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REVIEW

The Bacterial Microbiota of Gastrointestinal Cancers: Role in Cancer Pathogenesis and Therapeutic Perspectives

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Abstract: The microbiota has an essential role in the pathogenesis of many gastrointestinal diseases including cancer. This effect is mediated through different mechanisms such as damaging DNA, activation of oncogenic pathways, production of carcinogenic metabolites, stimulation of chronic inflammation, and inhibition of antitumor immunity. Recently, the concept of "pharmacomicrobiomics" has emerged as a new field concerned with exploring the interplay between drugs and microbes. Mounting evidence indicates that the microbiota and their metabolites have a major impact on the pharmacodynamics and therapeutic responses toward anticancer drugs including conventional chemotherapy and molecular-targeted therapeutics. In addition, microbiota appears as an attractive target for cancer prevention and treatment. In this review, we discuss the role of bacterial microbiota in the pathogenesis of different cancer types affecting the gastrointestinal tract system. We also scrutinize the evidence regarding the role of microbiota in anticancer drug responses. Further, we discuss the use of probiotics, fecal microbiota transplantation, and antibiotics, either alone or in combination with anticancer drugs for prevention and treatment of gastrointestinal tract cancers.

Keywords: microbiome, dysbiosis, antibiotics, probiotics, cancer treatment, prevention

Introduction

Cancer is considered as a main leading cause of death worldwide.[1] The International Agency for Research on Cancer reported an estimated 18.1 million new cancer cases and 9.6 million cancer deaths in 2018.[2] The hallmarks of cancer were early described to include six biological capabilities which have essential roles in contributing to tumor complexity.[3] They include sustaining proliferative capacity, evading growth suppressors, resisting cell apoptosis, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis.[3] In 2011, Hanahan and Weinberg[4] described two enabling characteristics underlying these hallmarks including genome instability and inflammation. In addition, advances in cancer research revealed another two emerging hallmarks including reprogramming of energy metabolism and evading immune destruction.[4] Mounting evidence indicates that tumors exhibit another dimension of complexity relating to the presence of unique tumor microenvironments, which are less easily assayed but have profound effects on cancer progression.[5] Substantial findings from in vitro, in vivo, and human studies point to the role of microbiota in cancer pathogenesis through modulating tumor microenvironment.[6,8]

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In the late 19th century, Rudolf Virchow, a German pathologist, described that cancer may be considered as a consequence of chronic inflammation elicited by hostile toxic triggers, including infections.[9] During the same period, the role of bacterial infections as a possible cause of cancer was suggested following the innovative work of Robert Koch and Louis Pasteur, upon the discovery of bacteria in tumor tissues.[9] However, only recent data from experimental and clinical work have conclusively demonstrated the bacterial role in oncogenesis and raised the possibility of its impact as a cause of malignancy.[10] The "human microbiome" is a term used to describe all microorganisms harboring the human body and their collective genomes.[11,12] Currently, around 20% of neoplasms worldwide can be attributed to infections,[13] with approximately 1.2 million cases every year.[14] The research in the microbiome field and mainly the role of bacteria in cancer pathogenesis is rapidly evolving, with more than 100 trillion bacteria already identified in the human body.[15,16] In this regard, there is convincing evidence linking bacterial dysbiosis to cancer, *Helicobacter Pylori* (*H. Pylori*) with gastric cancer[17] and mucosa-associated lymphoid tissue (MALT) lymphoma[18] as primary examples. This was further supported by the role of *Salmonella Typhi* (*S. Typhi*) in gallbladder cancer (GBC),[19] Chlamydia pneumonia in lung cancer,[20] and S*treptococcus bovis*/*gallolytucis* (*S. bovis*/*S. gallolytucis*) in colorectal cancer (CRC).[21]

The role of microbiome in tumor development and progression has been described to be driven through different mechanisms,[8,22] including: damaging DNA, activating oncogenic pathways and epithelial cell proliferation,[23] production of carcinogenic metabolites,[24] stimulation of chronic inflammation,[25,26] and inhibition of antitumor immunity.[22,24] These findings have highlighted the possible interactions between the tumor microenvironment and systemic microbial-immune networks to broader extents than previously thought.[7,23] Of note, microbial dysbiosis also has a major impact on therapeutic responses toward anticancer treatment.[27,28] This was mainly attributed to the microbial ability to metabolize drugs and to influence inflammation as well as immune responses within the tumor microenvironment, which in turn has a major role in treatment outcomes and drugs toxicities.[29] Indeed, the association between microbiota and responses to anticancer therapies has been described as a bidirectional way, where both factors can have a significant effect on each other.[27,30] Recently, the concept of "pharmacomicrobiomics" has emerged as a new field investigating the interplay between drugs and microbes.[27] In this regard, the role of probiotics and antibiotics either alone or in combination with anticancer drugs has been explored in order to manipulate the microbiota, which in turn might have positive outcomes in terms of cancer prevention and treatment.[27,31]

The human gastrointestinal tract (GIT) is a complex environment in the body which is inhabited by trillions of microorganisms, including bacteria, archaea, fungi, parasites, and viruses.[12,32] Bacteria are considered as the major microbiota colonizing the GIT.[33] Currently, cancers affecting the GIT system are well known as a major health problem.[2] According to the Global Cancer Statistics 2018,[2] GIT cancers have high incidence and mortality rates. Accumulating evidence points to the impact of bacterial infection on the pathogenesis and progression of many GIT diseases including cancers.[34,37] In addition, substantial data indicate the role of GIT microbiota in modulating tumor response to anticancer drugs including conventional chemotherapy and molecular-targeted therapeutics.[27,38] Therefore, bacterial microbiota can be an attractive target for prevention or treatment of GIT cancers.

Manipulating the microbiota is considered as a hot topic in cancer research. The concept of fecal microbiota transplantation (FMT) has recently been investigated as a novel method for treatment of diseases affecting the GIT.[39,40] FMT is defined as the transplantation of gut microbiota from healthy individuals to diseased individuals in an attempt to revert the intestinal microbiota to its healthy status.[41] Although FMT is still in its naive, promising results have been obtained regarding its clinical efficacy against Clostridium difficile infection.[42] Lately, there has been substantial interest regarding the therapeutic potential of FMT for treatment of other diseases affecting the GIT, including irritable bowel syndrome,[43] Crohn's disease,[44] and cancers.[39,45]

The present review discusses current knowledge on the relationship between the bacterial microbiota and pathogenesis of cancers affecting the GIT system. It will emphasize on its role as a potential target for therapeutic intervention including cancer treatment and prevention, in addition to its impact on tumor response to anticancer treatment. Figure 1 summarizes the most common bacterial species associated with cancers affecting GIT. Cancer types that will be discussed in this review include: oral carcinoma, esophageal cancer, gastric cancer, gastric mucosa-associated lymphoid tissue (MALT) lymphoma,

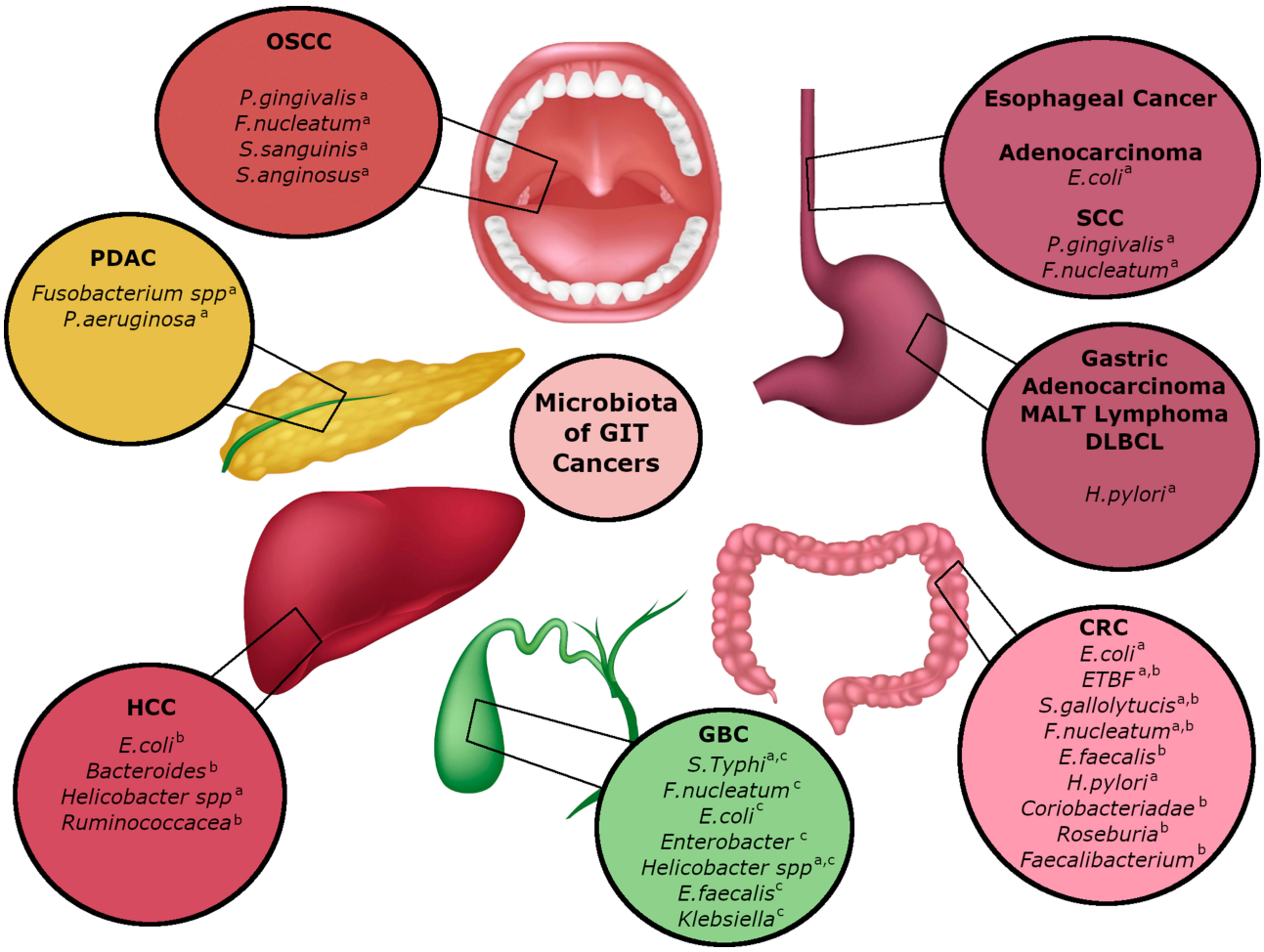

Figure 1 Most common bacterial microbiota associated with GIT cancers. Microbiota detected in cancer tissues (**A**), fecal samples (**B**), or bile secretions (**C**) from patients with GIT cancers.

Abbreviations: CRC, colorectal carcinoma; DLBCL, diffuse large B cell lymphoma; *E. coli*, *Escherichia coli*; *E. faecalis*, *Enterococcus faecalis*; ETBF, enterotoxigenic *Bacteroides fragilis*; *F. nucleatum*, *Fusobacterium nucleatum*; GBC, gallbladder carcinoma; GIT, gastrointestinal; HCC, hepatocellular carcinoma; *H. Pylori*, *Helicobacter Pylori*; MALT, mucosa-associated lymphoid tissue; OSCC, oral squamous cell carcinoma; PDAC, pancreatic ductal adenocarcinoma; *P. gingivalis*, *Porphyromonas gingivalis*; *S. anginosus*, *Streptococcus anginosus*; *S. gallolytucis*, *Streptococcus gallolytucis*; *S. sanguinis*, *Streptococcus sanguinis*; *S. Typhi*, *Salmonella Typhi*; SCC, squamous cell carcinoma; spp., species.

gastric diffuse large B cell lymphoma (DLBCL), colorectal cancer, pancreatic cancer, liver cancer, and gallbladder cancer.

Oral Carcinoma

Oral cancer, particularly oral squamous cell carcinoma (OSCC), remains a major health issue as it is usually detected at advanced stages.[46,47] The 5-year survival rate is less than 50% with high recurrence rates.[48,49] Many risk factors are involved in the pathogenesis of oral cancer,[50] with smoking and alcohol consumptions being the major risk factors.[51] Human papillomavirus (HPV) infection is also a well-known risk factor of OSCC, particularly among young patients and non-smoking females.[52] Genetic factors including genetic polymorphism of drug metabolizing enzymes and DNA repair mechanisms were also reported to increase the patient susceptibility to OSCC.[53,54] Nutritional deficiencies are also among the OSCC risk factors.[55] Chronic inflammation was also suggested to increase the risk for OSCC, particularly in patients with periodontal diseases.[56] Since the discovery of the role of bacterial infection in the initiation and progression of certain cancer types, as described earlier in this review, research has been directed to explore the role of bacterial infection in OSCC carcinogenesis.[56,58]

The oral cavity is enriched by different types of bacterial microbiota which play an important role in maintaining a "microbial homeostasis" and have commensal as well as mutualistic relation with the host.[59,60] However, the loss of the homeostatic state can cause an "ecological shift" or "dysbiosis" which in turn can contribute to the development of diseases including OSCC.[56,61,63] Nagy et al[64]

reported significantly higher levels of *Porphyromonas*, *Fusobacterium*, and other bacterial species (spp.) in OSCC tissue compared with adjacent healthy mucosa, using culture-based analysis of surface swabs. In addition, higher colonization of *Porphyromonas gingivalis* (*P. gingivalis*) was shown in gingival squamous cell carcinoma lesions compared to healthy gingival tissues.[65] Tateda et al[66] also showed that *Streptococcus anginosus* (*S. anginosus*) was observed in all studied samples of head and neck squamous cell carcinoma including OSCC, which was also supported by results from Sasaki et al,[67] where it was reported in 45% of OSCC samples. The comparison between bacterial species expression in saliva of patients with OSCC and cancer free controls showed that *Capnocytophaga gingivalis* (*C. gingivalis*), *Prevotella melaninogenica* (*P. melaninogenica*), and *Streptococcus mitis* (*S. mitis*) were significantly higher in the cases group.[68] In a subsequent study, Pushalkar et al[69] found the genera *Streptococcus, Rothia, Gemella, Peptostreptococcus, Porphyromonas, Micromonas*, and *Lactobacillus* to be highly abundant in the salivary secretion of individuals with OSCC. In comparison, *Prevotella Neisseria* (*P. Neisseria*), *Leptotrichia*, *Capnocytophaga, Actinobacillus*, and *Oribacterium* were higher in the saliva samples of healthy controls.[69] However, conflicting results were reported in a larger-scale study upon analysis of swabs from lesion and contra-lateral normal tissues from 18 OSCC patients, eight pre-cancer cases, and nine healthy individuals.[70] Schmidt et al[70] reported significantly lower genera of *Streptococcus* and *Rothia* in tumor samples compared with contra-lateral normal and pre-cancer samples. In contrast, the tumors were enriched with the genus *Fusobacterium*, while the phylum Bacteroidetes was remarkably higher in both cancer and normal tissues of OSCC patients compared with pre-cancer and healthy individuals.[70] However, due to limitations in previous detection techniques where classification was not possible beyond the genus level, accurate conclusion of the possible relation between bacteria and oral cancer cannot be achieved.[70] Recently, applying a novel bioinformatics techniques with 16S rRNA reference sequences enabled the classification to the species level.[71] Al-Hebshi et al[71] detected 228 bacterial species in three samples of OSCC DNA, of which 35 species were present in all samples. More recently, *P. gingivalis*, *Fusobacterium nucleatum* (*F. nucleatum*) and *Streptococcus sanguinis* (*S. sanguinis*) have been shown to be highly abundant in OSCC tissues, paracancerous tissues, and subgingival plaque samples in comparison to normal tissues, pointing to the role of periodontal pathogens in OSCC.[72] *P. gingivalis* infection was positively correlated with advanced clinical staging, low differentiation, and lymph node involvement in OSCC patients,[72] which was also associated with more severe periodontal diseases in these patients.[72] Table 1 summarizes findings from studies concerned with microbiota and GIT cancers.

Based on the aforementioned findings, it is obvious that there is limited agreement on which bacterial species are associated with OSCC and whether any microbial dysbiosis identified has a role in the etiology, progression of oral cancer, or it is just a consequence.[56,58] However, most in vitro and in vivo studies support the hypothesis that *P. gingivalis* can mediate OSCC pathogenesis through different mechanisms.[62,73,74] These include inhibition of apoptosis,[75,79] activation of cell proliferation,[80,82] promotion of cellular invasion,[83,86] acquisition of stem cell characteristics,[87] and induction of chronic inflammation.[84,88] Nakhjiri et al[75] found that *P. gingivalis* inhibited chemically-induced apoptosis in gingival epithelial cells (GECs). It has been suggested that *P. gingivalis* activated Janus kinase 1 (JAK1)/Signal transducer and activator of transcription 3 (STAT3) (JAK1/STAT3) and Phosphoinositide 3-kinase (PI3K)/Protein kinase B (PKB, Akt) (PI3K/Akt) signaling, which in turn affected the intrinsic mitochondrial apoptosis pathways.[76,77] In addition, *P. gingivalis* has been shown to increase microRNA-203 (*miR-203*) in GECs that can activate STAT3 upon the downregulation of suppressor of cytokine signaling 3 (SOCS3), resulting in apoptosis suppression.[89] *P. gingivalis* was also found to secrete a nucleoside diphosphate kinase (NDK), which can inhibit the adenosine triphosphate (ATP)-dependent apoptosis driven by purinergic receptor (P2X7) on GECs.[78] Recently, Gallimidi et al[79] have shown that chronic coinfection with *P. gingivalis* and *F. nucleatum* enhanced the progression of chemically-induced OSCC in an animal model through the activation of the interleukin-6 (IL-6)/STAT3 pathway. *P. gingivalis* was also reported to enhance GECs proliferation by increasing the progression of GECs through the S and G2 phases of the cell cycle.[80,81] These mechanisms were suggested to be mediated by fimbrillin (FimA) fimbriae as well as the bacterial lipopolysaccharide (LPS) through dysregulation of tumor protein p53 (p53).[90] Zhou et al[82] also suggested that *P. gingivalis* may increase GECs proliferation via β-catenin and gingipain-dependent proteolytic

process. In addition to its roles in apoptosis and proliferation, *P. gingivalis* was reported to affect the other hallmarks of cancer, including migration and invasion.[83,91] *P. gingivalis* infection was found to increase the expression level of pro-matrix metalloproteinase-9 (MMP-9) in OSCC cells.[83,91] In addition, it was demonstrated to enhance epithelial to mesenchymal transition (EMT) and increase the production of MMP-1 and MMP-10, with both mechanisms contributing to increased cellular invasion.[84,85] Chronic inflammation was also among the suggested mechanisms by which bacteria mediate oral carcinogenesis.[84,88] This might provide a possible explanation to the link between periodontitis and increased risk of development of OSCC.[72,88] In this regard, Groeger et al[92] reported increased expression of B7 homolog 1 (B7-H1) and B7 co-stimulatory family member on dendritic cells (B7-DC) receptors, which are known to be involved in chronic inflammation, in both GECs and OSCC cell lines upon infection by *P. gingivalis*. In addition, Andrian et al[93] demonstrated upregulation of the inflammatory mediators (IL-1, IL-6, IL-8, and tumor necrosis factor (TNF-α)) following infection in engineered human oral mucosa. These findings were further validated by recent bioinformatical analyses of OSCC clinical samples.[88]

Therapeutic Perspectives

In vitro investigations have evaluated targeting OSCC cell lines infected with *P. gingivalis* using acetylshikonin.[74] Acetylshikonin is a flavonoid with anti-inflammatory activity and was found to suppress OSCC cell proliferation and induce apoptosis. Cho et al[74] revealed that acetylshikonin significantly reduced the invasion of *P. gingivalis* infected OSCC cell lines via downregulation of IL-8 release and IL-8-dependent MMP release. However, evidence from clinical studies is needed to support the role of *P. gingivalis* eradication in OSCC prevention and treatment.

Infection with *P. gingivalis* has recently been shown to have a negative impact on OSCC cells response to chemotherapy.[86] Woo et al[86] showed that the tumor xenografts of *P. gingivalis* infected OSCC cells were more resistant to Taxane treatment in comparison with uninfected cells, which was attributed to Notch1 activation.

Esophageal Cancer

Esophageal cancer is considered to be the eighth most commonly diagnosed cancer worldwide and the sixth leading cause of cancer death.[2] Despite advances in the current treatment modalities including surgery, chemotherapy, and radiotherapy, the prognosis is poor, even in patients with total excision.[94,95] Therefore, more studies should be directed toward understanding the pathogenesis of esophageal cancer and the role of microbiomes which might have diagnostic and therapeutic implications.[15] Table 1 summarizes findings from studies concerned with microbiota and GIT cancers.

Adenocarcinoma and squamous cell carcinoma (SSC) are the most common histopathological subtypes of esophageal cancer.[96] Narikiyo et al[97] described the enrichment of normal and neoplastic esophageal tissues excised from patients with esophageal cancer with the oral periodontopathic spirochete *Treponema denticola* (*T. denticola*), *S. mitis*, and *S. anginosus*. However, the pathological subtypes, whether SSC or adenocarcinoma, have not been determined.[97] In addition, Blackett et al[98] revealed that Campylobacter were significantly more dominant in Gastroesophageal reflux disease (GERD) and Barrett's esophagus than in esophageal adenocarcinoma.

Many in vivo studies have explored the relationship between the microbiome and esophageal adenocarcinoma development.[99,100] The effect of using antibiotics (penicillin G and streptomycin) on the development of esophageal adenocarcinoma was evaluated using a rat animal model and showed that the proportions of *Lactobacillales* were reduced in the antibiotic treated group, while *Clostridium* were elevated in comparison with control.[99] However, the incidence of esophageal adenocarcinoma was not affected by such microbiota alteration.[99] Zaidi et al[100] reported a high level of *Escherichia coli* (*E. coli*) in Barrett's esophagus and esophageal adenocarcinoma compared with normal epithelium among the studied patients. In addition, increased expression of toll-like receptor (TLR) 1–3, 6, 7, and 9 signaling pathways were significantly observed in esophageal adenocarcinoma, pointing to a potential mechanism by which *E. coli* might drive the carcinogenesis of esophageal adenocarcinoma.[100] Changes in the microbiota composition were suggested to mediate the progression of GERD and Barrett's esophagus toward adenocarcinoma.[101] However, currently, limited evidence is available about the exact role of microbiome in esophageal adenocarcinoma initiation and progression.[15,101]

The role of microbiome in SSC of the esophagus is not well defined.[15] Inverse correlation between esophageal microbial complexity and esophageal squamous dysplasia was described.[102] Yu et al[102] suggested that esophageal squamous cell dysplasia might be more common among

Table 1 GIT Cancers and Microbiota

Study	Source of Samples	Microbiota	Findings
OSCC			
Nagy et al[64]	Tissues	*Veillonella, Fusobacterium, Prevotella, Porphyromonas, Actinomyces, Clostridium, Haemophilus, Enterobacteriaceae, Streptococcus* spp.	Higher in OSCC vs adjacent healthy mucosa
Katz et al[65]	Tissues	*P. gingivalis*	Higher in gingival SCC vs normal gingiva
Tateda et al[66]	Gingival smears	*S. anginosus*	High in HNSCC
Sasaki et al[67]	Tissues/plaque	*S. anginosus*	High in OSCC tissues and dental plaque
Mager et al[68]	Saliva	*C. gingivalis*, *P*[3]*. melaninogenica*, *S. mitis*	Higher in OSCC patients vs healthy controls
Pushalkar et al[69]	Saliva	*Streptococcus, Rothia, Gemella, Peptostreptococcus, Porphyromonas, Micromonas, Lactobacillus*	Higher in OSCC vs healthy controls
		P[3]*. Neisseria, Leptotrichia, Capnocytophaga, Actinobacillus, Oribacterium*	Lower in OSCC vs healthy controls
Schmidt et al[70]	Tissues	*Streptococcus* and *Rothia*	Lower in OSCC vs contra-lateral normal
		Fusobacterium	High in OSCC vs contra-lateral normal
Chang et al[72]	Tissues/plaque	*P. gingivalis*, *F. nucleatum*, *S. sanguinis*	High in OSCC, paracancerous and subgingival plaque vs normal tissues
Esophageal Cancer			
Narikiyo et al[97]	Tissues/saliva	*T. denticola*, *S. mitis*, and *S. anginosus*	High in esophageal cancer and normal tissues from patients vs saliva from healthy controls
Zaidi et al[100]	Tissues	*E. coli*	High in Barrett's esophagus and EAC vs adjacent normal, dysplasia, and GERD within patients
Nasrollahzadeh et al[103]	Tissues	*Clostridiales, Erysipelotrichales*	High in gastric corpus of esophageal cancer vs normal esophagus
Chen et al[105]	Saliva	*Lautropia, Bulleidia, Catonella, Corynebacterium, Moryella, Peptococcus, Cardiobacterium*	Lower in ESCC vs healthy controls
Gao et al[106]	Tissues	*P. gingivalis*	High in ESSC, adjacent mucosal vs healthy controls
Peters et al[107]	Mouthwash samples	*T*[3]*. forsythia*	High in EAC
		P. gingivalis	High in ESCC
Meng et al[104]	Saliva	*P. gingivalis*	High in ESCC vs healthy controls
Yamamura et al[109]	Tissues	*F. nucleatum*	Higher in ESCC vs normal controls and significantly linked to shorter survival time
Gastric Cancer			
Nomura et al[407]	Serum IgG Ab	*H. Pylori*	Higher in GC vs normal controls
Kikuchi et al[133]	Serum CagA Ab	*H. Pylori*	*H. Pylori* are related to risks of intestinal-type, diffuse-type, early, advanced, and distal GC
Bartchewsky et al[129]	Tissues	*H. Pylori*	CagA, VacA virulence factors are higher in GC vs chronic gastritis, *H. Pylori*-positive, and uninfected individuals
Correa et al[143]	HPE	*H. Pylori*	HPE (patients with multifocal nonmetaplastic atrophy and/or intestinal metaplasia, precancerous lesions) interferes with the precancerous process and increases the rate of regression of precursor lesions

(*Continued*)

Table 1 (Continued).

Study	Source of Samples	Microbiota	Findings
Chen et al[148] Rokkas et al[149]	HPE	*H. Pylori*	HPE was linked to reduced risk, when the lesions were non-atrophic or atrophic gastritis but not in intestinal metaplastic or dysplastic lesions
Gastric MALT Lymphoma			
Wotherspoon et al[157]	Tissues	*H. Pylori*	Expression in most investigated samples Gastric MALT lymphoma
Parsonnet et al[160]	Serum	*H. Pylori*	Higher *H. Pylori* in gastric lymphoma vs non-gastric lymphoma
Stolte et al[161]	HPE	*H. Pylori*	Complete remission in 80% of low grade stage E1 lymphomas patients
Gastric DLBCL			
Morgner et al[191]	HPE	*H. Pylori*	HPE led to complete remission in 7/8 patients with DLBCL.
Kuo et al[186]	HPE	*H. Pylori*	HPE led to complete pathological response in most of DLBCL cases
Kuo et al[187]	CagA	*H. Pylori*	CagA detected in gastric DLBCL and is associated with *H. Pylori* dependence
Chen et al[192]	HPE/long-term follow-up	*H. Pylori*	No tumor recurrence was observed in DLBCL (MALT) after more than 5 years in complete responders
CRC			
Klein et al[209]	Fecal sample	*S. bovis*/*S. gallolytucis*	Higher in colon cancer vs controls
Abdulamir et al[210,408]	Feces, mucosa of colorectum, and colorectal tissues	*S. bovis*/*S. gallolytucis*	High in CRC tissues vs healthy controls 25–80% of patients with *S. gallolytucis* bacteremia had CRC
Sobhani et al[214]	Fecal sample	Bacteroides/*Prevotella*	Higher in CRC patients vs controls
Wang et al[215]	Fecal sample	*B. fragilis*, *Enterococcus*, *Escherichia*/*Shigella*, *Klebsiella*, *Streptococcus*, *Peptostreptococcus*, *Roseburia*, *Lachnospiraceae*	Higher in CRC patients vs controls Lower level
Purcell et al[216]	Mucosal tissue	ETBF	Higher in early-stage lesions
Boleij et al[222]	Mucosal tissues	ETBF	Higher in CRC patients vs controls
Maddocks et al[224]	Tissues	*E. coli*	Higher in CRC vs normal colonic mucosa of CRC patients
Buc et al[226]	Tissues	*E. coli*	Cnf and Cdt higher in CRC vs diverticulosis
Bundgaard-Nielsen et al[232]	Tissues	*F. nucleatum* and *B. fragilis*	Higher in CRC and diverticular vs adenoma
Amitay et al[233]	Fecal samples	*F. nucleatum*	Higher in CRC vs advanced adenomas, non-advanced adenomas and normal controls
Balamurugan et al[240]	Fecal samples	*E*[3]*. faecalis*	Higher in CRC vs normal controls
Rokkas et al[149] Wu et al[244] Chen et al[245]	CRC/adenomas vs healthy controls	*H. Pylori*	Positive association between *H. Pylori* and the risk of CRC
Teimoorian et al[246]	Serum	*H. Pylori*	*H. Pylori* higher in colon cancer and adenomatous polyps vs healthy controls
Marchesi et al[250]	Tissues	*Coriobacteridae, Roseburia, Fusobacterium and Faecalibacterium*	Higher in cancer, vs healthy tissues within CRC patients

(*Continued*)

Table 1 (Continued).

Study	Source of Samples	Microbiota	Findings
		Enterobacteriaceae, Citrobacter, Shigella, Cronobacter, and *Salmonella*	Lower in CRC tissues
Shah et al[251]	CRC vs adjacent tissues/fecal samples	*Fusobacterium, Parvimonas, Streptococcus* *Faecalibacterium, Ruminococcaceae*	Higher in CRC Lower in CRC vs tumor-adjacent tissues/ fecal samples from same cases
HCC			
Zhang et al[302]	Fecal/cecal samples	*Lactobacillus*, *Bifidobacterium*, *Enterococcus* *E. coli* and *Atopobium* cluster	Lower in rat model of (DEN) induced HCC Higher level
Yoshimoto et al[304]	Fecal sample	*Clostridium* genus producing DCA	High in genetically or (HFD)-induced obesity in mice model. Higher incidence of HCC upon the administration of the chemical carcinogen (DMBA)
Xie et al[305]	Fecal sample	*Atopobium, Bacteroides, Clostridium, Desulfovibrio*	High in mice model mimics the development of steatosis and subsequent progression to NASH and HCC. Correlated with LPS levels and the pathophysiological features
Fox et al[307]	Liver tumors	*H. hepaticus*	Intestinal colonization was sufficient to promote aflatoxin- and HCV transgene-induced HCC in exposed mice
Huang et al[308]	Tissues	*Helicobacter* spp.	Higher in HCC vs controls
Dore et al[309]	Tissues	*H. Pylori*	VacA and CagA higher level in HCC
Lu et al[312]	Tongue coat	*Oribacterium* and *Fusobacterium*	Higher in HCC vs healthy controls
Grat et al[313]	Fecal samples	*E. coli*	Higher in HCC in cirrhosis/HCC vs cirrhosis only
Ponziani et al[314]	Fecal samples	*Bacteroides* and *Ruminococcaceae* *Bifidobacterium*	Higher in NAFLD-cirrhosis/HCC vs NAFLD-cirrhosis Lower level
Pancreatic Cancer			
Raderer et al[337]	Blood samples	*H. Pylori*	Twofold increase in risk in infected patients with pancreatic carcinoma vs controls
Stolzenberg-Solomon et al[338]	Serum level of Abs of *H. Pylori* and CagA+	*H. Pylori*	Smoker men, seropositive males for antibodies or CagA+ strains had increased risk for pancreatic cancer compared with seronegative.
Michaud et al[359]	Blood samples/Abs	*P. gingivalis*	Twofold increase in risk of pancreatic cancer in patients with high *P. gingivalis*
Mitsuhashi et al[364]	Tissues	*Fusobacterium* spp.	Found in 8.8% of PDAC tissues
Gaida et al[365]	Tissues/cell lines	*P*^{wc}. *aeruginosa*	Enhanced the expression of ABCB1 in PDAC and promoted cell invasion and metastasis

(*Continued*)

Table 1 (Continued).

Study	Source of Samples	Microbiota	Findings
Gallbladder Cancer			
Nagaraja et al[377]	*S*. *Typhi* Ab/GBC vs control	*S*. *Typhi*	Chronic *S*. *Typhi* carrier state is important risk factor among GBC patients
Caygill et all[385]	Long-term typhoid carriage	*S*. Typhi	Chronic typhoid carriers have an almost 167-fold higher risk of GBC
Shukla et al[386]	Culture/*S*.*Typhi* Vi Ab	*S*.*Typhi*	Eightfold more risk of GBC in culture-positive typhoid carriers than non-carriers
Yakoob et al[380]	Bile/GB tissues	*H. Pylori*	Higher in chronic cholecystitis and GBC
Parajuli et al[399]	GB tissues	*H. hepaticus*	Higher in GBC vs chronic cholecystitis
Murata et al[400]	GB tissues	*H. bilis*	Higher in GBC, bile duct cancer vs cholecystolithiasis
Fallone et al[401]	Bile	*Helicobacter* spp.	Not detected in patients diagnosed with gallstones or hepato-biliary malignancies
Csendes et al[404]	Bile	*E. coli, E*. *faecalis, Klebsiella* and *Enterobacter*	Higher in GBC, gallstones vs controls
Roa et al[405]	Bile	*E. coli, Streptococci-Enterococci, Enterobacter, Klebsiella, Proteus*	Higher in GBC vs controls, *S*. *Typhi* not detected
Tsuchiya et al[381]	Bile	*F. nucleatum, E. coli, Enterobacter*	High in GBC, *S*. *Typhi* not detected

Note: Plain rows represent clinical studies, rows highlighted with pink represent meta-analysis/systematic reviews and rows highlighted with blue represent in vivo studies.
Abbreviations: Ab, antibody; ABCB1, ATP-binding cassette sub-family B member 1; B, *Bifidobacterium*; C, *Capnocytophaga*; CagA, cytotoxin-associated gene A; Cdt; cytolethal distending toxin; Cnf, cytotoxic necrotizing factor; CRC, colorectal cancer; CYP450, Cytochrome P450 enzymes; DCA, deoxycholic acid; DEN, diethylnitrosamine; DLBCL, diffuse large B cell lymphoma; DMBA, dimethylbenz(a)anthracene; DMH, 1;2-dimethylhydrazine; E, *Escherichia*; E*, *Enterococcus*; EAC, esophageal adenocarcinoma; ETBF, Enterotoxigenic *Bacteroides fragilis*; ESCC, esophageal squamous cell carcinoma; F, *Fusobacterium*; FAP, familial adenomatous polyposis; GB, gallbladder; GBC, gallbladder cancer; GC, gastric cancer; GERD, gastroesophageal reflux disorder; GIT, gastrointestinal tract; H, *Helicobacter*; HCC, Hepatocellular carcinoma, HCV, hepatitis C virus; HFD, high-fat diet; HNSCC, head and neck squamous cell carcinoma; HPE, *H. Pylori* eradication therapy; IgG, immunoglobulin G; L, *Lactobacillus*; LPS, Lipopolysaccharide; MALT, mucosa-associated lymphoid tissue; NAFLD, non-alcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; OSCC, oral squamous cell carcinoma; PDAC, pancreatic ductal adenocarcinoma; P, *Porphyromonas*; P*, *Prevotella*; P*, *Pseudomonas*; S, *Streptococcus*; S*, *Salmonella*; SCC, squamous cell carcinoma; spp, species; T, *Treponema*; T*, *Tannerella*; VacA, vacuolating cytotoxin A; vs, versus.

people with lower esophageal microbiota. On the other hand, Nasrollahzadeh et al[103] reported a predominance of *Clostridiales* and *Erysipelotrichales* in the gastric corpus microbiota of patients with esophageal squamous cell dysplasia and SSC, when compared to control cases. This suggests a possible involvement of gastric microbial imbalances in the transformation of esophageal squamous dysplasia to SSC.[103] Changes in bacterial microbiota in the saliva of patients with esophageal SCC were also reported.[104] Less enrichment of genera *Lautropia, Bulleidia, Catonella, Corynebacterium, Moryella, Peptococcus, and Cardiobacterium* was observed in comparison with controls.[105] In addition, *P. gingivalis*, which was detected in esophageal SSC and adjacent mucosal tissues,[106,107] has recently been shown to be significantly dominant in the saliva of patients with esophageal SCC, compared with healthy individuals.[104] Meng et al[104] described that *P. gingivalis* enhanced the proliferation and motility of SCC cell lines via the nuclear factor kappa B (NF-κB) signaling pathway. These findings suggest a role of oral pathogens in inducing esophageal SCC tumorgenesis, metastasis, severity, as well as poor prognosis.[104,106,107] Findings from previous studies and others indicate that poor oral health might contribute to higher risk of esophageal SSC.[104,106,108]

Recently, possible correlation between the presence of *F. nucleatum* and the prognosis of esophageal SSC has been demonstrated.[109] *F. nucleatum* was found in esophageal cancer tissues of nearly 23% of patients with esophageal cancer (74/325) and was significantly linked to shorter survival time.[109] Increased gene expression of the specific chemokine *CCL20* has been observed, suggesting that *F. nucleatum* promotes an aggressive tumor phenotype by activating the cytokine–cytokine receptor interactions.[109]

Therapeutic Perspectives

Currently, limited evidence is available regarding the role of microbiomes in esophageal cancer treatment or prevention, which might be considered as an attractive topic to be investigated.[110] Iida et al[111] showed that disruption of the microbiota using antibiotics reduced the sensitivity of

xenograft tumors in animal models to subsequent CpG-oligonucleotide immunotherapy and platinum chemotherapy (oxaliplatin). These findings were also observed in germ-free mice models.[111,112] It has been suggested that intact commensal microbiota is needed to obtain optimal cancer treatment, since microbiota promotes the effect of cancer therapy through myeloid-derived cell functions in the tumor microenvironment.[111,112] However, future studies are required to clarify the clinical implications of microbiome in esophageal cancer.

Gastric Cancer

The cause of gastric cancer (GC) is multifactorial including; environmental, dietary, and host-related factors.[113,114] In addition, genetic and epigenetic alterations were described to interplay in the etiology of gastric cancer.[114,116] According to the World Health Organization (WHO), *H. Pylori* was described as a class I carcinogen since it has a crucial role in the initiation of GC.[117] *H. Pylori* was found in the gastric mucosa of 50% of the human population.[118] Currently, two main mechanisms in which *H. Pylori* infection may result in intestinal-type GC have been suggested; the indirect processes through inflammation mediation and direct pathological role through bacterial virulence factors.[119] Chronic inflammation caused by *H. Pylori* infection accelerates gastric cell turnover, which may lead to mitotic errors. This, in turn, enhances epithelial transformation and eventually can cause gastric adenocarcinomas.[120,121] The sequential processes of *H. Pylori* chronic inflammation was described by Correa model.[122] *H. Pylori* can initiate early pre-neoplastic lesions such as atrophic gastritis and enhance the progression to advanced lesions, including metaplasia, dysplasia, and ultimately development of gastric adenocarcinomas.[120,123,124] The inflammatory process is complex and indirect, involving the interplay between *H. Pylori*, acidic environment, immune cells, reactive oxygen, and nitrogen species, collectively, leading to increased oxidative stress, DNA damage, and the expression of pro-inflammatory mediators.[125,127] Increased levels of cytokines (IL1B, IL-6, IL-8, and TNF-α) and cyclooxygenase-2 (COX-2) in the nucleus of gastric mucosal cells was described to enhance the progression of atrophic changes and induce intracellular signaling transformation.[128,129] In addition to *H. Pylori*-associated inflammatory response, aberrant DNA methylation and gene silencing were observed in gastric epithelial cells and were described to be involved in the development of *H. Pylori*-related gastric carcinomas.[130,131] These include genes involved in cell adhesion, cell cycle regulation, DNA mismatch repair, inflammation, transcription, autophagy, and tumor suppression.[130,131]

The direct effects of *H. Pylori* infection are mainly mediated by the virulence factors.[132] Cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA) are among the most frequently investigated virulence factors.[117,132] Both factors were found to mediate the transition of precancerous gastric lesions toward malignant ones.[133,134] CagA has been suggested to potentiate the inflammatory reactions, which in turn facilitate the progression of gastritis to GC.[135,136] In addition, together with the cag pathogenicity island (cag PAI), CagA was found to affect multiple cellular signaling pathways, such as the mitogen-activated protein kinase (MAPK) cascade, NF-κB expression, PI3K/Akt signaling pathways, and EMT through the oncogenic yes-associated protein (YAP) pathway.[134,137] Moreover, cag PAI was shown to have an impact on GC through induction of gene mutation of *p53*.[138,140] On the other hand, VacA was found to affect the epithelial cell barrier and inhibit the T-cell mediated immune response, which results in a favorable environment for *H. Pylori*.[141,142] Table 1 summarizes findings from studies concerned with microbiota and GIT cancers.

Therapeutic Perspectives

The role of *H. Pylori* eradication for prevention of gastric carcinoma was investigated by many researchers.[143,144] Despite the fact that *H. Pylori* is considered amajor risk factor of GC, studies showed that eradication therapy was not enough for absolute effective prevention of GC development, indicating that *H. Pylori* is not the sole cause for gastric cancer.[145] Findings from one clinical trial among Colombian people with high risk for GC showed no significant difference in cancer incidence among groups treated with anti-*H. Pylori* triple therapy and untreated groups after a 6-year follow-up.[143] However, a significant increase in the regression rate of cancer precursor lesions was reported among the treated group.[143] Results from meta-analysis of six randomized controlled trials revealed that eradication of *H. Pylori* can contribute to a 44% reduction in GC incidence among healthy, asymptomatic, infected patients in comparison to untreated individuals.[144] In addition, Ma et al[146] reported a 39% reduction in incidence of precancerous lesions upon *H. Pylori* eradication in a placebo-controlled clinical trial with a 15-year follow-

up. Vannella et al[147] also showed that, after 8 years of eradication, reversal of atrophic body gastritis was observed in 50% of treated patients.Findings from a meta-analysis of 10 studies involving 7,955 participants showed that *H. Pylori* eradication significantly reduced the risk of GC among treated patients.[148] This was further supported by results from a recent systematic review and meta-analysis of 26 studies (10 randomized controlled trials and 16 cohort studies) in which 52,363 subjects were included.[149] The risk of GC was shown to significantly lower in patients in whom successful eradication of *H. Pylori* was achieved in comparison to untreated controls.[149] However, regarding *H. Pylori* eradication in patients with precancerous lesions, subgroup analyses revealed that reducing the risk of GC was mainly when the lesions were non-atrophic or atrophic gastritis, but not in intestinal metaplastic or dysplastic lesions.[148,149] Based on the aforementioned findings, it is obvious that *H. Pylori* eradication has an essential role in reducing the risk of GC, which can have a major impact and application for gastric cancer prevention. However, *H. Pylori* eradication therapy is recognized to be highly valuable if initiated at early stages of the infection, before the development of intestinal metaplasia, which is currently considered as a "point of no return" in the precancerous cascade of gastric cancer pathogenesis.[148,149]

Results from animal studies showed that the use of DNA demethylating agent, 5-aza-2′-deoxycytidine (5-aza-dC), resulted in suppression of aberrant DNA methylation and reduced the incidence of gastric cancer development.[150] However, limited evidence is available regarding the use of demethylating agents as chemoprevention for gastric cancer in humans, due to their high toxicity profile.[130] Novel DNA demethylating agents with minimal side-effects should be designed to be used for chemoprevention, particularly in patients who are at high-risk for gastric adenocarcinoma.[130]

According to the United Nations and WHO, Probiotics are defined as "live microorganisms which when administered in adequate amounts confer a health benefit for the host".[151] Investigations on probiotics use in gastric cancer are mainly directed toward eradication of *H. Pylori* infection since it is a major risk factor.[31] The use of probiotics showed inhibitory effects on *H. Pylori* infection using animal models.[152] In addition, findings from recent meta-analysis on clinical trials investigating the use of probiotics as a supplementation with antibiotic therapy reported positive effects.[153,154] These include a reduction in side-effects, better patient compliance, and enhanced eradication.[153,154] Table 2 summarizes findings from studies concerned with probiotics interventions in GIT cancers.

Gastric MALT Lymphoma

Normal gastric mucosa contains no lymphoid tissues, however, the GIT is considered as the most common site for the extranodal lymphomas, with 30–45% of the cases reported in the stomach.[155,156] Primary lymphomas affecting the stomach were described to have the properties of mucosa-associated lymphoid tissue (MALT),[157] which accounts to 2–8% of gastric tumors.[156] Gastric MALT lymphoma is a low-grade tumor with expression of dense lymphoid infiltrate of small-size lymphocytes that have the ability to invade and destroy gastric glands.[158] The development of gastric MALT lymphoma was reported to be associated with local infections such as *H. Pylori* infections.[158,159] This was first reported by Wotherspoon et al[157] in 1991. Among 450 patients with *H. Pylori*-associated gastritis, 125 showed mucosal lymphoid follicles and, in eight patients, B lymphocytes were found to infiltrate the epithelium, which is a main feature of MALT lymphoma.[157] In addition, 92% of tissues diagnosed with gastric MALT lymphoma were found to be enriched by *H. Pylori*.[157] Since then, *H. Pylori* infections were also reported by other studies, supporting its association with development of gastric MALT lymphomas.[160,161]

In contrast to gastric carcinoma, the virulence factors of *H. Pylori* appear to not have a significant role in the pathogenesis of gastric lymphoma.[162] CagA positive strains did not have a crucial role in low-grade MALT lymphoma in comparison to high grade lymphomas or what is currently known as diffuse large B cell lymphoma (DLBCL).[163] *H. Pylori* has been shown to drive the pathogenesis of MALT lymphoma through different mechanisms.[156] It was described to induce the production of a proliferation inducing ligand (APRIL) by macrophages in the tumor microenvironment,[164] which is a novel cytokine that plays an important role in sustained B-cell proliferation and hence is highly associated with *H. Pylori* MALT lymphoma.[165] In addition, *H. Pylori* infections were shown to cause genetic alterations leading to B cells transformation into a malignant clone.[156] Three chromosomal translocations were described to be involved in the activation of NF-κB, and thus affect the immunity, inflammation, and apoptosis.[166,167] Of note, the t(11;18)(q21;q21) was found in approximately one third of MALT

Table 2 In vivo Studies and Clinical Trials of Probiotics Interventions in GIT Cancers: Gastric Cancer, CRC, and HCC

Probiotic Strains	Model of Investigation	Findings
Gastric Cancer		
B. bifidum, L. acidophilus, L. rhamnosus, L. salivarius	Animal models	Inhibition of *H. Pylori* infection as a major risk factor of gastric cancer.[152]
L. acidophilus LB	Clinical trial	Increase *H. Pylori* eradication rate.[409]
L. acidophilus La5 *B. lactis* Bb12	Clinical trial	• Increase *H. Pylori* eradication rate. • Reduction of adverse effects caused by *H. Pylori* eradication therapy.[410,411]
L. casei	Clinical trial	Increase *H. Pylori* eradication rate.[412]
L. reuteri	Clinical trial	Increase *H. Pylori* eradication rate.[413]
L. reuteri	Clinical trial	Reduction of adverse effects caused by *H. Pylori* eradication therapy.[414]
CRC		
VSL#3 (*S. thermophiles*, *B. breve, B. longum, B. infantis, L. paracasei, L. Bulgaricus, L. acidophilus, L. plantarum*)	Mice model	Reduction of adenoma and adenocarcinoma formation.[260]
VSL#3	Rat model	Reduction of adverse effects caused by irinotecan (Weight loss, moderate and severe diarrhea).[262]
KFRI342 *L. acidophilus*	Rat model	• Reduction of the development of colorectal preneoplastic lesions. • Reduction of *E. coli* and aerobic bacteria.[263]
B. longum and *L. gasseri*	Mice model	• Inhibition of tumor induction by DMH. • Reduction of colon tumor size and number. • Inhibition of colonic mucosa cellular proliferation.[264]
L. casei	Rat models	Downregulation of CYP450 expression and activity.[266]
L. salivarius REN	Rat model	• Inhibition of tumor induction by DMH. • Rehabilitation of gut microbiota.[265]
VSL#3/inulin	Clinical trial	• Inhibition of cell proliferation. • Potentiation of detoxification capacity of pouch mucosal cells in FAP patients.[272]
L. rhamnosus LC705 (LC705) and *P. freudenreichii* ssp. Shermani JS (PJS)	Clinical trial	Reduction of the bacterial enzymes β-glucosidase, and urease.[273]
L. gasseri (LG21)	Clinical trial	• A deterioration of the intestinal environment in CRC patients. • Improvement in intestinal environment.[415]
L. rhamnosus GG	Clinical trial	Reduction of adverse effects caused by 5-FU (diarrhea).[274]
HCC		
VSL#3	Rat model	• Inhibition of DEN-induced hepato-carcinogenesis. • Reduction of LPS serum levels, number and size of HCC.[302]
Prohep (*L. rhamnosus* GG, viable *E. coli*Nissle 1917 and heat-inactivated VSL#3 (1:1:1)).	Mice model	• Reduction of tumor growth and size. • Rehabilitation of fecal microbiota. • Induction of the anti-inflammatory cytokine IL-10 and suppression of the secretion of the inflammatory cytokines IL-17, IL-6, and interferon (IFN)- γ. • Reduction of the tumor populations of migratory Th17 cells. • Differentiation of type I regulatory T cells in the gut and enhancement of T regulatory cell immune-response by bacteria-derived metabolites. • Downregulation of proangiogenic genes.[317]
L. rhamnosus LC705 and *P. freudenreichii* ssp. Shermani	Clinical trial	Reduction of the biologically effective dose of aflatoxin exposure and aflatoxin-DNA toxic adduct.[319]

Abbreviations: B, *Bifidobacterium*; CRC, colorectal cancer; CYP450, Cytochrome P450 enzymes; DEN, diethylnitrosamine; DMH, 1,2-dimethylhydrazine; E, *Escherichia*; FAP, familial adenomatous polyposis; 5-FU, 5-Fluorouracil; H, *Helicobacter*; HCC, Hepatocellular carcinoma; IL, interleukin; L, *Lactobacillus*; LPS, Lipopolysaccharide; P, *Propionibacterium*; S, *Streptococcus*.

cases and is often the only cytogenic alteration reported.[168] The resulting translocation interferes with B cells apoptosis which contributes to monoclonal expansion.[169] *H. Pylori* infection was also reported to mediate epigenetic alterations in gastric MALT lymphoma.[170] Aberrant DNA methylation linked to inactivation of tumor suppressor genes was observed in 61.9% of MALT lymphomas, but none of the control group specimens.[170] However, the underlying mechanism by which *H. Pylori* infection leads to CpG island hypermethylation is yet to be elucidated.[170] Table 1 summarizes findings from studies concerned with microbiota and GIT cancers.

Therapeutic Perspectives

Currently, *H. Pylori* eradication therapy is highly recommended for early stage, low-grade, MALT lymphoma; that is when the neoplasia is confined in the stomach or in perigastric lymph nodes.[159,171] The first evidence regarding complete histological remission of gastric MALT lymphoma upon *H. Pylori* eradication was shown in the early 1990s,[172] in 83% of gastric MALT patients (N=6 cases).[172] Findings from a systematic review on 32 studies, including 1,408 patients, described that. *H. Pylori* eradication is effective in treating approximately 75% of patients with early stage gastric lymphoma.[173] Since probiotics use as an adjuvant to *H. Pylori* eradication therapy showed promising results in GC, as described previously, future studies are needed to explore the outcome of probiotics administration in gastric MALT lymphoma, as limited evidence is available in this regard.

Different predictive factors for gastric MALT lymphoma cure by *H. Pylor*i eradication were recognized. These include the stage, the level of gastric wall penetration, and localization in the stomach.[174] However, the reinfection with the same strain of *H. Pylori* can cause relapse and regrowth of the lymphoma.[18] In addition, at advanced stages, adjunctive anti-tumor therapy might also be prescribed as the tumor might be *H. Pylori* independent evolved from low-grade lymphomas.[175] The patient ethnicity was also found to play a role in the patient response to *H. Pylori* eradication, with a higher response rate reported in an Asian population in comparison to western populations.[175] The presence of t (11;18)(q21:q21) chromosomal translocation with increasing chromosomal damage was also suggested to make gastric MALT lymphomas less responsive to *H. Pylori* eradication therapy.[176,178] Recent findings have also shown that this translocation is associated with disseminated disease involving the stomach, small intestine, colon, and lung.[179] The ratio of Forkhead Box P3/cluster of differentiation 4 ($FOXP3^+/CD4^+$) regulatory T cells (Treg) and the absolute number of $FOXP3^+$ cells were also shown to be significantly higher in gastric MALT lymphomas sensitive to *H. Pylori* eradication as compared with resistance ones.[179,180] This suggests a possible role of microbiome-immunity interactions within the tumor microenvironment in the therapeutic response of low grade MALT lymphoma.[180] In contrast, increased expression of either *miR-142-5p* (ie, hematopoietic specific microRNA) or *miR-155* (ie, potential oncogenic microRNA) in MALT-lymphoma tissues were linked to treatment resistance.[181] In this regard, future studies are needed to identify other biomarkers for therapeutic response of MALT lymphoma and understand the underlying causes for treatment failure.[182]

Gastric DLBCL

Diffuse large B cell lymphoma (DLBCL) is another form of extranodal non-Hodgkin's lymphoma that affects the stomach.[182] It is a clinically heterogeneous aggressive disease with a histopathological appearance of a large number of transformed cells.[183] Tumors without histological evidence of MALT lymphoma, dense infiltration of centrocyte like cells in the lamina propria, and typical lymphoepithelial lesions are classified as pure or de novo DLBCL.[183,184] In contrast, those with evidence of MALT are classified as DLBCL (MALT).[184] DLBCL (MALT) was previously known as "high-grade" MALT lymphoma and was suggested to be developed from gastric MALT lymphoma that has undergone high-grade transformation.[177,184]

The involvement of *H. Pylori* in the pathogenesis of DLBCL remains controversial.[185] Studies have shown that *H. Pylori* has an important role in DBLCL (MALT) with the expression of *H. Pylori* virulence factor CagA being more frequent in *H. Pylori*-dependent cases.[186,187] DLBCL was also described to gain *H. Pylori*-independent growth through indirect activation of NF-κB.[188] Overexpression of B-cell activating factor of the TNF family (BAFF), with subsequent B-cell lymphoma/leukemia 10 (BCL10) upregulation and indirect NF-κB activation was reported.[188] More recently, *H. Pylori* involvement has also been observed in de novo gastric DLBCL.[186] As with gastric MALT lymphoma, hypermethylation and epigenetic silencing were highly prevalent in DLBCLs (93.3%).[170,189] However, the chromosomal translocation t(11;18)(q21:q21) is uncommon in gastric DLBCL with or without MALT properties.[182] Table 1 summarizes findings from studies concerned with microbiota and GIT cancers.

Therapeutic Perspectives

H. Pylori eradication therapy was found to play an essential role in the treatment of DLBCL cases.[184] It was shown as potential curative therapy for the DLBCL (MALT) cases.[186,190] The expression of CagA was associated with rapid response to *H. Pylori* eradication and suggested as predictive marker for the candidate patients with gastric DLBCL for eradication therapy without chemotherapy.[187] Morgner et al[191] reported that a complete pathological response had been achieved in seven of eight cases with DLBCL (MALT) upon eradication of *H. Pylori*. In addition, Chen et al[192] have shown long-term results of *H. Pylori* eradication in early-stage gastric DLBCL (MALT) lymphomas confined to mucosa and submucosa, with complete pathological response reported in 64% of cases. However, with more penetration, the success of eradication therapy is limited.[193] Another study from Japan showed that a complete pathological response was found in four of six cases with DLBCL (MALT) confined to the mucosa/submucosa, but in only one of four cases with invasion beyond the muscularis propria.[193] In such cases, chemotherapy is considered the standard treatment modality.[184] Of note, BAFF overexpression was reported in 70% of DLBCLs that were resistant to eradication therapy in comparison with 18.8% of those that were sensitive.[188]

Currently, there are sufficient data about the application of *H. Pylori* eradication in de novo DLBCL.[186] In a retrospective study conducted by Kuo et al,[186] it has been shown that complete pathological response was achieved in more than two thirds of the cases with de novo DLBCL upon eradication therapy. Therefore, the recommendations are to treat these cases with antibiotics, thus saving the patients from the harmful effects of conventional chemotherapy.[182,184]

Colorectal Cancer

Colorectal cancer (CRC) is considered as the third most commonly diagnosed cancer in males and the second in females. According to the Global Cancer Statistics, 1.8 million new CRC cases were diagnosed in 2018 and 881,000 deaths were reported in the same year.[2] Adenocarcinoma is the most common histopathological subtype of CRC.[194] Although the etiology of this highly lethal disease remains unclear, many environmental factors such as smoking, diet, and lifestyle were shown to determine individual's risk for CRC.[195] CRC incidence is well known to be increased with age.[196] Individuals with certain genetic disorders such as Adenomatous Polyposis Coli (APC) and with family history of CRC are highly susceptible for CRC development.[196] In addition, ulcerative colitis and Crohn's disease are risk factors for CRC.[197] However, 80% of CRC cases are sporadic.[198]

The role of infectious implications and alterations of the gut microbiome in CRC pathogenesis and therapy has also been suggested.[199,200] Human intestine is a perfect habitat for more than 500 different species of bacteria, with the highest concentration found in the colon.[201] The majority of gut microbiota are strict anaerobes such as *Bacteroides, Eubacterium, Bifidobacterium, Fusobacterium, Peptostreptococcus,* and *Atopobium*.[33,202] Facultative anaerobes contribute to the minor percentage of gut inhabitants including *Enterococci, Lactobacilli, Enterobacteriaceae,* and *Streptococci*.[33,203] Dysbiosis has been implicated in the pathogenesis of many diseases affecting the colon including inflammatory bowel disease, colitis, and CRC.[202,203] Findings from in vitro and in vivo studies support the microbiome hypothesis of CRC.[202,203] CRC was identified in 20% of germ-free rats using chemically induced CRC models in comparison to 93% of conventional rats.[204] In addition, the tumor size was smaller in the germ-free group.[205] However, the specific mechanism of the intestinal flora in causing CRC is unclear.[206]

Results from human studies have also supported the role of the gut microbiome in CRC.[207,210] McCoy and Mason[207] first reported a case of enterococcal endocarditis associated with a carcinoma of the cecum. It has been suggested to be caused by *S. gallolytucis* (previously known as *S. bovis*).[207] The correlation between *S. gallolytucis* septicemia and CRC has been observed by many studies.[208,210] Between 25% and 80% of patients with *S. gallolytucis* bacteremia had CRC.[209,210] In addition, patients with CRC showed higher fecal carriage of *S. gallolytucis* in comparison with control subjects.[209] The prevalence of *S. gallolytucis* in CRC patients was reported to be from 33% to 100%, while it was found in only 2.5–15% of the normal population.[210] However, the exact underlying mechanism by which *S. gallolytucis* promotes CRC is yet to be elucidated.[202,208,211] Animal studies showed that *S. gallolytucis* increased the expression of proliferation markers and polyamines.[21] Colonic adenoma was observed in 50% of affected rats and a higher number of aberrant colonic crypts were reported.[21] In addition, increased production of IL-8 in the colonic mucosa was suggested to be caused by *S. gallolytucis*.[211] It was shown that IL-8 enhanced the generation of free radicals which

promoted the neoplastic process.[211] *S. gallolytucis* was also described to colonize and grow in colorectal tissues via collagen-binding proteins and histone-like protein A that allow adherence to collagen I, IV, fibronectin, fibrinogen, and proteoglycans in colon tissues.[210] Accordingly, it is highly recommended that all patients with *S. gallolytucis* bacteremia should undergo a complete endoscopic screening of the colon.[212]

Bacteroides fragilis (*B. fragilis*) strains account for 0.1% of colon normal flora with 80% of children and adults carriers of *B. fragilis* in their colonic flora.[213] However, the "enterotoxigenic *B. fragilis*" (ETBF), producing metalloprotease fragilisyn, has been shown to be increased in fecal samples as well as colonic mucosal tissues of CRC patients.[214,216] Fragilisyn interferes with cell-to-cell adhesion as it causes cleavage of the extracellular domain of the E-cadherin, which is an invasion suppressor.[217,218] In vitro studies showed that treatment of HT29/C1 cells with *B. fragilis* toxin promoted cell proliferation through the β-catenin pathway, with subsequent c-myelocytomatosis oncogene product (c-MYC) and cyclin D1 transcription and translation.[219] The activation of β-catenin signaling via mutations in one or more of the APC complex proteins was found to be associated with inherited and sporadic forms of CRC.[220] Results from clinical studies showed that the enterotoxin gene is highly expressed in mucosal samples from CRC patients compared to control groups.[221,222] ETBF resulted in CRC development in multiple intestinal neoplasia (Min) in mice.[219] This was mediated through the activation of STAT3 and a selective T helper 17 (TH17) cells response.[223] In contrast, ETBF-induced tumor development was inhibited upon antibody-blockade of IL-17 and IL-23 receptor involved in TH17 responses.[223]

E. coli is part of the normal colonic flora.[9] The colonic mucosa of patients with adenomas and carcinomas exhibited increased carriage of E. coli.[224] This bacteria harbors cytotoxic necrotizing factor (Cnf) and cytolethal distending toxin (Cdt), which are significantly associated with CRC biopsies.[225] In addition, Colibactin, a polyketide-peptide genotoxin, was most frequently associated with *E. coli* colonizing CRC.[226,227] *E. coli* strains of the phylogenetic group B2 have a genomic island called "*pks*" which codes for the production of colibactin.[228] Animal studies showed that infection with *E. coli* harboring the *pks* Island caused the formation of sporadic CRC in infected mice.[228,229] Colibactin was described to interfere with the cell cycle and promote proliferation of epithelial cells via DNA damage, mutation, and genomic instability.[230]

F. nucleatum was described in colorectal adenomas.[231] In addition, it was reported to be significantat higher levels in CRC tissues and fecal samples of CRC patients compared to healthy controls.[232,233] It was linked to high CRC mortality, low overall survival, and increased CRC metastasis.[234] *F. nucleatum* was suggested to stimulate CRC expansion via its Fap2 protein that interferes with the antitumor immune cell activity.[235,236] FadA is another virulence factor of *F. nucleatum* that was described to mediate adhesion to E-cadherin, activate β-catenin signaling, and enhance subsequent inflammatory and oncogenic responses.[237] Yang et al[238] showed that *F. nucleatum* enhanced CRC cell lines proliferation and invasion, as well as in vivo tumors formation. This was mediated through TLR4 signaling, NF−κB stimulation, and enhanced *miR-21* expression.[238]

Enterococcus faecalis (*E. faecalis*) has been recognized as a human pathogen,[239] and a significantly high level was observed in fecal specimens of CRC patients compared to healthy controls.[240] The role of *E. faecalis* in the generation of reactive oxygen and nitrogen species (RONS) with subsequent DNA break, point mutation, and chromosomal instability has been suggested as the main driving mechanism of its oncogenic activity in CRC.[239,241]

The association between *H. Pylori* and CRC is much less clear in comparison with its role in gastric carcinoma.[242] Several meta-analyses demonstrated statistically significant association between *H. Pylori* and the risk of CRC.[243,245] A recent study has revealed a significant increase in *H. Pylori* infection among patients with colon cancer and adenomatous polyps compared with the healthy controls.[246] The role of *H. Pylori* in mediating microenvironment hypergastrinemia has been suggested as the underlying mechanism behind its association with CRC.[247,248] In addition, the seropositivity of CagA toxin was linked to increased risk for CRC.[249]

Results from clinical studies also described the alteration of other bacterial species in samples derived from CRC patients.[214,250] Bacteroides/*Prevotella* species were found to be abundant in fecal samples of CRC patients compared with controls.[214] *Coriobacteridae, Roseburia, Fusobacterium,* and *Faecalibacterium* were shown to be highly expressed in tumor tissues, compared to healthy tissues within CRC patients.[250] In contrast, the *Enterobacteriaceae,* such as *Citrobacter, Shigella,*

Cronobacter, and *Salmonella*, were significantly lower in CRC tissues.[250]

Findings from aforementioned studies support the microbiota hypothesis in CRC pathogenesis, however, limited evidence is available regarding how bacterial species expressed in CRC tissues differ from the microbiota of adjacent non-tumorous tissues or fecal samples within the same investigated cases.[251] In this regard, recent findings from Shah et al's[251] pooled analysis using 16S rRNA gene sequence data from CRC patients revealed that F*usobacterium, Parvimonas*, and *Streptococcus* were consistently abundant within tumor biopsies. In addition, *Faecalibacterium* and *Ruminococcaceae* levels were decreased in tumor tissues compared to tumor-adjacent tissues and fecal samples from the same cases.[251]

Most of the previous investigations were concerned with the differential expression level of gut microbiota, however, little is known regarding how specific bacteria species are selected and whether the host might have an effect on microbial gene expression. Liu et al[252] identified fecal miRNAs and showed that miRNAs can affect specific bacterial gene expression as well as gut microbial growth. Recent investigations by Yuan et al[253] have revealed differential expression of 76 miRNAs from CRC tumors and normal tissues that were linked to the relative enrichment of several bacterial taxa, including Firmicutes, Bacteroidetes, and Proteobacteria. The detected miRNAs were suggested to have an impact on targets involved in host-microbiome interactions as well as glycan production, which may enhance the recruitment of pathogenic microbiota.[253,254]

The association between gut microbiota dysbiosis and different early precursor lesions of CRC has also been suggested.[255,257] Shen et al[256] found higher Proteobacteria and lower Bacteroidetes numbers in tumor cases compared with controls upon assessing adherent bacteria in 21 adenoma and 23 non-adenoma subjects. A case-control study among an Iranian population of different ethnicities has shown increased levelsof *F. nucleatum*, *E. faecalis*, *S. bovis*, ETBF, and *Porphyromonas* species in fecal samples of tubular adenoma and villous/tubulovillous polyps' patients than in healthy controls and patients with hyperplastic or sessile-serrated polyps (SSPs). In contrast, lower levels of *Lactobacillus, Roseburia*, and *Bifidobacterium* species were found.[255] A very recent prospective study among individuals undergoing screening or surveillance colonoscopy has shown that both the gut microbiome analysis combined with advanced machine learning and colonoscopy had comparable results for polyps detection.[257] This suggests that gut microbiome analysis might be considered as a promising non-invasive approach for polyps detection.[257] Table 1 summarizes findings from studies concerned with microbiota and GIT cancers.

Therapeutic Perspectives

Based on the aforementioned studies, the gut microbiome might be considered as an attractive target for personalized treatment of CRC.[225] However, limited clinical evidence is available regarding the role of bacterial eradication in the treatment of CRC. In this regard, *E. coli* was one of the targeted bacteria for CRC treatment.[225] In vitro investigations using small molecule inhibitors against colibactin-activating peptidase (ClbP), a key enzyme involved in colibactin synthesis, showed blockage of the subsequent pathways activated by this toxin in a dose-dependent manner. In addition, using a murine colon loop model, these compounds suppressed the genotoxic activity of colibactin and significantly inhibited tumor growth and numbers.[225] *Fusobacterium* was also investigated as a potential target for CRC treatment.[258] The use of metronidazole in mice with colon cancer xenograft reduced the *Fusobacterium* load, cancer cell proliferation, and overall tumor growth.[258]

Manipulation of gut microbiota using probiotics might be considered as novel therapeutic modality for prevention of CRC development or reduction of chemotherapy induced adverse effects.[27,202,259] Probiotics were shown to affect the gut microbiota through different mechanisms described previously in Compare and Nardone's[9] review. In vitro and animal studies reported positive outcomes and protective anticancer effects of probiotics in CRC.[260,261] Bassaganya-Riera et al[260] evaluated the role of VSL#3 in modulating mucosal immune responses using mouse models of inflammation driven CRC. It was found that both adenoma and adenocarcinoma formation was diminished upon treatment.[260] In addition, VLS#3 administration resulted in reduction of irinotecan's adverse effects, including weight loss and diarrhea.[262] Many investigations also showed that administration of *Lactobacillus acidophilus* (*L. acidophilus*) KFRI342,[263] *Bifidobacterium longum* (*B. longum*), *Lactobacillus gasseri* (*L. gasseri*),[264] and *Lactobacillus salivarius* (*L. salivarius*) REN[265] reduced the development of 2-Dimethylhydrazine (DMH) induced colorectal preneoplastic lesions. The microbiota populations of both *E. coli* and aerobic bacteria were also

significantly reduced.[263] The probiotic *Lactobacillus casei* (*L. casei*) was also described to reduce the expression and activity of the drug metabolizing enzymes, cytochromes P450, which are known to be associated with CRC carcinogenesis.[266]

In comparison to preclinical studies, controversial results have been reported upon reviewing clinical studies. It is well known that yogurt and dairy products are a good source and rich in probiotics.[267] In this regard, high consumption in Finland has been linked to lower CRC incidence in comparison with other countries.[267] This was also supported in two population-based case-control studies, where an inverse association was observed between yoghurt/cultured milk consumption and CRC development.[268,269] In contrast, two American prospective studies did not show any evidence of the role of dairy products intake in reducing CRC risk.[270] Results from a cohort study in the Netherlands revealed a weak non-significant inverse association of fermented dairy products intake with CRC in an elderly population.[271] Recently, an intervention study using probiotics was conducted in 17 patients with familial adenomatous polyposis (FAP).[272] Patients were treated with (I) sulindac; (II) inulin/VSL#3; and (III) sulindac/inulin/VSL#3. It has been shown that cell proliferation was reduced upon treatment with sulindac or VSL#3/inulin.[272] Since FAP is a rare disorder, the small sample size of this single-center study was considered as the main drawback of its findings. The use of *Lactobacillus rhamnosus* (*L. rhamnosus*), however, resulted in downregulation of the bacterial enzymes β-glucosidase and urease, which might be involved in development of colon cancer by generating carcinogens.[273] In addition, *L. rhamnosus* reduced diarrhea incidence in cancer patients treated with 5-fluorouracil (5-FU).[274] Results from a prematurely terminated pilot study have also revealed that probiotics can reduce in the incidence and severity of gastrointestinal toxicity associated with irinotecan.[275] It is well known that many factors might negatively affect human studies. Therefore, evidence from in vitro, in vivo, and human studies is highly needed to clarify the role of probiotics in CRC prevention and treatment.[9,31] Table 2 summarizes findings from studies concerned with probiotics interventions in GIT cancers.

Manipulation of tumor microbiota using FMT has also been investigated as a potential therapeutic modality for CRC treatment and prevention.[276] Rosshart et al[276] described better resistance to CRC development and improvement of inflammation in mice treated with FMT from wild mice in comparison to control mice. However, limited evidence is available in this regard.[45] Therefore, further studies from animal and clinical investigations are needed to validate the concept of FMT in CRC.

The presence of microbiota in a CRC tumor microenvironment was described to modulate anticancer drug efficacy.[277] *F. nucleatum* was reported to be abundant in CRC tissues in patients with recurrence following chemotherapy.[277] It was associated with CRC resistance to oxaliplatin and 5-FU through a molecular network of the Toll-like receptor, microRNAs, and autophagy.[277] In vivo studies reported gemcitabine resistance in *Mycoplasma hyorhinis* (*M. hyorhinis*)-infected colon cancer cells.[278] This was due to deamination of gemcitabine to inactive metabolite mediated by *M. hyorhinis* nucleoside analog-catabolizing enzymes.[278] Gemcitabine resistance in a colon cancer mouse model was also caused by *Gammaproteobacteria* and attributed to the enzyme cytidine deaminase. Administration of the antibiotic ciprofloxacin resensitized the tumour response to gemcitabine, pointing to the role of these bacteria in treatment failure.[278] On the other hand, Idia et al[111] have shown that cisplatin resistance can be developed upon treatment of a colon cancer mouse model with antibiotics, which was linked to a decreased microbiota-dependent ROS production that plays an important role in platinum compounds mediated cytotoxicity. In addition, the cytotoxicity of the drug CB 1954 was found to be increased in the *E. coli* infected CT26 colon cancer cell line due to the ability of *E. coli*' nitroreductase enzyme to activate the prodrug CB 1954.[279]

Changes in the microbiota composition can also affect the efficacy of immunotherapeutic agents used for treatment of cancers, since microbiota can have a strong impact on inflammation and immunity.[38] Administration of intratumor CpG oligodeoxynucleotides in combination with an antibody against the IL-10 receptor to mice bearing MC38 colon carcinoma resulted in delayed tumor growth and prolonged survival.[111] In comparison, the efficacy was reduced in germ-free mice and in antibiotics treated mice.[111] The efficacy of Ipilimumab, which is a monoclonal antibody against cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), was also significantly reduced upon treatment of a MC38 colon carcinoma mice model with broad-spectrum antibiotics or using a germ-free model.[280]

Microbiota was also described to affect the drug toxicity profile. SN-38G, the inactive metabolite of irinotecan,

was reported to be reactivated to SN-38 inside the intestine by the bacterial β-glucuronidases, which was associated with severe intestinal toxicity.[281,282] However, animal studies showed that co-administration of irinotecan with a selective inhibitor of bacterial β-glucuronidase reduced the incidence of irinotecan adverse effects including colonic damage or diarrhea.[281] Lin et al[283] also reported enrichment of a colon cancer bearing rat model with *Clostridium cluster XI* and *Enterobacteriaceae* upon irinotecan treatment, which was highly associated with the development of diarrhea. On the other hand, results from metastatic CRC patients treated with irinotecan reported a reduction of diarrhea in patients receiving the antibiotic levofloxacin.[284] In addition, findings revealed a significant decrease in the microbial diversity of rats treated with irinotecan with an increase in Fusobacteria and Proteobacteria in fecal microbiota, which were linked to intestinal inflammation.[285] Gut microbiota was also linked to oxaliplatin-induced peripheral neuropathy. Shen et al[286] have shown that administration of antibiotics resulted in reduced oxaliplatin-induced pain in treated mice.

Liver Cancer

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer and the third most common cause of cancer-related death.[287,288] The majority of HCC cases are related to liver cirrhosis or fibrosis, with chronic infections caused by hepatitis B and C viruses, alcoholic cirrhosis, as well as hemochromatosis are well recognized for their role in the etiology of HCC.[289,290] Obesity and non-alcoholic fatty liver disease (NAFLD) are suggested as risk factors of HCC in developed countries, although the exact mechanisms are yet to be identified.[291] The role of bacterial infections in HCC in comparison to other risk factors is less well defined.[292] It is well known that the liver is generally considered sterile, however, it interacts directly with the gut through the hepatic portal and bile secretion systems.[293] Intestinal dysbiosis leads to disruption of the intestinal wall, increases the permeability, and enhances bacterial translocation with their active metabolites.[294,295] Therefore, the intestinal microbiome is considered as the main source of portal-vein endotoxins, such as LPS, and hence can mediate the progression of hepatic diseases.[296] As a consequence, gut microbiota can cause many harmful effects and hepatic diseases including NAFLD/nonalcoholic steatohepatitis (NASH), alcoholic liver disease (ALD), and liver cirrhosis.[297,301] However, only a few studies have reported any evidence of this association in HCC.[292,296] In this regard, most of the data about gut microbe's role in hepatocarcinogenesis comes from animal studies.[292,302,303] Dapito et al[303] reported a significant reduction in the total volume and number of HCC tumors in germ-free mice or in antibiotics-treated animals in comparison to controls, using the chemically induced HCC animal model. Analysis of the fecal and cecal microbiota in a rat model of a diethylnitrosamine (DEN) hepatocarcinogenesis showed an imbalance in gut microbiota composition.[302] This includes significant suppression of *Lactobacillus, Bifidobacterium,* and *Enterococcus* species and a significant growth of *E. coli* and *Atopobium* cluster as well as upregulation of serum LPS levels.[302] In addition, disruption of intestinal homeostasis by penicillin or dextran sulfate sodium (DSS) resulted in significant tumor formation.[302]

The potential role of obesity associated intestinal bacteria in HCC pathogenesis has also been explored.[304] It is well known that an increased level of the secondary bile acid deoxycholic acid (DCA) contributes to hepatocarcinogenesis.[304] It was found that genetically or high-fat diet (HFD)-induced obesity in a mice model increased the levels of DCA, which was correlated with higher incidence of HCC upon the administration of the chemical carcinogen dimethylbenz(a)anthracene (DMBA).[304] The fecal microbiota of this group showed an increase in the relative abundance of *Clostridium* genus producing DCA. On the other hand, control mice fed a normal diet failed to develop HCC.[304] Vancomycin use or reducing the levels of DCA also inhibited HCC development.[304] Results of Xie et al's[305] study also revealed significant changes in the gut microbiota during the progression of liver diseases and HCC using mice model mimics the development of steatosis and subsequent progression to NASH and HCC. The bacterial species, *Atopobium, Bacteroides, Clostridium*, and *Desulfovibrio* were significantly enriched in the fecal samples of a mice model and correlated with LPS levels as well as the pathophysiological features.[305] Recent findings by Yamada et al[306] showed that mice fed a steatohepatitis-inducing high-fat diet (HFD), namely STHD-01, developed HCC. In contrast, treatment with antibiotics significantly reduced tumor development and accumulation of secondary bile acids. In this study, secondary bile acids such as DCA were found to activate the mammalian target of rapamycin (mTOR) pathway in hepatocytes of mice fed STHD-01, which was suppressed upon treatment with antibiotics.[306]

In addition to the aforementioned bacterial species, the role of *Helicobacter* species in HCC was also explored. In vivo studies with intestinal inoculation of *Helicobacter hepaticus* (*H. hepaticus*) revealed disruption of enterohepatic

homeostasis and development of HCC.[307] This was suggested to be mediated through NF-κB and wingless-related integration site (Wnt) signaling pathways, hepatocyte turnover, and oxidative stress.[307]

Results from clinical studies showed the presence of *Helicobacter* species 16S rDNA in the liver of HCC patients, but not in controls.[308] In addition, *H. Pylori* virulence factors including VacA and CagA were detected in HCC tissues.[309,310] LPS from *H. Pylori* was found to enhance the growth and migration of liver cancer cell lines through the upregulation of IL-8 and the transforming growth factor (TGF-β1).[311] Recently, an altered microbiome profile was reported in the tongue coat of patients with HCC compared to healthy controls, using a metagenomics approach with abundance of both *Oribacterium* and *Fusobacterium* in the HCC group.[312] A recent study among patients with cirrhosis showed an increased fecal count of *E. coli* in patients with HCC in comparison to those without HCC, suggesting that the intestinal enrichment may mediate hepatocarcinogenesis of liver cirrhosis.[313] More recently, Ponziani et al[314] have shown that fecal microbiota of NAFLD-related cirrhosis and HCC has a higher level of *Bacteroides* and *Ruminococcaceae* in comparison to NAFLD-related cirrhosis without HCC and healthy controls, while *Bifidobacterium* was reduced. These findings suggest that gut microbiota is involved in the hepatocarcinogenesis process in patients with cirrhosis and NAFLD.[314] Table 1 summarizes findings from studies concerned with microbiota and GIT cancers.

Therapeutic Perspectives

Since dysbiosis of the gut microbiota has been shown to be associated with HCC pathogenesis, studies have been directed toward the investigation on modulation of gut microbiota using probiotics,[315] which can be considered as a novel therapeutic modality for prevention or treatment of HCC.[315] Findings from Kumar et al's[316] study using a rat model showed that the use of probiotic-fermented milk and chlorophyllin on Aflatoxin B1 (AFB1) induced HCC reduced the tumor incidence. In addition, the levels of c-MYC, BCL-2, cyclin D1, and RAS p21 were diminished.[316] Zhang et al[302] also reported that the administration of VSL#3 to rats inhibited DEN-induced hepatocarcinogenesis. LPS serum levels as well as the number and size of HCC were also reduced.[302] Recently, it has been shown that the administration of a novel probiotic mixture (Prohep) reduced the tumor growth and volume by 40% in treated mice in comparison to controls.[317] In addition, it increased the level of beneficial bacteria that resulted in induction of anti-inflammatory effects, stimulation of T-cell immune-responses, reduction of the tumor populations of migratory TH17 cells, and downregulation of pro-angiogenic factors, all of which might contribute to HCC prevention, treatment, and improved prognosis.[317]

In comparison to animal studies, there is little evidence from clinical studies regarding the beneficial outcome of using probiotics in HCC.[318] Accordingly, future studies should be conducted using extensive human clinical trials to confirm observations obtained from animal experimental studies.[318] El-Nezami et al[319] reported that using probiotics reduces the biologically effective dose of aflatoxin exposure and aflatoxin-DNA toxic adduct which is associated with an increased risk of liver cancer. Therefore, probiotics might be considered as an effective dietary approach to lower the risk of HCC.[319] Table 2 summarizes findings from studies concerned with probiotics interventions in GIT cancers.

Mounting evidence indicates the potential of using FMT as a therapy to control liver diseases.[320,322] This includes findings from animal models regarding protective effects of FMT against high-fat diet-induced and alcohol-induced liver injuries.[320,321] Results from clinical studies also supported the beneficial effects of FMT in patients with severe alcoholic hepatitis,[322] chronic hepatitis B,[323] advanced liver cirrhosis,[324] and hepatic encephalopathy.[325] However, future studies are needed to confirm whether FMT is also applicable in liver cancers.

Pancreatic Cancer

Pancreatic cancer is considered a rapidly progressive and fatal disease, with only a quarter of patients surviving 1-year after diagnosis.[326] The majority of the patients are diagnosed at late stages and, therefore, the main goal of cancer treatment is palliative, including radiotherapy or chemotherapy modalities, rather than surgery.[326] Pancreatic ductal adenocarcinoma (PDAC), which is the most common type of pancreatic cancer, is recognized as one of the leading causes of cancer death.[327]

The risk factors for pancreatic cancer have been studied extensively,[328] and chronic pancreatitis is currently known as an established risk factor.[329] Incidence rates were found to be 160% higher in patients with chronic pancreatitis compared with healthy populations.[330] In addition, a 13-fold higher risk of PDAC development was reported among patients with chronic pancreatitis.[331]

Mounting data suggest an association between bacterial infections and pancreatic carcinogenesis.[332,334] However, the role of microbiota might be better correlated with tumor progression, modulation of tumor microenvironment, activation of immune responses, and interplay with the inflammation processes rather than being causative of pancreatic cancer.[335,336] Nevertheless, understanding the role of the microbiome in pancreatic cancer pathogenesis is essential.[334] This will aid in the discovery of biomarkers and/or novel targets that can be utilized for early detection or for therapeutic intervention in terms of cancer prevention or treatment.[335]

Positive correlation between *H. Pylori* infections and pancreatic cancer has been described.[337,344] This was first reported by a case–control study where a 2-fold increase in risk was found in infected patients compared with controls.[337] Results from a prospective cohort study showed that, among male smokers, seropositive males for *H. Pylori* antibodies or CagA strains had increased risk compared with seronegative.[338] These findings were also supported by subsequent epidemiological and meta-analysis studies.[339,344] A positive correlation has also been observed between gastric peptic ulcer, which is known to be caused by *H. Pylori*, and pancreatic cancer in two large cohort studies.[345,346] Studies have shown that *H. Pylori* can promote pancreatic diseases including pancreatic cancer through production of ammonia, LPS, and inflammatory mediators.[347] In vitro investigations showed that the level of IL-8 and vascular endothelial growth factor (VEGF) as well as the activities of proliferation factors were increased in human pancreatic cancer cell lines when co-cultured with *H. Pylori*.[348] This resulted in dysregulation of cellular processes and promoting inflammation, both of which play an important role in pancreatic carcinogenesis.[348] In vitro and in vivo studies also reported that the LPS from *H. Pylori* can enhance *KRAS* genes mutation and initiation of pancreatic carcinogenesis.[349,350] In fact, *KRAS* gene mutations were described in more than 90% of pancreatic adenocarcinoma.[351] *H. Pylori* infection was also found to enhance STAT3 activation, which in turn has been suggested to mediate pancreatic cancer progression via increasing the level of anti-apoptotic and pro-proliferative proteins such as B-cell lymphoma-extra-large (Bcl-xL), myeloid cell leukemia-1 (MCL-1), survivin, c-MYC, and cyclin D1.[352,354] However, whether *H. Pylori* infection is a causative factor of pancreatic cancer, future work should include clinical interventional studies using eradication therapy to clarify the *H. Pylori* role in pancreatic cancer initiation.[336]

Many studies also reported a positive correlation between pathogenic bacteria involved in periodontal diseases and risk of pancreatic cancer.[355,357] In this regard, the association of *P. gingivalis* has been widely explored.[358,359] Findings from the European Prospective Investigation into the Cancer cohort revealed more than a 2-fold increase in risk of pancreatic cancer in patients with high levels of *P. gingivalis* antibodies.[359] Although the exact underlying mechanism is yet to be elucidated, *P. gingivalis*' LPS stimulation of the TLR4 pathway has been suggested.[360,361] In vitro and in vivo studies showed that TLR4 was highly expressed and has a key role in human PDAC, including suppression of apoptosis and promoting tumor growth, angiogenesis, as well as invasion.[360,362] *Fusobacterium* species, another oral bacterial group, were found in 8.8% of pancreatic cancer tissues.[363] The enrichment of pancreatic cancer tissues was linked to poor prognosis and suggested as negative independent biomarker for pancreatic cancer prognosis.[364] A recent study has shown *Pseudomonas aeruginosa* (*P. aeruginosa*) to be involved in pancreatic cancer. Gaida et al[365] described that *P. aeruginosa* enhanced the expression of the ATP-binding cassette sub-family B member 1 (ABCB1) and promoted cell invasion and metastasis. Table 1 summarizes findings from studies concerned with microbiota and GIT cancers.

Therapeutic Perspectives

Bacterial microbiota as a target for pancreatic cancer treatment was recently evaluated.[366] Pushalkar et al[366] have shown that treatment of mice bearing an invasive orthotopic PDAC model with an ablative oral antibiotic regimen resulted in ~50% reduction of tumor burdens. This was suggested to be driven by immunogenic reprogramming of the PDAC tumor microenvironment such as reduction in myeloid-derived suppressor cells and an increase in M1 macrophage differentiation.[366] In addition, antibiotics treatment enhanced the efficacy of checkpoint-targeted immunotherapy against programmed death receptor-1 (PD-1), synergistically reduced tumor size, and enhanced T-cell activation.[366] Accordingly, clinical trial of combination treatment using antibiotics with pembrolizumab, a checkpoint-based immunotherapy, is beginning prior to resection among patients with locally advanced PDAC.[334]

Limited evidence is available regarding the use of probiotics for prevention of PDAC. In fact, most available

data are mainly based on the correlation of probiotics effects on pancreatic cancer risk factors such as pancreatitis, diet, obesity, and diabetes.[367] Olah et al[368] have shown that administration of *Lactobacillus plantarum* 299 to patients with acute pancreatitis reduced the development of pancreatic sepsis and the need for surgical interventions compared with control patients. The route of administration as enteral nutrition resulted in positive outcomes in comparison to the parenteral route.[369] These include less fibrosis, acinar cell loss, parenchymal necrosis, inflammation, ductal damage, atypical reactive regeneration, and vacuolization that might prevent pancreatic cancer.[369]

The microbiota was also found to affect the response of PDAC toward treatment with gemcitabine.[278] Drug resistance was linked to the enrichment of PDAC tissues with *Gammaproteobacteria*, with 76% of investigated tissues positive for bacteria.[278]

Gallbladder Cancer

Biliary tract cancer includes tumors of the bile duct, gallbladder, and ampulla of Vater.[370] Gallbladder cancer (GBC) is the most prevalent cancer of the biliary tract.[371] Although it is rare among the western world population, high incidence rates are reported in Chile, central Europe, Thailand, Japan, Northeastern, India, and Pakistan.[372,374] The main risk factors include chronic gallbladder inflammation (cholelithiasis), the presence of gallstones, obesity, hormonal factors, environmental exposure to specific mutagens, genetic predisposition factors, as well as gallbladder abnormalities.[375] In addition, bacterial infection has been suggested to be involved in the malignant transformation of the gallbladder epithelium.[376] *S. Typhi* was found to be prominently associated with GBC.[372,377] In addition, *Helicobacter bilis* (*H. bilis*), *H. hepaticus*, and *E. coli* have been suggested to be involved.[378,381]

Salmonella enterica serovar Typhi, the causative pathogen of typhoid fever, has the ability to cause asymptomatic chronic infection in a small percentage (2–3%) of patients after acute infections.[382] Chronic typhoid carrier state was described to be correlated with an increased incidence of hepatobiliary diseases including GBC.[383,384] Results from a large cohort study on the 1964 Aberdeen outbreak revealed that chronic typhoid carriers have an almost 167-fold higher risk of GBC.[385] Many subsequent cohort and case control studies supported the increased risk for GBC among chronic typhoid carriers.[372,377,386] In contrast, findings from a recent case-control study regarding the metagenomics of microbial communities in gallbladder bile from Bolivia and Chile patients with GBC or cholelithiasis revealed *F. nucleatum*, *E. coli*, and *Enterobacter* species as the predominant species in investigated patients, but not *Salmonella* species.[381] The conflicting findings were suggested to be related to the small sample size of the Bolivian GBC patients and the reduction of infection rate of *S. Typhi* in the Chilean patients.[381] Currently, limited evidence is available regarding the causal mechanism(s) underlying the suggested correlation of chronic *S. Typhi* infection and development of GBC. Therefore, the hypothesis of this association is not generally accepted.[377] Results from preclinical and clinical studies described that gallstones have a fundamental role in enabling gallbladder colonization.[387,389] Hence, gallbladder excision (cholecystectomy) is the best treatment that is usually considered in chronic typhoid carriers.[390] Investigations showed that *S. Typhi* irreversibly transforms mice gallbladder organoids and mouse embryonic fibroblasts (MEFs) with mutated p53 and amplified c-MYC through Akt/MAPK pathways during infection.[391] This was also reported in GBC patients from India where GBC is marked by *S. Typhi* DNA.[391] In addition, the bacterial glucuronidase was found to produce a high-energy metabolite upon acting on bile which is potentially carcinogenic and has the ability to bind to DNA.[392] Increased concentrations of secondary bile acids that are known as tumor promoters and initiators have also been described in the gallbladder secretions of patients with GBC and are suggested to be caused by the bacterial enzymes.[393]

Helicobacter infection is another example of microbiota associated with GBC.[378,381] Studies have reported 2–3-fold higher risk for GBC among infected patients in comparison to controls based on the detection of *Helicobacter* species in bile or gallbladder tissue from GBC patients.[378,381] *Helicobacter* species are bile-resistant organisms that were described to cause persistent infection, chronic inflammation, and gallstone formation due to urease production.[394,395] Gallstones and chronic inflammation, in turn, can induce transformation that might be aggravated by many *Helicobacter* carcinogenic toxins and metabolites.[394,395] *H. hepaticus* was detected in the gallbladder, liver, and bile.[396,398] In addition, it was found in GBC.[399] *H. bilis* was reported in the biliary tract and GBC of Japanese, Thai, and Mexican populations.[400,401] Recently, Wang et al[402] found that *H. Pylori* was rapidly induced into *H. Pylori* L-form in human bile, and hence both forms should be considered for detection in bile. However, larger epidemiological studies are

required to clarify the role of *Helicobacter* species infections in GBC.

Mixed bacterial infections with *E. coli*, *E. faecalis*, *Klebsiella*, and *Enterobacter* species were also described at a significantly higher level in GBC.[403] *E. coli* and *Enterobacter sp. B10* (2014) were detected in the bile of GBC patients from Chile.[381,404,405] Since *E. coli* and *Enterobacter* species infections were described to promote colon cancer,[406] it has been suggested that both might be implicated in GBC by the same mechanisms.[381] However, further studies are required to clarify the exact role in GBC. Table 1 summarizes findings from studies concerned with microbiota and GIT cancers.

Therapeutic Perspectives

Limited evidence is available from experimental or clinical investigations on bacterial eradication using antibiotics or bacterial manipulation using probiotics as treatment or preventive measures of GBC. Findings from Scano et al[391] revealed that *Salmonella*- infected mouse embryonic fibroblasts were able to produce tumors upon transplantation into immunodeficient mice, even if these cells were pre-treated with ciprofloxacin to eradicate bacterial infection. It has been shown that *Salmonella* infection causes cell transformation with upregulation of Akt/MAPK activity, which were suggested to remain upregulated and mediate the carcinogenesis process, even after bacterial eradication.[391] Therefore, cholecystectomy remains the ideal treatment for chronic typhoid carriers in order to prevent GBC.[384] Future studies are needed to determine the therapeutic implications of GBC microbiota in terms of cancer prevention and treatment.

Conclusion

Gastrointestinal cancers have high incidence, mortality, and morbidity rates according to the latest estimates of the Global Cancer Statistics 2018. Many risk factors are well known and documented to be associated with the carcinogenesis process of GIT cancers. Currently, there is substantial evidence pointing to the role of bacterial microbiota in cancer pathogenesis. In this regard, *H. Pylori* was highly correlated with the development of gastric adenocarcinoma and MALT lymphoma. *S. Typhi* was also reported to have a major impact in gallbladder cancer, especially in patients with gallbladder stones and *S. gallolytucis* was linked to colorectal cancer. Therefore, currently bacterial eradication is highly recommended for cancer treatment and prevention, mainly in gastric cancer and MALT lymphoma, while cholecystectomy remains the ideal prevention modality of gallbladder cancer. In addition, complete endoscopic screening of the colon is required for patients with a previous history of *S. gallolytucis* bacteremia. Due to advances in diagnostic tools for bacterial isolation and identification in cancer tissues, mounting data indicate the contribution of many bacterial species in the pathogenesis process of GIT cancers. The underlying mechanisms were attributed to the microbiota impact on damaging DNA, activation of oncogenic pathways, production of carcinogenic metabolites, stimulation of chronic inflammation, and inhibition of antitumor immunity. Therefore, microbiota might act as an attractive target for cancer treatment and prevention. In this regard, promising results were obtained upon the use of antibiotics for eradication of bacterial infection for cancer treatment purposes. In addition, many studies revealed the positive effects of probiotics use, including enhancement of bacterial eradication, prevention of cancer development, and/or reduction of chemotherapy associated toxicities. These were mainly observed in gastric, colorectal, and hepatocellular carcinomas. However, most of the current evidence is based on findings from in vivo experimental models. Therefore, future clinical trials are needed to clarify the usefulness of antibiotics and probiotics for GIT cancer treatment and prevention.

Recently, the concept of "pharmacomicrobiomics" has emerged as a new field exploring the interplay between drugs and microbiota. The presence of certain types of bacteria was associated with reduced efficacy of anticancer drugs including conventional chemotherapy and molecular-targeted therapeutics. Microbiota was also described to affect the toxicity profile and adverse effects of anticancer drugs. Therefore, studies on GIT microbiota appear as wide filed with many potential pharmacological applications. These include investigations on the use of antibiotics and probiotics either alone or in combination with chemotherapy and immunotherapy. Very recently, manipulation of microbiota with fecal microbiota transplantation appears as a hot topic in cancer research. Promising results were observed against *Clostridium difficile* infection, and currently there is substantial interest regarding its therapeutic potential for treatment of other diseases including GIT cancers. In this regard, future studies are also needed to explore the potential application for personalized medicine.

Disclosure

All authors report no conflicts of interest in this work.

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