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The role of intestinal bacteria in the development and progression of gastrointestinal tract neoplasms

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Abstract

More than 100 trillion microorganisms inhabit the human intestinal tract and play important roles in health conditions and diseases, including cancer. Accumulating evidence demonstrates that specific bacteria and bacterial dysbiosis in the gastrointestinal tract can potentiate the development and progression of gastrointestinal tract neoplasms by damaging DNA, activating oncogenic signaling pathways, producing tumor-promoting metabolites such as secondary bile acids, and suppressing antitumor immunity. Other bacterial species have been shown to produce short-chain fatty acids such as butyrate, which can suppress inflammation and carcinogenesis in the gastrointestinal tract. Consistent with these lines of evidence, clinical studies using metagenomic analyses have shown associations of specific bacteria and bacterial dysbiosis with gastrointestinal tract cancers, including esophageal, gastric, and colorectal cancers. Emerging data demonstrate that intestinal bacteria can modulate the efficacy of cancer chemotherapies and novel targeted immunotherapies such as anti-CTLA4 and anti-CD274 therapies, the process of absorption, and

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Use of standardized official symbols: We use HUGO (Human Genome Organisation)-approved official symbols for genes and gene products, including AKT, BRAF, CCL20, CD274, CDH1, CTLA4, EGFR, IL6, IL10, IL17, IL18, IL22, IL23, MAPK, MMP9, NFKB, PDCD1, PIK3CA, PTGS2, STAT3, TLR2, TLR4, TP53, VEGFA, and WNT; all are described at www.genenames.org.

the occurrence of complications after gastrointestinal surgery. A better understanding of the mechanisms by which the gut microbiota influence tumor development and progression in the intestine would provide opportunities to develop new prevention and treatment strategies for patients with gastrointestinal tract cancers by targeting the intestinal microflora.

Keywords

Microorganism; Gastrointestinal carcinoma; Tumor location

Introduction

Cancer in the gastrointestinal tract is a leading cause of death worldwide [1]. Accumulating evidence indicates that gastrointestinal tract cancers develop through the accumulation of genetic and epigenetic alterations, which are influenced by host immunity, diet, and environmental and microbial exposures [2].

The human intestinal microbiome encompasses at least 100 trillion microorganisms, which can influence the immune system and health conditions, including cancer [3–5]. A growing body of evidence indicates that diet, lifestyle, and drugs can influence the composition of the gut microbiota and that the gut microbiota can modulate the development and progression of gastrointestinal tract neoplasms [6,7]. Recent data have shown that some bacterial species produce tumor-promoting metabolites such as secondary bile acids, which potentiate the development and progression of gastrointestinal tract neoplasms, whereas other species produce short-chain fatty acids (SCFAs) such as butyrate, which can suppress inflammation and carcinogenesis in the gastrointestinal tract [8,9].

Here, we review clinical studies on intestinal bacteria in relation to gastrointestinal tract cancers, including esophageal, gastric, and colorectal cancers. In addition, we describe emerging evidence for roles of intestinal bacteria in the efficacy of cancer chemotherapies and novel targeted immunotherapies such as anti-CTLA4 and anti-CD274 therapies, the process of absorption, and the occurrence of complications after gastrointestinal surgery.

Mechanisms by which intestinal bacteria influence the development and progression of gastrointestinal tract neoplasms

1. Bacterial genotoxins

Intestinal bacteria have been shown to potentiate carcinogenesis through specific toxins that induce DNA damage. Colibactin is encoded by the polyketide synthase island, which is expressed by *Escherichia coli* from phylogroup B2, and has been shown to induce DNA damage, affect genomic instability [10,11], and promote colon carcinogenesis in *Il10*$^{-/-}$ mice [12,13].

Enterococcus faecalis has been shown to produce extracellular superoxide that induces DNA damage and genomic instability in colonic epithelial cells [14–16], and activates macrophages to produce 4-hydroxy-2-nonenal, which promotes colon carcinogenesis in

Il10$^{-/-}$ mice [17,18]. In human gastric cancer cells, infection with *Enterococcus faecalis* causes reactive oxygen species (ROS) production and DNA damage [19,20].

Cytolethal distending toxin, which is produced by Gram-negative bacteria, including *Escherichia coli* from phylogroup B2 and the *Helicobacter* species, can cause DNA damage in mammalian cells [21–24].

2. Other microbial virulence factors

Helicobacter pylori expresses the cytotoxin-associated gene A (CagA) protein, a virulence factor that has been shown to promote cell proliferation through the activation of the PI3K-AKT, WNT, and NFKB signaling pathways [25–27], and reduce epithelial cell apoptosis by the inhibition of TP53 [28]. In addition, accumulating evidence suggests that CagA can activate stemness properties and induce the epithelial-mesenchymal transition in gastric epithelial cells [29–35]. *Helicobacter pylori* expresses the vacuolating cytotoxin A (VacA), which has been shown to suppress host immunity through the inhibition of T-cell activation and the induction of regulatory T cells [36–39].

Enterotoxigenic *Bacteroides fragilis* express the *Bacteroides fragilis* toxin, which is a virulence factor that activates the WNT and NFKB signaling pathways in colonic epithelial cells [40–42].

Fusobacterium nucleatum expresses the FadA virulence factor on the bacterial cell surface, which has been shown to bind to CDH1, activate the WNT signaling pathway in colorectal carcinoma cells, and promote colorectal tumor growth [43]. The Fap2 protein of *Fusobacterium nucleatum* has been shown to interact with T cell immunoglobulin and ITIM domain (TIGIT) receptor and inhibit the activities of NK cells and T cells [44]. Emerging evidence indicates that the Fap2 protein can potentiate the attachment of *Fusobacterium nucleatum* to colorectal cancers that express host polysaccharide Gal-GalNAc [45].

3. Microbial metabolites

Intestinal bacteria produce diverse metabolites that can influence the development and progression of gastrointestinal tract tumors [4]. Polyamines, which are produced by host cells and gut bacteria, play important roles in diverse biologic and pathologic processes, including translation, gene regulation, stress resistance, and cell proliferation and differentiation [46]. Polyamines have been shown to suppress antitumor immunity and potentiate the proliferation of cancer cells, invasion and metastasis [47]. Colonic mucosal biofilms have been associated with up-regulation of polyamine metabolites that can enhance the proliferation of colon cancer cells [48].

Accumulating evidence indicates a link between secondary bile acids and the development of gastrointestinal tract tumors. Cholic acid and chenodeoxycholic acid, which are primary bile acids, are produced in the liver from cholesterol, conjugated to glycine or taurine and excreted into the duodenum to facilitate fat digestion. In the distal small intestine and colon, conjugated bile acids can be deconjugated by the gut microbiota to produce secondary bile acids, namely, lithocholic and deoxycholic acid. Clinical studies have shown that high-fat diets can increase bile secretion [49] and that high faecal concentrations of bile acids are

found in colorectal cancer patients [50]. Experimental studies have shown that lithocholic and deoxycholic acid can activate the NFKB signaling pathway in colonic epithelial cells [51,52] and that deoxycholic acid can potentiate the development of colorectal tumors in rats receiving azoxymethane (AOM), a colorectal carcinogen [53]. A study based on a mouse model suggests that deoxycholic acid can promote the development of Barrett's esophagus and esophageal adenocarcinoma by damaging DNA [54].

Accumulating evidence indicates that SCFAs such as butyrate, which are produced by the gut microbiota, can suppress colonic inflammation and carcinogenesis by blocking activation of the NFKB signaling pathway and inducing the differentiation of regulatory T cells and IL10-producing T cells [55–57]. Experimental studies have shown that butyrate can function as a histone deacetylase inhibitor to inhibit cell proliferation, stimulate apoptosis, and suppress colonic tumor development [58–61]. In contrast, emerging data demonstrate that low concentrations of butyrate may promote the growth of colonic tumors that exhibit DNA mismatch repair deficiencies in a mouse model [62].

4. Modulation of host innate and adaptive immunity

Innate immunity is a rapid immune response that recognizes conserved microbial structures in a non-specific manner, typically through the action of pattern recognition receptors (PRRs) expressed on host cells, including Toll-like receptors (TLRs) and the nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) [63]. Accumulating evidence indicates that TLRs contribute to the development and progression of gastrointestinal tract tumors through the activation of the NFKB and STAT3 signaling pathways [64]. The activation of TLR4, which is the receptor for lipopolysaccharide produced by the gut microbiota, in colonic epithelial cells has been shown to potentiate colorectal tumor development through the up-regulation of PTGS2 expression and activation of the EGFR signaling pathway in a mouse model receiving AOM [65]. Additionally, activation of the STAT3 signaling pathway has been shown to up-regulate TLR2 expression in gastric epithelial cells, which promote gastric tumor development, in a mouse model [66].

The NLR family is a group of receptor proteins that respond to intracellular fragments of bacterial peptidoglycan and initiate the NFKB and MAPK signaling pathways in intestinal epithelial cells [67]. Studies have shown that activation of NOD-like receptor family pyrin domain containing 6 (NLRP6) in colonic epithelial cells can induce inflammation through the up-regulation of chemokine CCL5 and promote colorectal tumor development through the up-regulation of IL6 expression in the tumor microenvironment [68,69]. In the mouse model of colorectal cancer liver metastases, NLRP3 in Kuppfer cells increase the production of IL18, which can activate the function of NK cells and suppress colon cancer metastatic growth in the liver [70]. On the other hand, NOD2 can induce microbial dysbiosis and potentiate the development of inflammation-induced colorectal tumors through up-regulation of IL6 expression in colonic epithelial cells, suggesting a protective role for NOD2 in the maintenance of the composition of the gut microbiota [71].

Adaptive immunity is specific to the type of pathogen that is encountered by B and T cells with subsequent generation of memory cells [72]. The microbiota play an important role in the differentiation of T cells [4]. Evidence suggests that the gut microbiota produce butyrate,

which can induce the differentiation of regulatory T cells and IL10-producing T cells through interactions with GPR43, activation of histone deacetylase inhibition, and up-regulation of IL10 expression [55]. Accumulating evidence indicates that T helper 17 (T_H17) cells, which produce IL17 and IL22, can promote tumor development and progression in the gastrointestinal tract [73–75]. Enterotoxigenic *Bacteroides fragilis* induces T_H 17 cells, which activate the STAT3 signaling pathway in tumor cells in the $Apc^{Min/+}$ mouse model of colon cancer [76,77]. T_H 17 cells also produce IL22, which has been shown to promote colorectal tumor development and progression [78,79]. IL23, which is mainly produced by tumor-associated myeloid cells that are likely to be activated by bacterial products, has been shown to promote colorectal tumor development and progression through the induction of T_H17 cells in the microenvironment [75,80,81]. *Fusobacterium nucleatum* may inhibit T-cell-mediated immune responses against colorectal tumors through the recruitment of myeloid-derived suppressor cells into the tumor microenvironment in the $Apc^{Min/+}$ mouse model [44,82]. Recent study has shown an inverse association between the amount of tissue *Fusobacterium nucleatum* DNA and $CD3^+$ T-cell density in human colorectal cancer tissue specimens [83].

These findings from the experimental studies described here provide insights into strategies for targeting the gut microbiome towards the prevention and treatment of gastrointestinal tract cancer. Probiotics and prebiotics may restore the balance of normal gut microbiota, leading to a reduction in bacterial genotoxicity and tumor-promoting metabolites and to suppression of oncogenic signaling pathways. Antibiotics may be utilized to target genotoxic or deoxycholic acid-producing bacteria that have been shown to potentiate the development of gastrointestinal tract tumors. Hence, future investigations may be warranted to examine the potential influence of modifiable factors such as diet, probiotics and prebiotics, and antibiotics, on the intestinal bacteria and tumorigenic processes.

Clinical studies on associations of specific bacteria and bacterial dysbiosis with gastrointestinal tract cancers

1. Esophageal cancer

Esophageal carcinoma consists of two main histological types: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). ESCC constitutes the large majority of esophageal cancer cases worldwide and more than 90% of the cases in high-risk areas, such as China, Iran, and Japan [1]. EAC is one of the most rapidly increasing cancers in the United States [84]. Clinical studies have suggested associations of specific bacteria and bacterial dysbiosis (the condition of having imbalances in the microbial communities) with the development of ESCC and EAC (Table 1).

Clinical studies in China have shown that low microbial diversity (number of bacterial genera per sample) in saliva or esophageal tissues is associated with the presence of ESCC and esophageal squamous dysplasia, which is the precursor lesion of ESCC [85,86]. One study has shown that the composition of the gastric microbiota differs in stage I ESCC, stage II ESCC, and esophageal squamous dysplasia from that in healthy controls [87].

Meta-analyses demonstrate an inverse association between infection with *Helicobacter pylori* and risk of EAC [88,89]. Although the mechanisms underlying this inverse association remain unclear, one study suggests that infection with *Helicobacter pylori* is associated with a decreased prevalence of aneuploidy, which is a measure of genomic instability, in EAC [90].

Zaidi et al. have reported that a high amount of *Escherichia coli* in esophageal tissues is associated with Barrett's esophagus, EAC, and increased expression of TLRs [91]. A high amount of *Campylobacter concisus* in esophageal tissues is associated with Barrett's esophagus and increased expression of IL18, which is associated with carcinogenesis [92].

Yamamura et al. have reported that high amount of *Fusobacterium nucleatum* is associated with shorter cancer-specific survival and overall survival in esophageal cancers, including ESCC and EAC, and that the amount of *Fusobacterium nucleatum* correlates with tumor expression of chemokine CCL20. These results suggest that *Fusobacterium nucleatum* may contribute to the acquisition of aggressive tumor behavior through activation of chemokines in esophageal carcinomas [93].

2. Gastric cancer

In prospective epidemiological studies, chronic infection with *Helicobacter pylori*, which is a Gram-negative pathogen that selectively colonizes the gastric epithelium, has been associated with a greater than two-fold increased risk of gastric cancer overall [94]. *Helicobacter pylori* is categorized as a class I carcinogen by the International Agency for Research on Cancer. In addition to the infection with *Helicobacter pylori*, metagenomic studies have highlighted a potential link between gastric microbiota and gastric cancer (Table 2).

Metagenomic analyses have shown a gradual decrease in microbial diversity from non-atrophic gastritis to intestinal metaplasia to gastric cancer [95]. Among patients infected with *Helicobacter pylori*, microbial diversity is higher in gastric cancer compared with chronic gastritis or intestinal metaplasia [96,97].

3. Colorectal cancer

Clinical evidence suggests possible roles for specific bacteria and bacterial dysbiosis in the development and progression of colorectal tumors (Table 3).

Case-control studies have shown that microbial diversity in tumor tissue or stool specimens is higher in colorectal adenomas and carcinomas cases than in controls [98–107]. These findings suggest an association between bacterial dysbiosis and the development of colorectal tumors. Studies have revealed an enrichment of *Fusobacterium nucleatum* in human colorectal adenomas and carcinomas compared with adjacent normal tissues [83,108–116]. Recent studies have demonstrated that a high amount of tissue *Fusobacterium nucleatum* is associated with advanced disease stage [108,109,117], a lower density of T cells in colorectal carcinoma tissue [83], and worse patient survival [111]. Several studies have demonstrated that the proportions of colorectal cancers with specific molecular features such as microsatellite instability (MSI)-high, CpG island methylator phenotype (CIMP)-

high, and *BRAF* and *PIK3CA* mutations gradually increase along the bowel subsites from the rectum to the ascending colon [118–121]. The proportion of colorectal cancer enriched with *Fusobacterium nucleatum* increases linearly along the bowel subsites from the rectum to the cecum, suggesting a continuum model of pathogenic influences of intestinal bacteria on colorectal carcinogenesis [122]. Low fiber consumption and high meat intake have been associated with altered bacterial and metagenomic profiles [123,124]. Emerging data have shown that low fiber consumption and high fat intake are associated with an increased amount of *Fusobacterium nucleatum* measured by PCR in the stool [125]. Ingestion of non-digestible carbohydrates, such as fiber, has been shown to increase colonic fermentation, and increase the transit of gut contents, and decrease the pH of the intestinal lumen [8], which might influence colonic colonization by *Fusobacterium nucleatum*, although further investigations are required.

Clinical studies with a limited sample size suggest that the amount of *Escherichia coli* is higher in colorectal carcinoma tissue than in adjacent normal tissue and that a higher amount of *Escherichia coli* may be associated with advanced disease stage [126,127]. A few human studies have suggested a potential link between enterotoxigenic *Bacteroides fragilis* and colorectal cancer. Studies suggest that enterotoxigenic *Bacteroides fragilis* is detected significantly more often in the colon mucosa tissue or stool specimens of colorectal cancer cases than in the controls and that a higher amount of enterotoxigenic *Bacteroides fragilis* is associated with advanced disease stage [116,128,129]. Although experimental studies suggest that *Enterococcus faecalis* may promote the development of gastric and colorectal tumors [14–18], one clinical study has suggested that *Enterococcus faecalis* is detected significantly more often in the stool specimens of colorectal cancer cases than in the controls [130]. Studies have demonstrated that the amount of *Streptococcus gallolyticus* in human colorectal carcinomas is higher than in control tissue and that the amount of *Streptococcus gallolyticus* is correlated with the expression of PTGS2 (cyclooxygenase-2) in colorectal cancer tissue [131–133]. These findings suggest a potential role of *Streptococcus gallolyticus* in the development of colorectal tumors through inflammation.

These clinical studies have linked specific bacteria and bacterial dysbiosis to gastrointestinal tract cancers, including esophageal, gastric, and colorectal cancers. However, there are considerable study-to-study differences regarding reported bacterial species associated with colorectal carcinogenesis, which may be due to limitations including small sample sizes, undefined tissue sampling sites, and limited data on clinical features and tumor molecular features.

Gut microbiota, chemotherapy, and immunotherapy

Emerging data demonstrate that intestinal bacteria can modulate the efficacy of cancer chemotherapies. Colorectal cancers with unresectable distant metastases are treated with chemotherapy regimens that are based on oxaliplatin and irinotecan combined with molecularly targeted therapies such as a humanized monoclonal antibody against VEGFA (bevacizumab) and anti-EGFR antibodies (cetuximab or panitumumab) [134]. ROS are important for DNA damage and apoptosis in response to oxaliplatin [135]. The administration of oxaliplatin to germ-free mice or antibiotic-treated mice has been shown to

reduce oxaliplatin-mediated tumor cytotoxicity by down-regulating the production of ROS in myeloid cells, suggesting that the gut microbiota may influence the efficacy of oxaliplatin for gastrointestinal cancer by modulating the production of ROS in myeloid cells in the tumor microenvironment [136]. Irinotecan is converted to its active metabolite 7-ethyl-10-hydroxycamptothecin (SN38), which is subsequently detoxified to an inactive, glucuronidated form, SN38-glucuronide (SN38G), by hepatic uridine diphosphate glucuronosyltransferase 1A1 [137,138]. The bacterial β-glucuronidase then deconjugates SN38G to SN38, the active form, in the gut, which can cause severe diarrhea [139]. Bacterial β-glucuronidase-selective inhibitors have been shown to reduce the incidence of irinotecan-induced diarrhea in mice [140]. Cyclophosphamide, which is a prominent alkylating anticancer agent and one of several clinically important cancer drugs, can promote the differentiation of T_H17 cells that may stimulate antitumor immunity in melanoma [141]. In a mouse model of melanoma, cyclophosphamide has been shown to induce the translocation of several Gram-positive bacterial species, including *Lactobacillus johnsonii*, *Lactobacillus murinus*, and *Enterococcus hirae*, to secondary lymphoid organs, and the administration of cyclophosphamide to germ-free mice or antibiotic-treated mice has been shown to reduce the antitumor effects of cyclophosphamide by inhibiting the differentiation of T_H17 cells and the accumulation of tumor-infiltrating $CD3^+$ T cells, suggesting that the gut microbiota may influence cyclophosphamide-mediated anticancer immunity [142]. These findings suggest that the gut microbiota can influence the efficacy and toxicity of cancer chemotherapy.

Therapeutic antibodies specific for immune checkpoint molecules, including CTLA4, PDCD1 (programmed cell death 1; PD-1), and CD274 (programmed cell death 1 ligand 1; PD-L1) can effectively enhance antitumor T-cell activity in various cancers, underscoring an important role of T-cell–mediated adaptive immunity in inhibiting tumor progression [143–145]. Studies using a mouse model have shown that the oral administration of *Bacteroides thetaiotaomicron* or *Bacteroides fragilis* to germ-free mice can enhance the anticancer effect of the therapeutic antibody specific for CTLA4 [146] and that the oral administration of *Bifidobacterium* can potentiate the anticancer effect of the therapeutic antibody specific for CD274 [147]. These findings suggest that manipulating the gut microbiota may modulate the efficacy of cancer immunotherapy.

Evidence suggests that the gut microbiome develops early in life and that once established, the composition of the gut microbiota is relatively stable throughout adult life [148]. However, diet, lifestyle, pharmacological factors (including antibiotics), and probiotics and prebiotics have been shown to influence the composition of the gut microbiota [149–153]. Although further studies using human tumor tissue specimens are required for clinical application, we hope to utilize the gut microbiota to modulate the efficacy and toxicity of cancer chemotherapies in the future.

Gut microbiota and surgery for gastrointestinal tract cancers

Surgery for gastrointestinal tract cancers and intestinal reconstructions has been shown to influence the composition of the gut microbiota. Patients after Roux-en-Y gastric bypass (RYGB) are at increased risk of malabsorption, trace element deficiency, and dumping

syndrome [154]. In a mouse model of RYGB, the amount of *Bacteroidetes*, *Verrucomicrobia*, and *Proteobacteria* in stool increased, and transfer of the gut microbiota from RYGB-treated mice to non-operated, germ-free mice resulted in weight loss and decreased fat mass in the recipient animals, suggesting that altered gut microbiota may trigger weight loss after RYGB [155].

In a rat model after colon resection and anastomosis, the amount of *Escherichia* and/or *Shigella* and *Enterococcus* at the anastomotic segment of the colon increased [156]. In a mouse model of small bowel resection, changes in the ileal microbial community were observed up to 90 days after surgery [157]. The intestinal microbiota may influence anastomotic leak after gastrointestinal surgery. In a rat model of anastomotic leakage in which rats underwent preoperative radiation, distal colon resections, and intestinal inoculation with *Pseudomonas aeruginosa*, only the rats with both radiation exposure and intestinal colonization by *Pseudomonas aeruginosa* developed clinical anastomotic leaks [158]. Emerging data suggest that *Enterococcus faecalis* may contribute to anastomotic leak after colectomy by producing collagenases and activating MMP9 [159].

Postoperative complications have been associated with tumor recurrence and a worse patient survival in gastrointestinal tract cancers [160–165]. Manipulating the gut microbiota by diet, lifestyle, antibiotics, and probiotics and prebiotics might become useful towards preventing the occurrence of postoperative complications and improving postoperative recovery after gastrointestinal tract surgery.

Future directions

Accumulating evidence indicates that intestinal bacteria can influence the tumor development and progression in the gastrointestinal tract. Considering that diet, lifestyle, pharmacological factors (including antibiotics), and probiotics and prebiotics can influence the composition of the intestinal microbiota, future investigations may be warranted to examine the potential influences of these modifiable factors on the intestinal microflora and tumorigenic processes.

The main cause of gastrointestinal tract cancer-related death is distant metastasis, and the liver is commonly affected by distant metastases from primary gastrointestinal cancers. The liver is exposed to the gut microbiome via blood from the portal vein and hepatic artery and has many immune cell types, including T cells and macrophages [166]. Colorectal cancer patients with high-level T-cell infiltration in liver metastasis tissues exhibit high sensitivity to anticancer agents and have good prognosis [167]. Furthermore, emerging data have shown that there is a higher amount of *Fusobacterium nucleatum* in liver metastatic lesions from colorectal cancer compared with non-cancerous liver tissue [45]. Hence, intestinal bacteria might inhibit the anticancer immune response, and contribute to the formation of liver metastases from gastrointestinal tract cancers.

Experimental studies suggest that the gut microbiota may influence the efficacy of cancer chemotherapies and immunotherapies. Because the relationship between the complex gut microbiome and tumor cells in humans cannot be completely recapitulated in the mouse

model, analysis using human cancer tissue is required for clinical application. Hence, interdisciplinary research in relation to oncology, microbiology, immunology, gastroenterology, pathology, and surgical oncology would provide valuable data for the development of new prevention and treatment strategies for gastrointestinal tract cancers by targeting the gut microbiome. A better understanding of the roles of the gut microbiota in the process of absorption after gastrointestinal reconstruction and the occurrence of complications after gastrointestinal surgery may provide new opportunities to utilize the gut microbiota for postoperative recovery in patients with gastrointestinal tract cancers.

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Abbreviations

CagA	cytotoxin-associated gene A
CIMP	CpG island methylator phenotype
EAC	esophageal adenocarcinoma
ESCC	esophageal squamous cell carcinoma
MSI	microsatellite instability
NOD	nucleotide-binding oligomerization domain
NLR	NOD-like receptor
NLRP6	NOD-like receptor family pyrin domain containing 6
PRR	pattern recognition receptor
ROS	reactive oxygen species
RYGB	Roux-en-Y gastric bypass
TIGIT	T cell immunoglobulin and ITIM domain
TLR	Toll-like receptor
VacA	vacuolating cytotoxin A

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Highlights

- Microorganisms can influence host immunity and human diseases, including cancer.
- Microbial dysbiosis may influence gastrointestinal tract tumor progression.
- Gut microbiota may influence efficacies of cancer chemotherapy and immunotherapy.
- Gut microbiota may influence complications after surgery for gastrointestinal tract cancers.

Table 1

Clinical studies on specific bacteria and bacterial dysbiosis in esophageal cancer

Specific bacteria or bacterial dysbiosis	Findings (References)
Esophageal squamous dysplasia and squamous cell carcinoma	
Bacterial dysbiosis	• Lower microbial diversity in the esophagus was associated with the presence of esophageal squamous dysplasia (85).
	• Lower microbial diversity in oral microbiota was associated with the presence of esophageal squamous cell carcinoma (86).
	• The composition of the gastric mucosal microbiota differs in early stage esophageal squamous cell carcinoma and esophageal squamous dysplasia from the healthy esophagus (87).
Fusobacterium nucleatum	• A high amount of *Fusobacterium nucleatum* was associated with shorter cancer-specific survival and overall survival in esophageal cancer, and the amount of *Fusobacterium nucleatum* correlated with tumor expression of the chemokine CCL20 (93).
Barrett's esophagus and esophageal adenocarcinoma	
Helicobacter pylori	• Infection with CagA-positve strains of *Helicobacter pylori* was associated with decreased risk of esophageal adenocarcinoma (88, 89).
	• Infection with *Helicobacter pylori* in the stomach was associated with decreased genomic instability in Barrett's esophagus (90).
Escherichia coli	• A high amount of *Escherichia coli* was associated with Barrett's esophagus and esophageal adenocarcinoma and the activation of the Toll-like receptor signaling pathway (91).
Campylobacter concisus	• A high amount of *Campylobacter concisus* was associated with increased expression of IL18 that was associated with carcinogenesis in Barrett's esophagus (92).

Table 2

Clinical studies on specific bacteria and bacterial dysbiosis in gastric cancer

Specific bacteria or bacterial dysbiosis	Findings (References)
Gastric cancer	
Helicobacter pylori	• Infection with *Helicobacter pylori* was associated with an increased risk of gastric cancer (94).
Bacterial dysbiosis	• Microbial diversity decreased gradually from non-atrophic gastritis to intestinal metaplasia to gastric cancer (95). • Among patients infected with *Helicobacter pylori*, high microbial diversity in the stomach was associated with gastric cancer (96, 97).

Table 3

Clinical studies on specific bacteria and bacterial dysbiosis in colorectal cancer

Specific bacteria or bacterial dysbiosis	Findings (References)
Colorectal adenoma	
Bacterial dysbiosis	• Microbial diversity in tumor tissue specimens was higher in colorectal adenoma cases than in control cases (98, 99).
Fusobacterium nucleatum	• High amount of *Fusobacterium nucleatum* was associated with colorectal adenoma (110).
Colorectal cancer	
Bacterial dysbiosis	• Microbial diversity in tumor tissue or stool specimens was higher in colorectal cancer cases than control cases (100–107).
Fusobacterium nucleatum	• A high amount of *Fusobacterium nucleatum* was associated with colorectal cancer (108–117).
Escherichia coli	• A high amount of *Escherichia coli* was associated with colorectal cancer (126, 127).
Bacteroides fragilis	• A high amount of *Bacteroides fragilis* was associated with colorectal cancer (116, 128, 129).
Enterococcus faecalis	• *Enterococcus faecalis* is detected significantly more often in the stools of colorectal cancer cases than those of control cases (130).
Streptococcus gallolyticus	• The amount of *Streptococcus gallolyticus* was higher in colorectal carcinoma cases than in control cases (133).