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# Intratumoral microbiome and gastrointestinal cancers

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Emerging studies have revealed the role of microbiota in regulating tumorigenesis, development, and response to antitumor treatment. However, most studies have focused on gut microbiota, and little is known about the intratumoral microbiome. To date, the latest research has indicated that the intratumoral microbiome is a key component of the tumor microenvironment (TME), and can promote a heterogeneous immune microenvironment, reprogram tumor metabolism to affect tumor invasion and metastasis. In this review, we will summarize existing studies on the intratumoral microbiome of gastrointestinal cancers and reveal their crosstalk. This will provide a better understanding of this emerging field and help to explore new therapeutic approaches for cancer patients by targeting the intratumoral microbiome.

## KEYWORDS

tumor microenvironment, intratumoral microbiome, gastrointestinal cancer, commensal microbiota, tumor metabolism

## Introduction

Interactions between the microbiome and human body are well known to be complex (1, 2). The microbiome can affect different physical processes in several ways, most importantly through metabolism and immunity. Approximately 20% of human malignant tumors are associated with the microbiome (3), of which gastrointestinal cancers, including *Helicobacter pylori*-associated gastric cancer, hepatitis B virus-associated hepatocellular carcinoma (HCC), and *Fusobacterium nucleatum*-associated colorectal cancer (CRC), account for a vast proportion.

The commensal microbiota mainly resides in the gut (4). Emerging evidence has indicated an association between gut dysbiosis and various tumors (5), as well as revealed the potential of gut microbiota as a non-invasive diagnostic marker for tumors. For example, Ren et al. reported a decrease of butyrate-producing bacteria but increased lipopolysaccharide-producing bacteria in early HCC (6). Similarly, a decrease of methanogenic archaea, *Saccharomycetes*, and *Pneumocystidomycetes*, but enrichment of halophilic archaea, *Malasseziomycetes* in fecal samples of patients with CRC were also

found (7). In addition, a series of microbial prognostic models are established to discriminate cases from control individuals (6, 8). Moreover, the dysbiosis of microbiome is stage-specific and specific microbial markers are associated with the survival of patients, independently of tumor stage, lymph node metastases, or clinical parameters (8). Gut dysbiosis can lead to alterations in key proteases and metabolites, such as toll-like receptor, nuclear factor-kappa B (NF- $\kappa$ B), and short-chain fatty acids, regulate immunity and metabolism so as to induce tumorigenesis and development (9). Furthermore, the key role of gut microbiota in mediating tumor responses to chemotherapy and immunotherapy has also been highlighted (10, 11).

Considering the outstanding progression of gut microbiota, studies on intratumoral microbiome have also substantially advanced in recent years. The intratumoral microbiome is reported to interact with TME and play important roles in regulating tumorigenesis, development, and response to antitumor treatments (1, 12, 13). Here, we will review studies on the intratumoral microbiome of gastrointestinal cancers.

## Intratumoral microbiome of gastrointestinal cancer

As early as in the last century, scientists have detected the presence of bacteria in tumor tissues (14). However, characterizing the intratumoral microbiome remains difficult because of the extremely low microbial biomass of tumors and limited detection technology. With the development of next-generation sequencing technology, emerging studies have begun to explore the composition of the intratumoral microbiome and its role in tumorigenesis and progression. A recent study detected intratumoral bacteria in 1526 tumor tissues of melanoma, pancreatic cancer, lung cancer, ovarian cancer, glioblastoma, bone cancer, and breast cancer using multiple technologies (e.g., 16S rRNA sequencing, immunohistochemistry, immunofluorescence hybridization, and bacterial culture) (15). Intratumoral bacteria were found to be tumor-specific and associated with smoking history and immunotherapy response. Moreover, they may affect tumor occurrence, development and their therapeutic responses by regulating inflammation and immunity, participating in metabolic processes, and destroying DNA stability (16). In the next section, we will elaborate on the research progress about intratumoral microbiome in different types of gastrointestinal cancers.

## Esophageal cancer

Esophageal cancer is the fourth leading cause of cancer-related death in China with 5-year survival rate less than 20%. It is associated with squamous dysplasia, alcohol consumption, cigarette smoking, and dietary habits (17, 18). Epidemiologic

studies have shown the association between variations of the esophageal microbiota and esophageal disease (19, 20). For example, normal esophagus was found to be with higher abundance of *Streptococcus*, while esophagitis and Barrett's esophagus is enriched in gram-negative bacteria, such as *Veillonella*, *Prevotella*, *Haemophilus*, *Neisseria*, *Granulicatella*, and *Fusobacterium* (21). In contrast, esophageal cancer is associated with specific Gram-negative bacteria (e.g., *Escherichia coli* and *Fusobacterium nucleatum*) (22, 23). Similarly, a decrease of *Veillonella* and *Granulicatella* while an enrichment of *Lactobacillus fermentum* were found in esophageal adenocarcinoma (EAC) patients compared to controls and Barrett's esophagus patients (24, 25). Attentionally, the relative abundance of *Fusobacterium* spp. was also gradually increased from physiological normal esophagus to esophageal squamous cell carcinoma (ESCC) (26), associated with advanced tumor stage and poor overall survival (27), while the abundance of Proteobacteria was decreased. In a word, esophageal cancers of various pathological types are all complicated with microbial dysbiosis, meanwhile, with decreased microbial diversity compared with control individuals (24, 26).

Although the composition and diversity of the esophageal microbiota correlate with esophageal disease (22), while most data on esophageal microbiota are derived from small-scale cross-sectional studies and the evidence is insufficient to assume causality.

## Gastric cancer

Gastric cancer is a common gastrointestinal cancer and a leading cause of cancer-related death. Proteobacteria (e.g., *H. pylori*) are primarily detected in gastric cancer (28, 29) and have been reported to promote precancerous lesions, such as gastric atrophy, intestinal metaplasia, and atypical hyperplasia, which can eventually lead to gastric cancer (30). Previous hypotheses suggest that an acidic microenvironment in the stomach causes a lack of bacterial diversity. While the microbial diversity in gastric cancer have been found significantly increased as compared with that in chronic gastritis and intestinal metaplasia, with higher relative abundance of *Streptococcus* (31, 32). Microbial alpha-diversity increases with disease severity, that is, chronic gastritis has the lowest microbial diversity, whereas gastric cancer has the highest (31). As reported, *Proteobacteria*, *Firmicutes*, *Bacteroidetes*, *Fusobacteria*, and *Actinobacteria* are the dominant bacteria at the phylum level, and potential cancer-promoting bacteria (e.g., *Lactobacillus*, *Escherichia-Shigella*, *Lachnospiraceae*) are enriched in gastric cancer at the genus level (33). This is consistent with the discovery in other types of tumors (34–36). Altered microbiota in gastric cancer (e.g., bacterial overgrowth and diversified microbial community) might potentially promote inflammation and carcinogenesis (33).

The community structure and microbial diversity of gastric cancer remain poorly understood. Nonetheless, bacterial overgrowth is potentially associated with the development of gastric cancer, and the microbial community construct in gastric cancer and its potential role in carcinogenesis also remain to be further explored.

## Pancreatic cancer

Pancreatic cancer is one of the most aggressive human malignancies with a five-year survival rate of 8%. The pancreas used to be considered a sterile organ. However, emerging studies have demonstrated the presence of bacterial species in the pancreas. A variety of bacteria were detected in 76% of pancreatic ductal adenocarcinoma (PDAC) tissues with a higher proportion in pancreatic cancer tissues compared with normal pancreatic tissues (12, 37). *Proteobacteria*, *Bacteroidetes*, and *Firmicutes* were found to be the dominant phyla in tumor tissues (12). Higher alpha-diversity of tumor microbiome and high abundances of a microbial signature (*Pseudoxanthomonas-Streptomyces-Saccharopolyspora-Bacillus clausii*) were correlated with longer survival, which could contribute to the anti-tumor immune response by favoring recruitment and activation of CD8 + T cells (11, 38). In addition, bacterial species cultured from fresh PDAC tumor tissues were found to induce resistance to chemotherapeutic drug gemcitabine by preclinical study (37). Beyond intratumoral bacteria, Aykut et al. explored the fungal community of PDAC (39, 40). They showed that fungi migrated from gut lumen to the pancreas, and PDAC showed an alarming increase in fungi compared to normal pancreatic tissue both in humans and mouse models. Specifically, patients with PDAC could be distinguished from healthy individuals by the abundance of markedly enriched *Malassezia* spp.

Attentionally, the origin of tumor-associated bacteria is also a research hotspot. Considering constant interactions between the pancreas and gut, the development of pancreatic cancer is closely related to the dysregulation and mislocation of gut microbiota (12, 41). Consistent with the above, studies have estimated that PDAC-associated bacteria can be translocated from the gastrointestinal tract in a retrograde manner (12, 37). These findings provide the possibility for further exploration of intratumoral microbiome and for development of new strategies for the diagnosis and treatment of pancreatic cancer (42).

## CRC

CRC is a common malignant tumor of the digestive tract with poor prognosis (43). The etiology of CRC involves genetic and environmental factors (44), in which dietary habits, obesity, and heavy drinking play important roles in the occurrence of sporadic CRC. Furthermore, emerging studies have shown the

potential role of gut microbiota in the development, diagnosis and treatment of CRC (7, 45–49).

Compared with control individuals, there is no doubt that the gut microbiota in CRC patients is dysbiosis (50–53). Gut commensal bacteria (e.g., *E. coli*, *Fusobacteria*, enterotoxin-producing *Bacteroides fragilis*, and *Peptostreptococcus anaerobius*) have been found to be increased in patients with CRC than in healthy individuals (54–60). *Enterococcus faecalis*, *Salmonella* (61) and *F. nucleatum* are also revealed with significant associations with CRC (56, 62, 63). Special species have been shown to promote tumor cell proliferation *in vitro* and *in vivo* (64), and even predict a poor prognosis (51, 65). Although studies on fungal communities of CRC are limited, but some new findings have been obtained. Coker et al. revealed higher *Basidiomycota: Ascomycota* ratio in CRC patients and different clusters of fungal components in early-stage and late-stage CRC patients, indicating that mycobiome profiles were stage-specific (7). *Ascomycota*, *Glomeromycota*, and *Basidiomycota* were found to be the dominant phyla by characterized fungal microbiota profiles in 27 cases of colorectal adenomas and adjacent tissues (66). Adenoma size and disease stage were closely associated with fungal microbiota. Furthermore, a series of intestinal microbial biomarkers were identified to distinguish CRC patients from controls (7, 66). This indicates the potential of intestinal microbiome as a tool towards targeted non-invasive biomarkers for CRC.

Many studies on the intestinal microbiome of CRC are performed using fecal samples because of its easy and non-invasive procedure. However, tissue samples from colonic mucosa are more valuable to disentangle the physiopathology of CRC disease and cumulative studies have shown different microbiome profiles between mucosal and fecal samples (67–71). So far, the unified microbial community structure associated with CRC has not been determined and sample collection is another challenging in microbiome studies of CRC. Accordingly, further studies are warranted to determine which is more representative of the real microbial structure change.

## HCC

Hepatitis virus is well known to be closely related to HCC, but the role of bacteria in the occurrence and development of HCC remains unclear. In 1992, the Frederick Cancer Research Center identified a spiral bacterium-*Helicobacter hepaticus* from the liver tissue, and considered it as a cause of hepatitis and liver tumors in mice (14). Since then, scientists have carried out a series of studies on the association between *Helicobacter* spp. and chronic liver diseases (72–75). The *Helicobacter* 16S rRNA gene was sequentially detected in liver tissues of patients with chronic liver diseases and HCC (76–78). In addition, an association between *H. pylori* infection and mortality of patients with HCC has been observed (79). However, studies on the intratumoral

microbiota of HCC are scarce and further investigations on the role of other bacteria in HCC are needed.

The above are reported researches on intratumoral microbiome of gastrointestinal cancers, and we summarize the intratumoral microbiome in Table 1.

## Crosstalk between intratumoral microbiome and TME

Emerging studies have demonstrated intratumoral microbiome as a component of TME, and the crosstalk between intratumoral microbiome and TME is mutual and highly dynamic (1, 15). Specifically, the intratumoral microbiome can induce immunosuppression or immunoactivation, reprogram tumor metabolism, and form a heterogeneity TME so as to promote or inhibit tumor development (80, 81). The potential crosstalk reported between the microbiome and TME is shown in Figure 1.

The reprogramming of immune infiltration plays important roles in the crosstalk between the intratumoral microbiome and TME (2, 82). A recent research revealed that microbial components (e.g., DNA, RNA, bacterial peptides, and lipopolysaccharides) could be detected in tumor and immune cells, indicating that intratumoral microbiome might affect immune infiltration in TME (15). Similarly, bacterial polypeptide fragments were found to be directly presented on the surface of tumor cells or antigen-presenting cells through human leukocyte antigens. They could promote T cell activation and potential tumor immune response (83). Tumor monocytes can be induced to produce interferon- $\gamma$ , regulate macrophage

polarization, promote communication of natural killer and dendritic cells, and reprogram the TME (84). In addition, the microbiota may regulate immune invasion in different tumors in different ways. Proteus bacteria (mainly *E. coli*) in CRC may destroy the intestinal barrier, migrate and colonize the liver through the damaged intestinal barrier, and promote immune cell recruitment in the liver (e.g., macrophages, neutrophils, and monocytes) to induce liver metastasis (85). *F. nucleatum* is reported to bind to the immunosuppressive receptor T cell immunoglobulin through its surface adhesin, thereby inhibiting T cell activation and natural killer cell lethality (86). Pushalkar et al. demonstrated that intratumoral bacteria in pancreatic cancer could promote oncogenesis by inducing innate and adaptive immune suppression (12). While bacterial ablation induced immunogenic reprogramming, including reduction of myeloid-derived suppressor cells, increase of M1 macrophage differentiation, promotion of Th1 differentiation of CD4+ T cells, and activation of CD8+ T cells (12). Mechanistically, the immune-suppression characteristic of PDAC were generated by bacteria through differentially activating select toll-like receptors in monocytic cells. Furthermore, special bacterial species were found to favor recruitment and activation of CD8+ T cells, contribute to the anti-tumor immune response and affect clinical outcomes of pancreatic cancer (11).

Many of the above findings are still arguable and need further research. While, some preclinical models have clarified potential mechanisms by which microbiota can contribute to tumorigenesis and established a more causative role. *P. gingivalis* infection was found to enhance proliferation of PDAC cells by cell lines and a xenograft model (87). This was independent of

TABLE 1 Gastrointestinal cancer-associated intratumoral microbiota.

Cancer type	Bacteria	References	Fungi	References
Esophageal cancer	<i>Escherichia coli</i>	(22, 23)	-	-
	<i>Fusobacterium nucleatum</i>	(22, 26)		
	<i>Lactobacillus fermentum</i>	(24, 25)		
Gastric cancer	<i>Helicobacter pylori</i>	(28, 29)	-	-
	<i>Streptococcus</i>	(31, 32)		
	<i>Lactobacillus</i>	(31, 33)		
	<i>Escherichia-Shigella</i>	(33)		
	<i>Lachnospiraceae</i>	(31, 33)		
Pancreatic cancer	<i>Pseudoxanthomonas</i>	(11, 38)	<i>Malassezia</i>	(39, 40)
	<i>Streptomyces</i>	(11, 38)		
	<i>Saccharopolyspora</i>	(11, 38)		
	<i>Bacillus clausii</i>	(11, 38)		
Colorectal cancer	<i>Escherichia coli</i>	(55, 59)	<i>Ascomycota</i>	(7, 66)
	<i>Peptostreptococcus anaerobius</i>	(57, 58)		
	<i>Fusobacterium nucleatum</i>	(51, 53, 56, 62, 64)	<i>Basidiomycota</i>	(7, 66)
	<i>Bacteroides fragilis</i>	(54, 60)		
	<i>Enterococcus faecalis</i>	(61, 63)		
	<i>Salmonella</i>	(61, 63)		
Hepatocellular carcinoma	<i>Helicobacter hepaticum</i>	(14, 72, 75)	-	-
	<i>Helicobacter pylori</i>	(73, 74, 76, 77)		

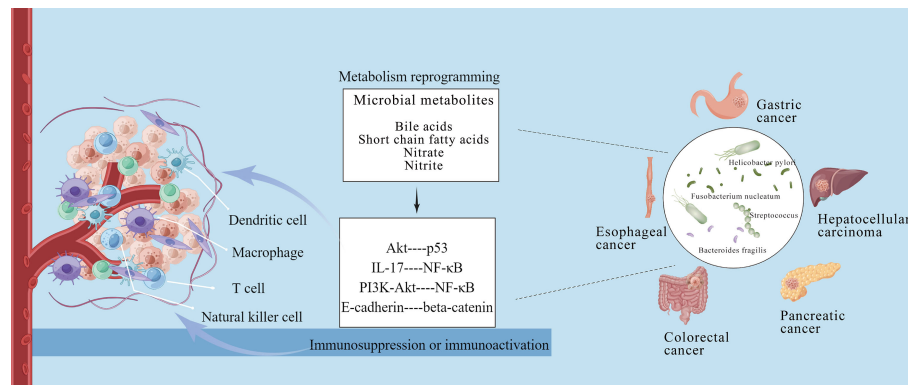


FIGURE 1

Crosstalk between intratumoral microbiome of gastrointestinal cancers and tumor microenvironment. The intratumoral microbiota can induce immunosuppression or immunoactivation via metabolism reprogramming, and form a heterogeneity tumor microenvironment to affect tumor occurrence and development. This figure is drawn by Figdraw.

TLR2 signaling and associated with augmentation of the Akt signaling pathway (87). Similarly, Akt signaling pathway activated by *H. pylori* can also result in subsequent degradation of tumor suppressor p53 in gastric epithelial cells and increase survival of gastric epithelial cells with sustained DNA damage (88). Enterotoxigenic *B. fragilis* can lead to colitis that triggers IL-17 production and inflammatory pathway activation, such as NF- $\kappa$ B, to facilitate tumor growth (54, 89). While PI3K-Akt pathway activated in CRC can lead to increased cell proliferation and NF- $\kappa$ B activation (58). *F. nucleatum* may selectively bind and activate E-cadherin/beta-catenin signaling via its FadA adhesin, inducing inflammation and CRC (90). *Enterococcus faecalis* in CRC induces superoxide production, thus damaging the DNA of epithelial cells (91, 92).

Additionally, tumor microbiome is reported to directly affect the response to antitumor therapies (93, 94). The enrichment of Firmicutes, reciprocal changes in abundance of Verrucomicrobia and Proteobacteria, were found to be correlated with better immunotherapy response across various tumors (93, 94). In addition, *F. nucleatum* is found to promote the resistance of colorectal cancer to chemotherapy (95). Mechanistically, *F. nucleatum* activated the autophagy pathway by targeting at TLR4 and MYD88 innate immune signaling and specific microRNAs to promote chemoresistance (95). A study about CD47-based cancer immunotherapy revealed that accumulative *Bifidobacterium* in TME facilitates local anti-CD47 treatment by a stimulator of interferon genes (STING)- and interferon-dependent fashion (96). Besides, disruption of gut microbiota is estimated to affect the response of tumors to immunotherapy and chemotherapy both in preclinical models and cancer patients (97–100). Antibiotic treatment can reduce response to ICI, while the presence of certain bacteria strains correlates with

better outcomes (10, 101). Mechanistically, gut microbiota could modulate the expression of immune checkpoints, the function of dendritic cell, the homing and recruitment of lymphocyte (82, 83), as well as the production of critical metabolites, such as short chain fatty acids (SCFA) (102, 103).

The microbiome participates in the modulation of human metabolism and microbial dysbiosis can induce systemic metabolic alterations (104, 105). To date, intratumoral microbiome has been shown to reprogram tumor metabolism through derived metabolites, and a differential enrichment of metabolic functional pathways induced by microbiota may correlate with clinical outcome. As reported, patients with PDAC who are enrichment in xenobiotics biodegradation and lipids metabolism pathways have shown better outcomes (11). Metabolites, such as the secondary bile acids (e.g., deoxycholic acid, lithocholic acid) and SCFA (e.g., butyrate), have been reported to regulate inflammation and T cell differentiation (106–108) and implicated in the tumorigenesis (109, 110). HCC oncogenesis is found to be closely associated with intestinal flora, bile acid metabolism, and tumor immunity (111). Gut microbiota-mediated bile acid metabolism regulates the occurrence and progression of HCC by affecting the accumulation of hepatic CXCR6<sup>+</sup> natural killer T (NKT) cells through mediating the expression of CXCL16 in liver sinusoidal endothelial cells (111). SCFAs, mainly butyrate, can directly modulate CD8(+) cytotoxic T lymphocytes and Tc17 cells, as well as induce senescence-like phenotypes and the development of CRC (106, 107). The secondary metabolites produced by microbiota, such as reactive nitrate and nitrite, can lead to accumulation of carcinogenic N-nitroso compounds and associate with tumor development (26, 112). These studies shed light on a new theoretical basis for tumor treatment by regulating microbial metabolism and the microbiota.

## Conclusions

Despite decades of research, gastrointestinal cancers remain the most lethal malignant tumor with limited treatment options and poor clinical outcomes. Emerging understanding of microbiome in gastrointestinal cancers will potentially provide new insights and opportunities for the development of novel biomarkers and treatment strategies. Current studies have revealed the role of microbiota in regulating tumorigenesis, development, and response to antitumor treatment, while challenges remain in our understanding of intratumoral microbiome. For example, how are the mechanisms of action of intratumoral microbiome in various tumor types? How are they different? What are the effects of microbial metabolites on tumors? How does intratumoral microbiota regulate the inflammatory carcinogenic pathway and immune response? Moreover, research discoveries on the various types of tumors have been discrepant, and this may be due to several factors, such as the tumor type, research methods, and microbial complexity. Moreover, almost no good clinical data exists for the claims. Therefore, the diversity, origin, and mechanism of action of intratumoral microbiome require further clarification. However, intratumoral microbiome has the potential to be used as diagnostic tools for tumor typing and to be considered as a potential new therapeutic target. Further in-depth researches on the intratumoral microbiome are expected to reveal the complex correlation between intratumoral microbiome and gastrointestinal cancers. Overall, this exciting field will allow us to explore the mystery of carcinogenesis from another perspective and to discover novel targets for precision medicine in the management of gastrointestinal cancers.

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## Author contributions

SL: Data curation, Writing-original draft preparation. WL, QL: Writing- reviewing and editing. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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