating pathogen infections, gut inflammatory diseases, and dysbiosis. FMT has demonstrated efficacy in treating recurrent *Clostridium difficile* duodenal infections [185, 186]. Additionally, its application in Graft Versus Host Disease (GVHD) post-allogeneic stem cell transplantation is promising [187]. In the realm of anti-tumor therapy, preclinical studies in murine models have indicated the potential of FMT in reducing colon tumorigenesis. However, the translation of these findings into clinical efficacy requires further validation [188]. Currently, several trials are underway to assess the utility of FMT in cancer patients, focusing on the prevention and mitigation of intestinal side effects associated with anticancer treatments.

Conclusions

Nowadays it is widely accepted that changes in the normal gut microbiome causing dysbiosis and immune dysregulation play a role in carcinogenesis, especially for GI cancers. Many conditions may cause variations in the gut microbial equilibrium and promote cancer, such as environment, diet, and antibiotics intake. Moreover, the knowledge of the interacting role of gut microbiome in the treatment of GI cancers has evolved rapidly over the past decade. Indeed, gut microbiome can interfere with chemotherapy effectiveness and enhance toxic adverse events and at the same time can significantly influence the host response to PD-1/PD-L1 blockade and CTLA-4 inhibition.

Targeted microbiome interventions with nutraceuticals including probiotics and prebiotics are being developed to improve therapeutic outcomes and mitigate toxicities associated with anticancer treatment. In addition, fecal microbiota transplantation has shown promising activity in the prevention and mitigation of chemotherapy and immunotherapy intestinal side effects and is currently under assessment in different clinical trials.

Dietary interventions such as limitation of processed and animal foods and increased intake of fibers and pro-prebiotic foods together with the choice of Mediterranean diet are among the most immediate approaches to follow in order to positively manipulate the gut microbiome. In addition to this, rational drug use strategies should be promoted, with limitations in antibiotics to prevent gut dysbiosis and GI cancer onset. Further studies are warranted in order to introduce the microbiome among the available tools of precision medicine. In particular, research should develop innovative approaches for modulating the microbiota in order to get better responses and less toxicities from anticancer treatment.

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Declarations

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