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REVIEW

The Role of Microbiota in Gastrointestinal Cancer and Cancer Treatment: Chance or Curse?

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SUMMARY

With the widely accepted concept that human health is shaped by microbes, we present an overview of the involvement of microbiota in gastrointestinal cancer biology. This includes mechanistic insights as well as the impact on diagnostics and cancer treatment.

The gastrointestinal (GI) tract is home to a complex and dynamic community of microorganisms, comprising bacteria, archaea, viruses, yeast, and fungi. It is widely accepted that human health is shaped by these microbes and their collective microbial genome. This so-called *second genome* plays an important role in normal functioning of the host, contributing to processes involved in metabolism and immune modulation. Furthermore, the gut microbiota also is capable of generating energy and nutrients (eg, short-chain fatty acids and vitamins) that are otherwise inaccessible to the host and are essential for mucosal barrier homeostasis. In recent years, numerous studies have pointed toward microbial dysbiosis as a key driver in many GI conditions, including cancers. However, comprehensive mechanistic insights on how collectively gut microbes influence carcinogenesis remain limited. In addition to their role in carcinogenesis, the gut microbiota now has been shown to play a key role in influencing clinical outcomes to cancer immunotherapy, making them valuable targets in the treatment of cancer. It also is becoming apparent that, besides the gut microbiota's impact on therapeutic outcomes, cancer treatment may in turn influence GI microbiota composition. This review provides a comprehensive overview of microbial dysbiosis in GI cancers, specifically esophageal, gastric, and colorectal cancers, potential mechanisms of microbiota in carcinogenesis, and their implications in diagnostics and cancer treatment. (Cell Mol Gastroenterol Hepatol 2022;13:857–874; https://doi.org/10.1016/j.jcmgh.2021.08.013)

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The gut microbiota has arguably become one of the most exciting frontiers in health in the past decade. Since the development of next-generation sequencing technologies and their application within clinical research, our understanding of the human microbiome and its role in health and disease has increased exponentially.[1,2] The influence of the gut microbiota, which consists of trillions of bacteria along with fungi, archaea, and viruses, extends to other body compartments including the liver, brain, and immune system, and alterations in gut microbiota have been reported consistently in various pathologic conditions. In addition, there is increasing appreciation of the gut microbiota's contribution to cancer development,[3] with 15%–20% of cancers known to be driven by specific infectious agents,[4] while other malignancies are linked to the collective gut microbiota with/without involvement of specific trigger organisms.[5–7] Microbiota influence on cancer risk is multifactorial, impacting host metabolism, immune function, host/microbial sensing pathways, and cellular proliferation.[6] For instance, carbohydrate structures, which are present on gastrointestinal mucins, act as binding sites and/or metabolic substrates for bacteria and are important determinants in site-specific microbial colonization.[8]

Microbially induced chronic inflammation is a key risk factor in cancer initiation/progression with processes, including metastasis and tumor invasion, being accelerated as a result.[5–7] Microbially induced pro inflammatory cytokine level increases can lead to epithelial DNA damage

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including epigenetic regulatory changes, which in turn induce genetic instability. These factors influence cancer initiation, promotion, dissemination, and also impact treatment.

In this review, we explore the contribution of gut microbes in esophageal, gastric, and colorectal cancers. We also offer a glimpse toward future developments in relation to microbial manipulation strategies in the context of cancer prevention and management.

Esophageal Cancer

Esophageal cancer is a major cause of global cancer mortality, with 2 distinct histologic types (ie, esophageal squamous cell carcinoma [ESCC] and esophageal adenocarcinoma [EAC]).[9] Globally, ESCC incidence is decreasing whereas a rapid increase in EAC cases has been seen alongside a widespread adoption of a Western diet and an increase in obesity, both factors contributing to gastroesophageal reflux disease (GERD), the main risk factor for EAC. In most cases, EAC is preceded by its precancerous lesion, Barrett esophagus (BE).[10]

Several studies have assessed microbiota signatures in esophageal carcinogenesis (Supplementary Table 1), with microbiota composition mostly being assessed in tissue specimens or oral mucosal swabs, with no significant differences in biopsy and oral swab microbial signatures seen.[11–13] Overall, decreased species diversity/richness is seen in ESCC, EAC, and BE compared with normal esophageal tissue (Supplementary Table 1). Genera that are more consistently enriched in BE include *Campylobacter*, *Streptococcus*, *Prevotella*, *Veillonella*, *Leptotrichia*, and *Actinobacillus* members with distinct microbial profiles associated with ESCC and EAC. In ESCC, *Streptococcus* species, *Veillonella parvula*, and *Porphyromonas gingivalis* are the most abundant species, whereas *Lautropia*, *Bulleidia*, *Catonella*, *Corynebacterium*, *Moryella*, *Peptococcus*, *Treponema*, and *Cardiobacterium* genera are depleted (Figure 1, Supplementary Table 1).[14,15] Other studies have reported an increased abundance of Fusobacteria in ESCC compared with controls.[16,17] In contrast, EAC patients show an enrichment of *Lactobacillus fermentum*,[18] *Prevotella*, *Leptotrichia*, *Enterobacteriaceae*, and *Akkermansia muciniphila*, and a depletion of Streptococci, specifically *Streptococcus pneumoniae* (Figure 1, Supplementary Table 1).[19,20]

Studies investigating cancer risk stratification based on microbial composition analysis have highlighted that *P gingivalis*, *Streptococcus*, *Neisseria*, *Actinomyces*, and *Atopobium* are the main predictors for ESCC development,[11,21] whereas lower ESCC risk is associated with the presence of *Prevotella* oral taxon 306 and *Aggregatibacter* paraphrophilus.[22] Regarding EAC risk, an association with the periodontal pathogen *Tannerella forsythia* was identified, as well as other oral species including *Actinomyces cardiffensis*, *Selenomonas* oral taxon 134, and *Veillonella* oral taxon 917.[22] Reduced EAC risk is linked to a higher abundance of Firmicutes (*Lachnoanaerobaculum umeaense*, *Oribacterium parvum*, and *Solobacterium moorei*), Proteobacteria (*Neisseria sicca*, *Neisseria*

flavescens, and *Haemophilus* oral taxon 908), *Corynebacterium durum*, *Prevotella nanceiensis*, and *S pneumoniae* (Figure 2).[22] It remains to be determined whether these microbial changes have a causative effect or represent merely a consequence of the cancer being present.

The Curious Case of Helicobacter pylori in EAC

Epidemiologic evidence suggests an inverse relationship between *H pylori* eradication and EAC incidence, potentially induced by a shift in the gastric microbiota.[23–25] A recent meta-analysis (72 studies including 84,717 cases and 390,749 controls) showed that *H pylori* infection was associated with a reduced risk for dysplastic BE.[26] However, a large retrospective study of 36,803 US veterans could not confirm the association between either *H pylori* status or treatment status and EAC incidence.[27] Similarly, a Swedish nationwide, population-based cohort study (N = 81,919) showed that *H pylori* status was associated inversely with BE, although a link with EAC incidence was not found.[28] Furthermore, studies investigating the association between *H pylori* and reflux disease confirmed an increased risk of erosive reflux esophagitis after *H pylori* eradication, but did not show an increase in GERD-related symptoms.[29] These contradictory findings highlight the need for a more comprehensive understanding of the role of *H pylori* in the development of esophageal cancer.

Microbial Involvement in Esophageal Carcinogenesis: Mechanistic Insights

Evidence from many preclinical models has shaped our mechanistic understanding of microbiota involvement in gastrointestinal carcinogenesis. Although the limitations of such models are extensive, it nevertheless remains that significant understanding and shaping of clinical studies has benefitted from these studies.

Through the use of nude mice xenograft studies, using intraperitoneal injection of esophageal cancer cells, significant alterations have occurred in the microbiota structure including a depletion of Pasteurellales and enrichment of carbohydrate/lipid metabolic pathways in the esophageal microbiota. Furthermore, fecal microbiota transplantation (FMT) of "healthy" mouse stool to antibiotic-treated xenograft-bearing mice significantly improved liver metastases, highlighting a protective role of the gut microbiota.[30] Other xenograft models also have shown the effect of pathogenic species, including *P gingivalis*, which induced epithelial mesenchymal transition within the esophagus and enhanced metabolic glucose uptake (Figure 3A).[31]

Diet also has an impact on the microbiota composition in esophageal carcinogenesis. Sprague Dawley rats fed a high-fat diet (HFD) have an altered esophageal microbiota compared with rats fed a normal chow diet, with an increase in *Clostridium* species and depletion of *Escherichia*, *Shigella*, and *Lactobacillus* genera (Figure 3A).[32] In addition, transgenic interleukin (IL)2–IL1β mice fed with a HFD developed esophageal tumors more rapidly than mice fed with a normal diet. This acceleration was associated with gut
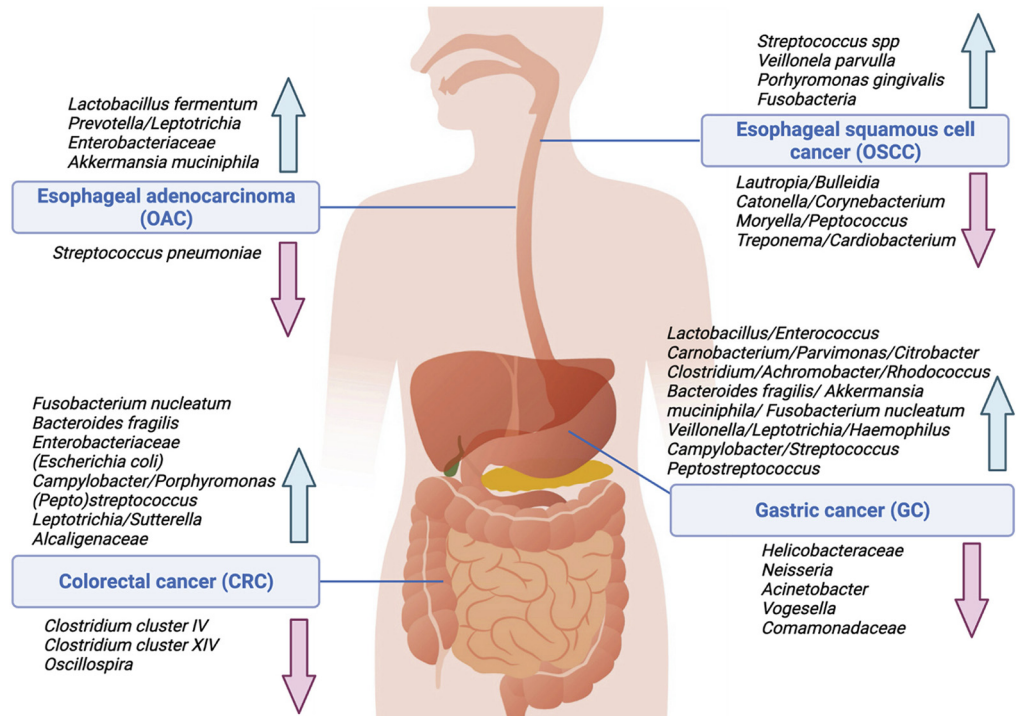
Figure 1. Overview on microbiota and cancers of the luminal GI tract. Bacterial genera/species abundantly present (*blue arrow*) or depleted (*red arrow*) in esophageal, gastric, and colorectal cancers.

microbiota changes as well as immune alterations including Toll-like receptor (TLR) expression, an increased ratio of neutrophils:natural killer cells, and aberrant levels of T-cell recruiting factors (chemokin [C-C motif] ligands 6 and 12: CCL6, CCL12), granulocyte colony-stimulating factor (G-CSF), and chemokine (C-X-C motif) ligand 1 (CXCL1), leading to an increase of C-X-C motif chemokine receptor 2 (CXCR2)-positive immune cells (Figure 3*A*). Organoid studies further confirmed that CXCR2 stimulation initiated

expansion of Lgr5 progenitor cells, causing initiation of metaplasia.[44]

The proinflammatory effect of a HFD on the esophageal tract can be synergized further by the addition of deoxycholic acid to drinking water. Deoxycholic acid promotes the development of BE and chronic HFD + deoxycholic acid treatment results in a higher microbial diversity, an increase in inflammation, and a lipid tissue signature useful for early BE diagnosis.[45]
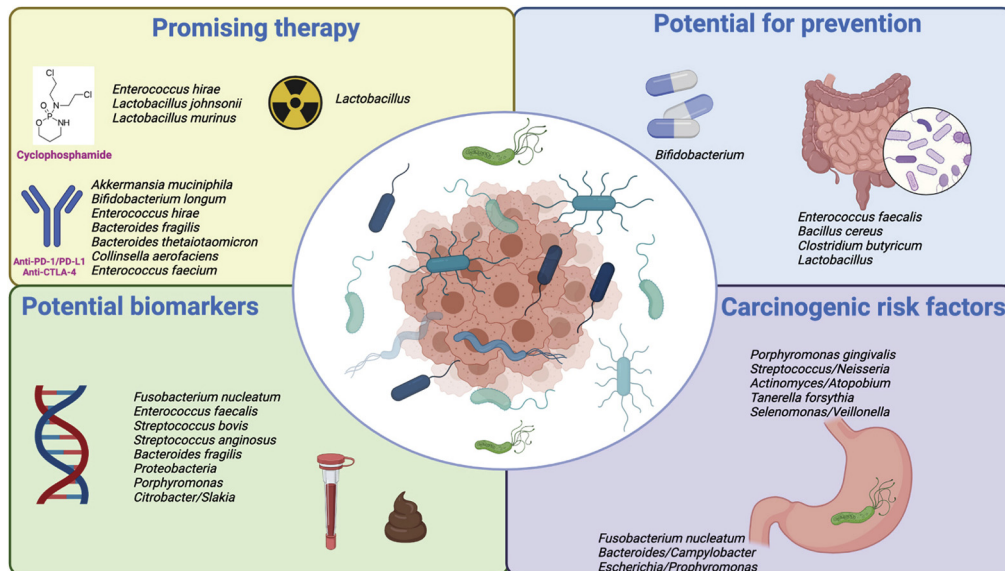

Figure 2. Impact of the microbiota on GI cancers. The GI microbiota and its potential implications in cancer development, diagnostics, treatment interventions, and prevention by probiotics. CTLA-4, cytotoxic T-lymphocyte–associated protein 4; PD-L1, programmed cell death 1 ligand.
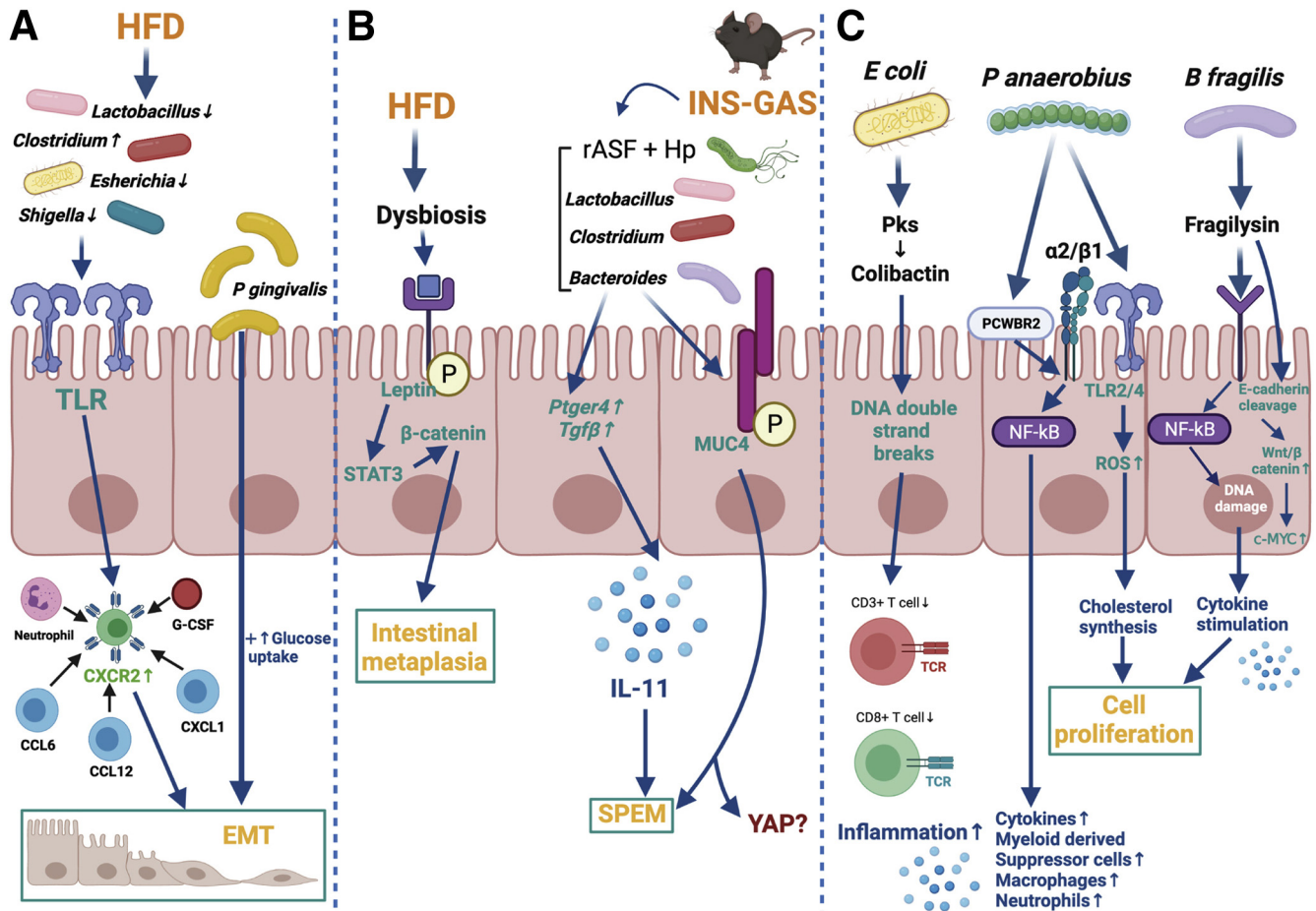
Figure 3. Role of the microbiota in GI carcinogenesis. (*A*) A HFD impacts microbiota composition resulting in *Clostridium* abundance and *Lactobacillus*, *Escherichia*, and *Shigella* depletion and acceleration in esophageal tumor development.[32] The oral *P gingivalis* pathogen alters the esophageal mucosal environment, resulting in epithelial mesenchymal transition induction and enhanced metabolic glucose uptake.[31] (*B*) Gastric colonization of INS-GAS (insulin-gastrin) mice with an intestinal flora (including *Clostridium*, *Lactobacillus*, and *Bacteroides* species) in combination with *H pylori* infection induced a strong inflammation as characterized by an increased expression of IL11 and the cancer-related genes *Ptger4* and *Tgf-β* and the development of spasmolytic polypeptide-expressing metaplasia (SPEM), possibly mediated by the yes-associated protein 1 (YAP1).[33–35] In GC, a HFD induces gastric dysbiosis (characterized by increased *Lactobacillus* abundance), intestinal metaplasia, the expression of leptin, phosphorylated leptin receptor and STAT3 and intracellular *β*-catenin accumulation.[36,37] (*C*) In the context of CRC, certain microbes such as pks + *E coli*, *P anaerobius*, and *B fragilis* are able to produce toxins that can influence carcinogenic processes. These include the induction of the DNA damage checkpoint pathway and proinflammatory responses, TLR interaction, impairment of the antitumor T-cell response, nuclear factor-*κ*B (NF-*κ*B), and Wnt/*β*-catenin pathway activation, further promoting cell proliferation.[38–43] CCL, chemokin (C-C motif) ligand; c-MYC, MYC proto-oncogene; CXCR2, C-X-C motif chemokine receptor 2; EMT, epithelial-mesenchymal transition; G-CSF, granulocyte colony-stimulating factor; Hp, *H pylori*; MUC4, mucin 4; PCWBR2, putative cell wall binding repeat 2; rASF, restricted altered Schaedler's flora; ROS, reactive oxygen species; STAT3, signal transducer and activator of transcription 3.

Surgical alteration of the upper gastrointestinal (GI) tract leads to functional modification affecting host metabolism and mucosal homeostasis. Esophagojejunostomy to induce BE in rats affects both TLR expression and esophageal microbiota composition, characterized by a significant decrease of *Lactobacillus* and an increase of *Clostridium*, *Enterococcus*, and *Streptococcus*.[46,47] Furthermore, this effect is aggravated by the introduction of antibiotics but is reversed by the addition of rebamipide, a mucosal protective agent used for peptic ulcer disease.[46,48] Another factor that can affect the balance between esophageal mucosal integrity and the gut microbiota is riboflavin. Riboflavin

deficiency in rats is linked to esophageal epithelial atrophy and reduced activity of xenobiotic metabolic pathways. Riboflavin supplementation of riboflavin-deficient rats has a direct impact on gut microbiota composition with a reduction in Firmicutes abundance and an increase of Proteobacteria.[49,50]

Gastric Cancer

Gastric cancer (GC) is a multifactorial disease with different genetic, molecular, and environmental factors influencing disease development, with the most frequent

cause being *H pylori* infection.[51–54] This class I carcinogen plays a crucial role in initiating steps of gastric carcinogenesis by causing enhanced inflammation and progressive changes in the architecture and function of the gastric mucosa, resulting in a life-long infection unless an eradication strategy is implemented.[55,56]

Because of the acidic environment and other local antimicrobial factors, it was long thought that the stomach was inhabited exclusively by *H pylori* and was considered inhospitable to other microorganisms.[57,58] However, from a certain timepoint in the course of progression of mucosal changes, gastric carcinogenesis is *H pylori*–independent because colonization levels decrease in patients with intestinal metaplasia and dysplasia, and essentially is absent by the adenocarcinoma stage.[55] *H pylori* thus may act by a hit-and-run mechanism, priming the gastric mucosa for further oncogenic changes, which are accomplished by other microbes.[55,57–60] Furthermore, stomach microhabitats are not always as uniform as previously thought. Local pH, mucin distribution, nutrients, ions, and chemical levels vary considerably in tumor and adjacent tumor-free tissue. These factors heavily influence microbial composition and diversity.[57]

Recent advances in sequencing technologies have highlighted significant differences in the gastric microbiota compared with the oral and/or esophageal microbiota, with the stomach harboring a distinct microbial ecosystem comprising Proteobacteria, Firmicutes, Bacteroidetes, Actinobacteria, and Fusobacteria.[61,62] Studies also have shown the presence of a specific fungal consortium (mycobiome).[63] One question that remains unanswered is related to transient vs persistent gastric colonization and its role in disease pathogenesis. Studies have tried to address this question, but the full potential of the gastric microbiota remains to be elucidated, including the contribution of the various gastric microbiota components and the extent of microbe:microbe crosstalk/interactions.[64]

Microbiota Diversity in Gastric Carcinogenesis

Studies assessing human gastric microbiota profiles have shown significant differences between patients with chronic (atrophic) gastritis, metaplasia, and GC, highlighting that dysbiosis in the stomach is a dynamic process that correlates with cancer progression (Supplementary Table 2).[55,57,59,61,63–72] Microbiota profiles in patients with *H pylori*–induced superficial gastritis or even glandular atrophy are dominated by *Helicobacter* and, to a much lesser extent, *Streptococcus*, *Prevotella*, and *Neisseria*, resulting in decreased phylotype richness, diversity, and evenness compared with patients with a normal gastric mucosa (Supplementary Table 2).[73–78] The loss of specialized glandular tissue and decreased acid secretion in GC tissue results in *H pylori* loss and enrichment of intestinal commensals, including *Lactobacillus*, *Enterococci*, *Carnobacterium*, *Parvimonas*, *Citrobacter*, *Clostridium*, *Achromobacter*, and *Rhodococcus*,[55,67,79] as well as oral species; *Fusobacterium nucleatum*, *Veillonella*, *Leptotrichia*, *Haemophilus*, and *Campylobacter* (Figure 1, Supplementary Table 2).[59,65,66,68–71,80] Furthermore, species, including *F nucleatum*, are associated with worse prognosis in Laurén's diffuse-type GC (Supplementary Table 2).[81] In addition to differences in microbial communities, metabolic pathways, including amino acid and nitrate metabolism, membrane transport, and carbohydrate digestion and absorption have been shown to be up-regulated in GC compared with healthy gastric tissue.[55]

Proton pump inhibitors (PPIs) frequently are used to treat GI disorders including erosive esophagitis and GERD. Although effective at improving GI symptoms, use of PPIs also promotes microbial growth that has genotoxic potential, with an increase in bacterial nitrate/nitrite reductase function, which is linked with cancer development.[82] Moreover, the higher gastric pH, resulting from PPI use, can lead to an increase of *Peptostreptococcus stomatis*, *Streptococcus anginosus*, *Parvimonas micra*, *Slackia exigua*, and *Dialister pneumosintes*.[83] It remains unclear whether microbiota changes resulting from PPI therapy influence an individual's gastric cancer risk.

Microbial Involvement in Gastric Carcinogenesis: Mechanistic Insights

The differential susceptibility to *H pylori*–induced GC development has been partly attributed to differences in virulence of *H pylori* isolates, but also to the involvement of non–*H pylori* bacteria. Gastric colonization of INS-GAS mice (insulin-gastrin mice, with constitutional expression of gastrin regulated by the insulin promotor) with different types of intestinal microbes, including restricted altered Schaedler's flora (ie, *Clostridium*, *Lactobacillus*, and *Bacteroides* species) and specific pathogen-free (with undefined complex intestinal flora) in combination with or without *H pylori* co-infection, showed that mice exposed to intestinal flora + *H pylori* co-infection show the strongest inflammatory responses, with 40% developing gastric cancer. This phenomenon also was seen in approximately 25% of mice exposed to restricted altered Schaedler's flora (ASF) + *H pylori* co-infection. Furthermore, *H pylori* colonization induced the expression of IL11 and cancer-related genes *Ptger4* and *Tgf-β* (Figure 3B).[33] In terms of host changes, ASF + *H pylori* co-infection colonization resulted in gastric mucosal changes including the development of spasmolytic polypeptide-expressing metaplasia accompanied by aberrant mucin 4 (MUC4) expression and the presence of Ulex europaeus lectin–positive foveolar hyperplasia.[34] This further supports a role for *H pylori* in accelerating gastric cancer development with the yes-associated protein 1, a key effector of the Hippo pathway, also being implicated in the process (Figure 3B).[35] HFD also has been shown induce gastric dysbiotic changes including increased *Lactobacillus* abundance, intestinal metaplasia, expression of leptin, phosphorylated leptin receptor, and signal transducer and activator or transcription 3 (STAT3) and intracellular *β*-catenin accumulation (Figure 3B),[36,37] whereas loss of the leptin receptor attenuates the effect of HFD on dysbiosis and intestinal metaplasia.[37]

Colorectal Cancer

In comparison with GC, in which a single microbe plays the dominant role, defining carcinogenic culprits from within the colonic microbiota and defining their involvement in colorectal cancer (CRC) development is incredibly challenging. Alterations in gut microbiota signatures consistently are reported in CRC, with tumor signatures differing from adjacent normal tissue. Differences include reduced diversity and altered community structure, which increase as CRC progresses (Supplementary Table 3).[7,84–87] Lower numbers of beneficial, potentially protective taxa, including butyrate-producing species belonging to *Clostridium* clusters IV and XIV, repeatedly are documented in CRC, whereas increased pro-oncogenic capacity has been attributed to an increase in species including *Fusobacterium*, *Bacteroides*, *Campylobacter*, *Escherichia*, and *Porphyromonas* (Figure 1, Supplementary Table 3).[5,7,88–91] *Firmicutes* and *Actinobacteria* phyla and the *Lachnospiraceae* family are detected more frequently in premalignant adenomas, Proteobacteria, *Alcaligenaceae*, *Enterobacteriaceae*, and *Sutterella* species are increased in CRC (Figure 1, Supplementary Table 3).[92] Studies also have suggested that specific species including *Oscillospira* are depleted in the transition from advanced adenoma to early CRC (Figure 1).[93]

Key Players in Colorectal Carcinogenesis

F nucleatum frequently is detected in CRC tissue, both at the adenoma and adenocarcinoma stages, in association with other oral commensal species, including *Peptostreptococcus*, *Leptotrichia*, and *Campylobacter* species (Figure 1, Supplementary Table 3).[5,89,90] Its presence also is associated with an increased risk of CRC recurrence and development of chemoresistance.[94] *F nucleatum* impacts on CRC development in a number of ways: *F nucleatum* frequently is detected at higher levels in the tumor microenvironment through its ability to localize with tumor-enriched lectins via the outer membrane protein (fatty acid binding protein 2, Fap2),[95] and *F nucleatum* modifies the tumor microenvironment; blocking natural killer cell antitumor responses and directing myeloid cell recruitment. *F nucleatum* also influences microbial metastatic dissemination as microbiota signatures associated with *Fusobacterium*-enriched but not *Fusobacterium*-negative cancers detected in distant metastases.[5,91]

Other bacteria that have been implicated in CRC pathogenesis include enterotoxigenic *Bacteroides fragilis* (ETBF) and *Escherichia coli* (shown to promote colon tumorigenesis in colitis-associated cancer rather than sporadic CRC), *Streptococcus gallolyticus* subspecies *gallolyticus*, and *Enterococcus faecalis*. The presence of *B fragilis*/ETBF in CRC tissue also is associated with a poorer prognostic outcome.[96–98]

Although studies consistently indicate an increased abundance of *Enterobacteriaceae* (particularly *E coli*) in inflamed colonic mucosa compared with uninflamed tissue, the evidence for *E coli* involvement in CRC is associated predominantly with data from preclinical studies. Higher numbers of *E coli* strains with the *pks* gene, which mediates production of the genotoxic colibactin, also have been found in the following: (1) CRC patients compared with controls, (2) CRC tissue compared with adjacent normal mucosa, and (3) late-stage compared with early stage CRC.[99]

Microbial Biofilms and CRC

Bacterial biofilms have long been recognized as contributors to chronic infections and diseases in human beings, however, their role in intestinal cancers received limited consideration until seminal work by the Sears laboratory showed that invasive polymicrobial biofilms are present in many right-sided colonic tumors but only in a small proportion of left-sided tumors; findings that subsequently have been validated in other cohorts.[87,100] Biofilm-positive tissues (tumor and normal mucosa) show well-established features of carcinogenesis including loss of E-cadherin and increased IL6 expression. Elucidation of CRC tissue biofilm composition showed specific microbial scaffolds: polymicrobial, polymicrobial with Fusobacteria, and Proteobacterial predominant.[87,100] Biofilms also have been detected in familial adenomatous polyposis patients. In contrast to the sporadic CRC biofilms, familial adenomatous polyposis–associated biofilms were composed predominantly of ETBF and *pks* + *E coli*.[101]

Microbial Involvement in Colorectal Carcinogenesis: Mechanistic Insights

In the context of CRC, intestinal microbes impact via various mechanisms, with certain microbes being able to produce toxins that can influence carcinogenic processes.[99,102] *E coli* strains belonging to group B2 harbor a genomic island pks which encodes for the polyketide-peptide genotoxin colibactin (Figure 3C).[103] Infection with pks$^+$ *E coli* can result in enterocyte DNA double-strand breaks and activation of DNA damage checkpoint pathways, cell-cycle arrest, and cell death.[98,99] Colibactin-positive *E coli* also can lead to impairment of antitumor T-cell responses including a decrease in CD3$^+$ and CD8$^+$ T cells and an increase in colonic inflammation in APC$^{min/+}$ mice (mice carrying a point mutation in the murine APC gene) (Figure 3C).[40] Furthermore, colibactin can shape gut microbiota composition/function, highlighting how microbes can compete for gut niche utilization.[104] Interestingly, the carcinogenic effects of colibactin-producing *E coli* are reversed by tumor necrosis factor blockade.[105] *F nucleatum* and *Peptostreptococcus anaerobius* are 2 anaerobic pathogens linked to CRC development. Both organisms adhere to the colonic mucosa and accelerate tumor development in APC$^{min/+}$ mice through interaction between outer membrane protein Fap2 (*F nucleatum*) and putative cell wall binding repeat 2 protein and integrin α_2/β_1 (*P anaerobius*). These interactions lead to increased cell proliferation and nuclear factor-κB activation, triggering proinflammatory responses including increased proinflammatory cytokine production and expansion of myeloid-derived suppressor cells, tumor-associated macrophages, and granulocytic tumor-associated neutrophils (Figure 3C).[5,41] Furthermore, both pathogens interact with

TLR2 and TLR4 on colonic epithelial cells, resulting in an increase of reactive oxygen species levels, further promoting cholesterol synthesis and cell proliferation (Figure 3C).[42,106]

ETBF originally was proposed as a microbial initiator of CRC based on the mechanism of action of its virulence factor fragilysin, which is one of the most potent known proinflammatory enterotoxins.[84,107] Fragilysin binds to colonic epithelial receptors activating nuclear factor-κB signaling pathways, inducing increased cell proliferation, proinflammatory cytokine production, and direct DNA damage (Figure 3C). Fragilysin also induces cleavage of E-cadherin, resulting in increased Wnt/β-catenin (Wnt: wingless/integrated) signaling, an increase in cell proliferation, and expression of the protooncogene *c-MYC* (Figure 3C).[43,108] A strong correlation between *S gallolyticus* and CRC also has been reported. *S gallolyticus* has the ability to colonize the intestinal tract and to promote tumor development in an azoxymethane-induced mice model of CRC, underscoring its importance in the functional relevance of CRC.[109] However, more studies are needed to unravel the mechanisms involved.

Mechanistic evaluation of colonic mucosal biofilms has been performed using microbial slurries from human biofilm-positive CRC mucosa, human biofilm-positive non-CRC mucosa, and biofilm-negative mucosa, inoculated into CRC-susceptible mice.[110] Biofilm-positive slurries induced robust invasive biofilm development, a phenomenon not seen in biofilm-negative slurries. Recruitment of immunosuppressive myeloid cells and associated IL17 production was seen within 1 week of biofilm-positive slurry inoculation, clearly showing the capacity of intestinal biofilms to drive intestinal mucosal changes and microbial architecture toward carcinogenesis. Further studies are needed to investigate biofilm-associated procarcinogenic and proinflammatory microbes as well as assessing their role in other gastrointestinal cancers.

Impact of the Microbiota on Diagnostic Tests

With altered microbiota signatures now being well accepted as a hallmark of progression in a number of gastrointestinal cancers, there is an ever-increasing interest in leveraging microbiota biomarker detection in cancer surveillance. Several studies have shown the value of including microbiota biomarker detection to complement existing screening tests and to improve early detection in CRC surveillance, with most success shown in the context of *F nucleatum* (Figure 2).[111–114] Inclusion of *F nucleatum* detection, in combination with the fecal immunochemical test (FIT), improved the sensitivity for CRC (92.3% vs 73.1%) and for advanced adenoma (38.6% vs 15.5%) compared with FIT alone, supporting *F nucleatum* as a valuable CRC marker that easily could be implemented in current practice (Figure 2).[115] Furthermore, combining tests for *F nucleatum*, *P stomatis*, and several other species associated with CRC allowed an accurate classification of CRC patients with an area under the curve (AUC) of 0.84 and an odds ratio (OR) of 23 (Figure 2).[114] Other studies have shown that the presence of *P micra*, *S anginosus*, and *Proteobacteria* in CRC resulted in an area under the concentration-time curve of 0.76, which increased to 0.83 when clinical markers were included (Figure 2).[116] Efforts have been made to implement machine-learning models in predicting CRC based on the composition of the gut microbiota from stool samples.[114,117–121] *F nucleatum*, *E faecalis*, *Streptococcus bovis*, *B fragilis*, *Porphyromonas* species, *Citrobacter* species, and *Slakia* were identified as potential biomarkers for the diagnosis of CRC and adenomatous polyps (Figure 2).[117–119,122–124] The combination of these bacterial candidates improved the diagnostic performance rather than assessment of each bacterium alone.[124] In addition, microbe-derived metabolic signatures in stool or serum also have been considered as potential tools in CRC detection.[125,126]

There are less data on similar approaches for gastric or esophageal cancer. Profiling of microbiota coating the tongue has been assessed alongside serologic markers for early detection of GC.[127] A predictive model also was developed that includes serologic testing of IgG anti–*H pylori* antibody and pepsinogen, nitrosating/nitrate-reducing bacteria abundance, and type IV secretion system gene-contributing bacteria in the stomach.[128] Both approaches have clear limitations and currently remain within the development space.

Impact on Cancer Treatment

Recently, there has been increasing interest in defining the impact of the gut microbiota on cancer treatment. There is a bidirectional interaction because many drugs are metabolized by gut bacteria, resulting in interindividual differences in drug metabolism and, thus, huge implications for efficacy and side effects of drugs across multiple disease indications.[129] On the other hand, systemic treatments also have an effect on the composition and functioning of the microbiota.[130]

Chemotherapy

Platinum-based cytotoxic compounds mediate their effects through causing DNA damage, including formation of DNA adducts and intrastrand cross-links, which induces apoptosis. Although the majority of the current evidence is still from preclinical models, there is increasing understanding that the gastrointestinal microbiota might serve as predictive indicators for treatment response. Commensal bacteria can influence therapeutic effects of oxaliplatin by modulating the production of reactive oxygen species in tumor-infiltrating myeloid cells, which can enhance tumor regression.[131] In the presence of antibiotics, oxaliplatin and cisplatin treatment reduce this effect and result in poorer survival in various murine models, with mice lacking TLR pathway components not able to respond to oxaliplatin. Cyclophosphamide, an alkylating anticancer agent, induces a reduction in regulatory T cells and increases the number of T helper (Th1) and Th17 cells as well as intestinal permeability.[132,133] Viaud et al[134] reported a specific association between luminal microbial

Table 1. Unresolved Questions

What are the optimal methods for profiling microbiota changes in the context of disease progression as well as therapeutic regimens?
What frequency of profiling is adequate to develop a comprehensive understanding of the microbiota?
What other factors that influence the gut microbiota should be monitored alongside microbiota profiles? (For example age, diet, lifestyle, ethnicity, or concomitant medicines?)
What is the ideal approach to microbial manipulation in the context of cancer therapies?
What studies are needed to show cause-and-effect relationships between the gut microbiota and the pathogenesis of GI cancers?

components and mucosal Th responses induced by cyclophosphamide treatment. Tumor-bearing mice with a reduced gut microbiota showed a reduction in Th17 cell numbers, with their tumors being refractory to cyclophosphamide treatment. Specifically, gram-positive bacteria *Enterococcus hirae*, *Lactobacillus johnsonii*, and *Lactobacillus murinus*, were shown to regulate cyclophosphamide efficacy (Figure 2); adoptive transfer of Th17 cells partially restored therapeutic efficacy. In the context of irinotecan treatment, targeted inhibition of gut bacterial β-glucuronidase enzymes improved cancer chemotherapeutic outcomes through a reduction in GI epithelial cell toxicity in preclinical models.

Other common CRC chemotherapeutic agents, including 5-fluorouracil, have been shown to induce gut dysbiosis in multiple preclinical studies, but do not seem to be affected by the gut microbiota in terms of their efficacy. After 5-fluorouracil and irinotecan therapy, levels of *Enterobacteriaceae* increase, whereas treatment with 5-fluorouracil alone also resulted in an increase of *Staphylococcus* and *Clostridium* species and a decrease of *Bacteroides* and *Lactobacillus* abundance.[135,136]

Radiotherapy

Radiation therapy is a core modality in cancer treatment and is associated with side effects including mucositis, dermatitis, and also bone marrow suppression.[137] From both clinical and mechanistic studies, it is well documented that radiotherapy results in significant alteration of both gut microbiota abundance and diversity. Radiation treatment is associated with a reduction in Firmicutes and Bacteroidetes (although increases in Bacteroidetes also have been documented),[138] along with a consistent increase in Proteobacteria, most often *Enterobacteriaceae*.[139] Gerassy-Vainberg et al[138] showed that radiation treatment induced localized dysbiosis, which was associated with postradiation tissue damage. No studies have been published that assess the effect of the gut microbiota on the efficacy and outcome of radiotherapy, but there are data indicating that the gut microbiota impacts tissue radiosensitivity.[140–142]

Radiotherapy-induced diarrhea (RID) is a significant problem. Across the developed world, it is estimated that 150,000 to 300,000 patients require treatment for RID

every year.[143] The potential for ameliorating RID through probiotic supplementation has been a focus of recent studies.[144] In an analysis of 8 trials with a total of 1116 participants, probiotics were associated with a lower risk of RID (relative risk, 0.62; 95% CI, 0.46-0.83) compared with placebo, but the baseline characteristics of the patients included were diverse. This notion also has been supported by a systematic review showing the potential of probiotics containing *Lactobacillus* species for the prevention of RID (Figure 2). However, additional well-designed research in the field is required.[145]

Immunotherapy

Multiple studies have highlighted the role of the gut microbiota in modulating immunotherapy efficacy across various cancers.[146–149] Initial studies focused on understanding how the gut microbiota impacted CpG-oligonucleotide immunotherapy responses, which activates innate immune cells through TLR9.[131] Subsequently, investigations assessed gut microbiota influence on immune-stimulatory cyclophosphamide chemotherapy treatment through shaping T-helper cell portfolios, namely the generation-specific subsets of Th17 and memory Th1 cells. More recently, the role of specific microbes was assessed in response to immune checkpoint inhibitor (ICI) therapies, including cytotoxic T-lymphocyte–associated protein 4 and programmed cell death 1 (PD-1)/PD-1 ligand inhibitors.

Vétizou et al[150] showed that the efficacy of anti–cytotoxic T-lymphocyte–associated protein 4 therapy was dependent on *B fragilis* and/or *Bacteroides thetaiotaomicron* and Burkholderiales populations, with T-cell responses specific for *B fragilis* and *B thetaiotaomicron* associated with therapeutic efficacy. In addition, the reintroduction of *B fragilis* cells and/or polysaccharides or adoptive transfer of *B fragilis*–specific T cells restored therapeutic efficacy and reduced immune-mediated colitis through activation of Th1 cells with cross-reactivity to bacterial antigens and tumor neoantigens (Figure 2).[150,151] In terms of PD-1/PD-1 ligand acting agents, differences in clinical response have been linked to gut microbiota composition. In particular, an abundance of *A muciniphila* and *E hirae* have been shown to be more abundant in anti–PD-1 treatment responders compared with nonresponders (Figure 2).[147] This responder/nonresponder phenotype also has been shown to be transmissible because mice receiving FMT subsequently acquire donor responder/nonresponder efficacy. The nonresponsive phenotype was rescued by addition of *A muciniphila* alone or in combination with *E hirae*.

Taking the concept of the impact of the gut microbiota on ICI efficacy one step further, several studies investigated if FMT could safely and effectively improve response to ICI treatment in anti–PD-1–refractory patients.[148,152,153] Anti–PD-1–refractory patients were given oral antibiotics (vancomycin and neomycin) and bowel preparation to deplete their microbiota, followed by FMT from donors who had achieved a complete response with anti–PD-1 therapy. Microbiota analysis confirmed that recipient gut microbiota

profiles resembled donor profiles, although no microbial features clearly differentiated between responders and those who remained refractory. FMT treatment was shown to induce antitumor changes in immune cell infiltrates and gene expression profiles in the gut lamina propria and the tumor microenvironment.

Impact of Probiotics on Postsurgical Outcome

Digestive surgery has a dramatic effect on the microbiota, usually causing surgery-induced dysbiosis. Many factors may alter the overall microbial numbers/composition: bowel preparation, antibiotics, anesthesia, surgical stress, parenteral nutrition, and surgical anatomic changes.[154] Loss of microbial diversity or abundance, an increase in potentially harmful species, and a decrease in beneficial species can slow wound healing and predispose patients undergoing abdominal surgery to infectious complications.[155,156]

A recent systematic review (21 clinical trials with 1831 patients who were subjected to elective colorectal surgery) suggested that probiotics could significantly decrease inflammation, postoperative infectious complications, and the duration of antibiotic therapy.[157] A similar conclusion was made by another meta-analysis, concluding that probiotics may have an effect on preventing postoperative infections and related complications in cancer patients undergoing surgery.[158] A Chinese group studied the impact of a probiotic compound containing *Bifidobacterium infantis*, *Lactobacillus acidophilus*, *E faecalis*, and *Bacillus cereus* on serologic inflammatory markers induced by gastrectomy.[159] Probiotic supplementation significantly enhanced the immune response and reduced the severity of inflammation through modification of the gut microbiota (Figure 2). However, it remains unclear whether this results in an actual clinical benefit. Overall, there is a clear need for more evidence to draw conclusions about the efficacy of probiotics given before or after cancer surgery to provide evidence-based clinical recommendations.

Summary and Glimpse to the Future

We live in an increasingly microbiota-focused world, a world where we understand that microbes strongly shape health and disease, including cancer, although our appreciation is still in its infancy. With this knowledge comes the requirement to fully appreciate the mechanistic impact of the microbiota in cancer development as well as in therapeutic regimens including microbiota manipulation strategies. Please note, that supplementary tables 1-3 list a detailed overview of the current literature on the interaction of microbiota and esophageal, gastric and colorectal cancer.[160–207] It is vital that we continue to increase our understanding because a number of unresolved questions remain (Table 1). Over the next few years, increasing emphasis on translating preclinical findings to the clinic setting is essential. As we move ever deeper into the precision medicine era, it has never been more important to be able to predict microbiota influence on human health.

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