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Mechanisms of Different Intestinal Flora in Gastric Cancer

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Abstract

As one of the global cancers, gastric cancer is characterized by "double-high" morbidity and mortality, which seriously jeopardizes human health. Therefore, early diagnosis of gastric cancer or better treatments are warranted to improve this situation. Although *Helicobacter pylori* has been recognized as the strongest oncogenic factor in gastric carcinogenesis, with the development of gene sequencing technology, researchers have found that the enrichment and diversity of intestinal flora are also involved in the whole process of gastric cancer development, progression, treatment, and prognosis. In this paper, we will review the mechanisms of different intestinal flora in gastric cancer from various aspects, which will help to further explore its clinical value and provide new directions for the early diagnosis and treatment of gastric cancer in the future.

Keywords

Gastric Cancer, Intestinal Flora, *Helicobacter pylori*

1. Introduction

As the main and most complex microbial system in the human body, the intestinal flora not only interdepends and coexists with the human host [1], but also participates in a variety of physiological processes such as the growth and development of the body, nutrient absorption, energy metabolism, immunomodulation, neuromodulation, and intestinal barrier [2]-[5], which play a crucial role in the health

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of human beings themselves. Gastric cancer (GC) is one of the most common cancers, and according to the global cancer statistics in 2022, the incidence and mortality of gastric cancer account for 4.9% and 6.8% of all cancers in the world, making it the fifth most prevalent malignant tumor in the world [6]. It not only seriously damages human health, but also creates a huge economic burden on society. With the rapid development of high-throughput sequencing technology, more and more studies have confirmed that different intestinal flora are involved in the process and therapeutic efficacy of gastric cancer. If we can further explore the relationship between intestinal flora and gastric cancer, as well as its clinical value, this will help to reduce the incidence of gastric cancer and provide more choices in prevention or precision medicine.

2. Composition and Function of Intestinal Flora

The intestinal flora is a collection of bacteria that colonize the human body for a long period of time and in large quantities, numbering about 10^{14}, which is 10 times the number of cells in the human body [7]. However, the percentage of such a large number of gut microbiota is different in healthy people and gastric cancer patients. The dominant phyla of the gastric mucosal microbiota in healthy individuals primarily include Proteobacteria, Firmicutes, Bacteroidetes, Actinobacteria, Clostridioides, and Campylobacter [8] [9]. Liu *et al*. conducted a retrospective analysis of gastric mucosal tissue from 276 gastric cancer patients, revealing a significant imbalance in the gastric microbiota at the genus level. Compared to healthy individuals, both the diversity and abundance of the gastric microbial microenvironment were markedly altered in gastric cancer patients [10]. Specifically, beneficial bacteria such as *Prevotella* and *Streptococcus* were markedly reduced [9]-[11], while genera including *Klebsiella pneumoniae*, *Neisseria*, *Lactobacillus*, Escherichia-Shigella, and Nitrospira showed substantial increases [12]. This suggests that gastric cancer is not caused by a single bacterium, but rather multiple pathogens are involved in destroying the function and structure of the gastric mucosa, thereby inducing and promoting the development of gastric cancer. Similarly, this is corroborated by the fact that many other studies have also confirmed that the normal gastric microenvironment is a barrier to prevent the development of the disease, while the alteration of the microenvironment provides an opportunity for the propagation of pathogenic bacteria, which in turn increases the risk of gastric cancer developing.

3. Existing Studies and Findings on the Association between Intestinal Flora and Gastric Cancer

3.1. *Helicobacter pylori* (*H. pylori*)

Helicobacter pylori is a microaerobic Gram-negative bacterium colonizing the gastric mucosa [13], which possesses urease, oxidase, and catalase activities [14]. Studies have shown that the pathologic process of most gastric cancer patients initially consists of chronic inflammation, gradually progressing to atrophic gastritis, in-

testinal epithelial hyperplasia, intraepithelial neoplasia, and ultimately to gastric adenocarcinoma [15]. Among them, *Helicobacter pylori* infection is not only involved throughout the development of the disease but is also the initiator of the process [14]-[17]. First, the pathogen enters the stomach through the mouth and is partly killed by gastric acid and partly adheres to the mucous layer of the gastric sinus, relying on its flagellum to pass through the mucous layer, settling on the surface of the mucous layer and mucosal epithelial cells of the gastric sinus, and generally does not invade into the gastric glands and lamina propria. This not only avoids the bactericidal effect of gastric acid but also makes it difficult for the body's immune function to clear [18]. Second, Hp breaks down urea by producing urease, and the ammonia thus broken down neutralizes the gastric acid that has backpenetrated into the mucus, creating a microenvironment conducive to the survival and reproduction of Hp, making the infection chronic [19]. Furthermore, the bacterial infection promotes the release of inflammatory mediators from epithelial cells, stimulating the accumulation of cytokines such as interleukin 1β (IL-1β), interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α), which changes the inflammatory response of gastric mucosa from the immune homeostatic mode of anti-infection and repair of tissue damage to the uncontrolled inflammation of immune imbalance, which activates multiple groups of oncogenic signaling pathways and leads to the development of gastric tissue carcinogenesis [20]. Recent studies have shown [21] that the mechanism of *H. pylori*-induced inflammation is to evade the host's immune check by adopting molecular mimicry, modulation of the host's immune response, as well as antigenic variability, suppression of innate immunity, etc. Meanwhile, the interaction with the host's immune system disrupts the balance between pro-inflammatory and anti-inflammatory signals, leading to an immune imbalance that results in persistent inflammation and tumor progression in the gastric mucosa. In addition, *H. pylori* has a variety of virulence factors, and its release of cytotoxin-associated proteins (oncoprotein CagA predominantly) and vacuolar cytotoxin (VacA) are the key causative toxins for inducing cancerous changes in gastric tissues [22]. On the one hand, relevant studies have shown that cytotoxin-associated proteins can promote gastric carcinogenesis and progression through multiple pathways, such as phosphatidylinositol 3-kinase/protein kinase B (PI3K/PKB), extracellular-regulated protein kinase/mitogen-activated protein kinase (ERK/MAPK), NF-κB-mediated miR-223-3p/ARID 1A axis, Ras, tyrosine protein kinase/signal transducer and activator of transcription inhibitor (JAK/STAT3), etc., and simultaneously induced mutations in the classical oncogene P53, which in turn significantly increased the risk of gastric carcinogenesis [23] [24]. In addition, Song [25] *et al.* demonstrated that miR-7 and miR-153 could promote apoptosis and autophagy, inhibit cell proliferation and inflammatory response in GES-1/HP cells through biological function experiments and in vivo experiments in mice, and further revealed that the down-regulation of the expression of miRNAs (miR-7, miR-153) was involved in the inflammatory and oncogenic roles of *H. pylori* CagA, which could become potential diagnostic mark-

ers for gastric cancer. On the other hand, vacuolar cytotoxins can act in different host cell types, such as gastric epithelial cells, immune cells (T-cells, antigen-presenting cells, phagocytes, mast cells, etc.), and can directly cause cellular vacuolization, disruption of cell-cell junctions, and inhibition of apoptosis [26] [27]. Furthermore, it has been found that vacuolating toxins can promote the expression of vascular endothelial growth factor in gastric cancer through the upregulation of the Wnt/β-catenin signaling pathway [28] and inhibit GSK3-induced autophagy and promote inflammatory responses through the c-Met-PI3K/Akt-mTOR signaling pathway [29].

3.2. Other Different Intestinal Flora

The susceptibility factors of gastric cancer mainly include the invasion of *H. pylori*, the decrease of immune function of the gastric mucosa, genetic factors, and the disruption of the dynamic balance of intestinal flora. Although *H. pylori* has been proved to be the main causative agent of most gastric cancers, researchers also found that some patients were not infected by *H. pylori* before the development of gastric cancer or received Hp curative treatment after the infection, so it is speculated that the development of gastric cancer is not only related to Hp infection, but also that there are other pathogenic microorganisms that have a carcinogenic or cancer-promoting effect, so removing the microorganisms that have a harmful effect on the gastric mucosa can effectively fight against the development of gastric cancer. Therefore, the elimination of other microorganisms that are harmful to the gastric mucosa could be effective in combating the development of gastric cancer. With the development of first- and second-generation high-throughput technologies and the application of 16rRNA technology, with the joint efforts of many researchers, it was found and proposed that the composition and abundance of the intestinal flora of gastric cancer patients and healthy populations are not consistent [8]-[12]. The intestinal flora of gastric cancer patients was significantly enriched in *Lactobacillus*, *Klebsiella pneumoniae*, *Helicobacter nitrophilous*, and *Trichoderma* spp. Compared to normal patients, there was a decrease in the number of *Prevotella* spp., *Porphyromonas* spp., and *Neisseria* spp., which are all bacteria with a specific function to promote gastric cancer development [30].

3.2.1. *Lactobacillus*

Lactobacillus is a common microorganism in the human gastrointestinal tract, and its role in human health is dual. On the one hand, *Lactobacillus* species exhibit multiple physiological functions [31]. For instance, lactic acid bacteria can suppress pathogenic colonization by occupying a dominant position in the gastrointestinal tract, while producing lactic acid to lower the pH of the gastrointestinal mucosa, thereby enhancing mucosal barrier function. *Lactobacillus salivarius* and *Lactobacillus plantarum* activate the immune system by stimulating inflammatory cells such as macrophages and NK cells, thereby maintaining immune homeostasis [32]. In probiotic research, *Lactobacillus acidophilus* has been found to enhance the anti-inflammatory effects of bifidobacteria and exert anticancer activity

by regulating multiple secretory cell lineages in the stomach [33]. On the other hand, *Lactobacilli* are involved in tumor development through various mechanisms, such as promoting inflammation, metastasis, epithelial-mesenchymal transition, immune evasion, and anti-*H*. Lactic acid produced by *Lactobacilli* provides a source of energy for tumor cell growth and angiogenesis through activation of the hypoxia-inducible factor-1 (HIF-1) pathway [34] [35]. In addition, some *Lactobacillus* bacteria can increase the level of reactive oxygen species, thus leading to DNA damage [36]. Li *et al*. [37] indicated that *Lactobacillus* bacteria can reduce nitrate to nitrite, which ultimately leads to the production of N-nitroso compounds in large quantities. These compounds promote gastric cancer development by mutating epithelial cells, increasing angiogenesis, and proto-oncogene expression. Therefore, dynamic monitoring of *Lactobacillus* counts might be useful as a therapeutic efficacy as well as a prognostic indicator for gastric cancer patients.

3.2.2. *Klebsiella pneumoniae*

Klebsiella pneumoniae are highly virulent and multidrug-resistant, conditionally pathogenic bacteria that can disrupt the balance between mucosal and material transport by promoting inflammation production, activating inflammatory factors (e.g., TNF-α, IL-6, IL-1β), increasing mucosal permeability, and disrupting the intestinal mucosal barrier [38]. Liu Jun *et al*. found [39]that *Klebsiella pneumoniae* can enhance its adhesion and invasion capabilities in intestinal epithelial cells by upregulating tolloid-like protein 1 (TLL-1) expression, thereby activating the TGF-β signaling pathway. Significantly, the TGF-β signaling pathway plays a crucial role in the progression of various cancers, including gastric cancer. For instance, in gastric cancer, activation of this pathway leads to downregulation of epithelial markers (e.g., E-cadherin) while promoting upregulation of mesenchymal markers (e.g., N-cadherin, Snail, Slug, and Twist), thereby enhancing tumor cell invasion and migration capabilities [40]. Furthermore, TGF-β promotes the proliferation and survival of gastric cancer cells by activating the PI3K/Akt/mTOR signaling pathway [41]. Based on these mechanisms, *Klebsiella pneumoniae* may indirectly participate in the initiation and progression of gastric cancer by regulating the TGF-β signaling pathway. The occurrence of inflammatory response, as well as the disruption of the mucosal barrier due to the increased population of *Klebsiella pneumoniae* in patients with gastric cancer, may be one of the microbial mechanisms involved in the development of gastric cancer after the imbalance of intestinal flora. However, more studies are needed to gain a deeper understanding of the specific mechanism of action of *Klebsiella* spp. in gastric cancer.

3.2.3. *Prevotella* spp.

Prevotella spp., as a key component of the human gut microbiota, not only promotes dietary fiber metabolism and suppresses inflammatory responses [42], but also enhances resistance to host-derived reactive oxygen species and produces the redox protein thioredoxin [43]. Thus, dysregulated *Prevotella* spp. promote gastric carcinogenesis and progression by affecting host immune function and met-

abolic changes, which are mainly characterized by increased production of helper T-type 17 (Th-17), *i.e.*, interleukin (IL-17), and inhibition of Th-2 (IL-4, IL-5, and IL-9), and similar Th-1, *i.e.*, the interferon-c (INF-c) cytokine [44] [45]. However, some scholars investigating the relationship between gastric microbiota relative abundance and gastric cancer risk in Korean populations reached opposite conclusions: *Prevotella* species were increased in the gut microbiota of gastric cancer patients, and *Prevotella* carriers exhibited a higher gastric cancer risk compared to non-carriers. Yet, compared to normal tissue, *Prevotella* showed lower absolute abundance in gastric tumors and the tumor microenvironment [46]. The causes of this contradiction may be related to the host's dietary habits, intestinal microenvironment, interactions with other microbial communities, and geographical environment.

3.2.4. *Nitrospiraea* and *Trichoderma*

Wang *et al*. [47] [48] found that nitrosating or nitrate-reducing bacteria in the genus *Nitrospiraea* were significantly enriched in gastric cancer patients, and increased the production of carcinogenic N-nitroso compounds through the metabolism of nitrate, which is an important risk factor for the development of gastric cancer. Therefore, controlling the intake of nitrate is beneficial in reducing the occurrence of gastric cancer. In addition, studies have found that increased numbers of *Trichoderma* can promote the development of gastrointestinal inflammation, thereby increasing the risk of cancer [49].

3.3. Effect of Gut Flora Metabolites on Gastric Cancer

Certain intestinal flora can produce metabolites, such as short-chain fatty acids, bile acids, and polyamines, that affect the development of gastric cancer. Studies have confirmed that short-chain fatty acids play a positive role in human immunity, with the functions of inhibiting tumor cell proliferation, promoting apoptosis, activating immune cell function, and promoting the secretion of anti-inflammatory factors by immune cells, thus inhibiting tumorigenesis [37]. The most important component of short-chain fatty acids in inhibiting disease development is butyrate, while more and more researchers have discovered the mechanism of action of butyrate in anticancer. Firstly, butyrate inhibits the progression of GC by binding to pyruvate kinase M2 (PKM2), which reduces ATP production and makes the tumor growth lack energy, and inhibits the Warburg effect in gastric cancer. Secondly, butyrate activates apoptotic signaling by producing cysteamine-containing aspartate protein hydrolase 9 (Caspase9) and inhibiting BCL-2 synthesis, resulting in programmed cell death of gastric cancer cells [50]. In addition to this, Liang *et al*. found that butyrate could inhibit the growth, migration, and invasion of gastric cancer cells by blocking the Wnt/β-catenin/c-Myc signaling pathway [51].

Bile acids and bile reflux are important risk factors for the development of gastric cancer [52], and the cytotoxic effect of bile acids is the main cause of damage to the gastrointestinal mucosa and tumor induction. In addition, it has been found

that intestinal microorganisms rich in bile salt hydrolases, such as *Lactobacillus* spp., *Enterococcus* spp., and *Mycobacterium* spp., can convert primary bile acids into secondary bile acids, which in turn act as signaling molecules involved in the regulation of cancer progression through the STAT3 pathway [53]-[55].

Polyamine secretion is essential for cell growth, but intestinal dysbiosis leads to polyamine overproduction, thereby adversely affecting the human body. First, polyamines can inhibit anti-tumor immunity and promote tumor cell growth; second, polyamines can also promote intestinal mucosal biofilm formation and exacerbate intestinal dysbiosis, leading to the production of more polyamines for cell growth, which ultimately promotes gastrointestinal tumorigenesis and development [56]. Therefore, modulation of the intestinal flora is expected to improve the efficacy of polyamine-targeted anticancer drugs. In addition, certain intestinal bacteria secrete outer membrane proteins, phospholipases, BAK proteins, and nickel-binding proteins, which contribute to bacterial colonization, promote the progression of chronic gastritis, and ultimately increase the risk of gastric carcinogenesis [57]. Thus, both the gut bacteria themselves and their metabolites play a driving role in the development of gastric cancer, as can be seen in the table below.

Gastric cancer-related gut microbiota and its mechanisms of action

Microbiome/ metabolites	Changes in gastric cancer patients	Mechanism of role	clinical significance	References
Helicobacter pylori	Increased quantity	- Inducing chronic inflammation → immune imbalance - Secretion of CagA/VacA toxins activates carcinogenic pathways such as PI3K/Akt and ERK/MAPK	Main carcinogenic factors; radical treatment can reduce risk	20 21 23 24 29
Lactobacillus	Increased quantity	-Anti-cancer: Strengthens the mucosal barrier -Pro-cancer: Lactic acid activates HIF-1 to promote angiogenesis	Selection of therapeutic targets	31 34 35
Klebsiella pneumoniae	Increased quantity	- Destruction of the mucosal barrier - Activation of the TGF-β pathway promotes invasion	Potential biomarkers	38 39
Prevotella spp	Decrease (controversy: some studies show an increase)	Immune imbalance (increased Th17/Th1 ratio)	Further verification of its protective or carcinogenic effects is needed	44
Nitrospiraea and Trichoderma	Increased quantity	Generation of carcinogenic N-nitroso compounds	Controlling nitrate intake may prevent gastric cancer	49
butyrate	Decrease	-Induced apoptosis in cancer cells -Inhibited the Wnt/β-catenin pathway	Probiotics/dietary supplements can be used as adjunctive therapy	51 52
secondary bile acid	Increased quantity	Promoted inflammation and cancer through the STAT3 pathway	Targeting bile acid metabolism may improve prognosis	55

3.4. Effect of Intestinal Flora on Gastric Cancer Treatment

An increasing number of studies have highlighted the important impact of gut microbes and their metabolites on tumor therapy. In the treatment of gastrointestinal tumors, gut microbes and chemotherapy are interacting with each other, which can metabolize and absorb a variety of chemotherapy-related drugs (e.g., oxaliplatin, irinotecan, gemcitabine, 5-fluorouracil, etc.), which can alter their therapeutic effects and also reduce the adverse effects on the organism [58]-[62].

Ren [59] *et al*. have found through in vitro experiments that the *Bifidobacterium animalis* subsp. *lactis* SF can produce a large amount of exopolysaccharide (EPS), which inhibits the activity of cancer cells and thus enhances the antitumor efficacy of irinotecan. Microorganisms with nitroreductase can enhance the activation of the gemcitabine prodrug CB 1954 to improve anti-tumor efficacy; however, cytosine deaminase (CDDL) containing long-chain forms (e.g., *γ*-amoebae) are able to metabolize gemcitabine to an inactivated form, 2',2'-difluorodeoxyuridine, which inactivates it [60] [61].

The relationship between intestinal flora and gastric cancer immunotherapy is a hot area of current research. Gut flora influences the development of gastric cancer by regulating intrinsic and adaptive immunity and affecting the tumor microenvironment, which in turn activates or suppresses the immune response [63]. Specific intestinal flora can support the growth of gastric immunosuppressive cells (e.g., BDCA2 + pDCs and Foxp3 + Tregs) and induce the development of immune escape [64]. In addition, intestinal flora can influence the function of adaptive immune cells by modulating relevant molecules, such as up-regulation of immune-related receptors CD80, CD86, and PD-L1 on gastric epithelial cells, and increasing the production of regulatory factors such as IL-7 and IL-33 [65] [66]. Han *et al*. discovered that *Lactobacillus* species were significantly enriched in responders to immunotherapy, and a higher relative abundance of *Lactobacillus* was associated with a better anti-PD-1/PD-L1 immunotherapy response in gastric cancer patients [67]. Similarly, metabolites from the gut microbiota also participate in regulating immune expression within the gastric cancer microenvironment. For instance, gut microbiota-derived butyrate inhibits PD-L1 and IL-10, immunosuppressive factors expressed by gastric cancer-associated macrophages [68].

In the field of radiation therapy, it has been suggested that intestinal flora may influence host sensitivity to radiation therapy. For example, lactobacilli are able to protect the intestinal epithelial surface from radiation damage in a TLR-2/ cyclooxygenase-2-dependent manner [69].

4. Potential Application of Intestinal Flora in the Treatment of Gastric Cancer

4.1. Probiotic Therapy

Probiotics are defined as "live microorganisms cultured in sufficient quantities to provide benefits to the host" [70]. Yan *et al*. [71] [72] found that probiotics have a variety of physiological effects in human and animal studies, including modulation of immune function, production of antimicrobial substances, and maintenance of intestinal epithelial homeostasis by competitive inhibition of the adhesion of pathogens and toxins to the intestinal epithelium. The curative treatment of *H. pylori*, whether triple or quadruple therapy, relies heavily on the use of antibiotics. However, the widespread use of antibiotics has led to a substantial increase in HP tolerance to a variety of drugs (e.g., clindamycin, metronidazole, levofloxacin) [73], and with it a decrease in the rate of HP eradication [74]. How-

ever, Kunishima [75] *et al*. found that probiotics could also inhibit the growth and affect the transmission of drug-resistant genes in ultra-broad-spectrum β-lactamase (ESBL)-producing *Escherichia coli* and carbapenem-resistant *Enterobacteriaceae* bacteria. This provides new ideas for antimicrobial treatment of Hp. Song [76] *et al*. combined probiotics with antibiotics, which not only improved the eradication rate, but also reduced the side effects of drugs. However, whether probiotics can inhibit tumor formation is still poorly known. Polyamines (putrescine, spermidine, and spermine) play an important role in cell proliferation and differentiation. These small amines are necessary for maintaining cell growth through elevated DNA, RNA, and protein synthesis in precancerous tissues and in tumor tissues, from which, in turn, Russo [77] *et al*. suggested that "probiotics can act as antigastric mucosal tumor drugs by affecting the content and function of polyamines".

4.2. Fecal Microbiota Transplantation

Fecal microbiota transplantation (FMT) is a therapeutic approach to improve intestinal dysbiosis in patients by isolating beneficial bacteria from healthy human feces and transplanting them to the patient's intestinal tract [78]. FMT is gradually becoming an alternative therapeutic modality to regulate the gastrointestinal microenvironment, and has made great progress in relieving symptoms, treating diseases, and so on. In the current study, FMT not only effectively relieves gastrointestinal symptoms such as *C. difficile* infection and inflammatory bowel disease, but also helps to improve the species diversity of intestinal flora, modulate the immune response, restore the integrity of the mucosal barrier, and alter microbial metabolites, thereby restoring the health of the gastrointestinal tract [79]-[82]. He *et al*. pointed out [83] that diarrhea occurs in 50% - 80% of cancer patients who receive chemotherapy, and the mechanism of occurrence is not just the effect of chemotherapy drugs on the gastrointestinal tract. The mechanism of occurrence is not only due to the damage of chemotherapeutic drugs to the gastrointestinal mucosa, but also related to the reduction of the host intestinal flora. Diarrhea not only reduces the immunity and quality of life of patients, but also increases the risk of infection, electrolyte disorders, and even shock, prolongs the length of hospitalization, increases the burden of hospitalization costs, and, in severe cases, chemotherapy may even need to be suspended, affecting the therapeutic effect. Thus, maintaining the balance of intestinal flora by means of flora transplantation has a significant impact on the prognosis of chemotherapy for gastric cancer patients. In addition, in tumor immunotherapy, studies have shown [84] that FMT is able to reconfigure the tumor microenvironment, which in turn is beneficial in solving the problem of tumor cell resistance to PD-1 inhibitors. The results of preliminary data from a clinical trial of a chemotherapeutic agent (FMT capsule in combination with Nivolumab) carried out by Peng Z and other investigators [85] also corroborate that FMT may alter the intestinal microbiota structure and may overcome resistance to anti-PD-1 therapy for gas-

trointestinal cancers. Finally, radiation therapy plays a crucial role for gastric cancer patients. However, the radiation therapy process often causes radiation enteritis, which leads to a decrease in patient weight and radiotherapy tolerance [86] [87]. It has been found that radiation enteritis can also be alleviated and prevented by correcting intestinal flora disorders through FMT [88], which is based on the mechanisms of decreasing intestinal leakage, enhancing intestinal function and epithelial integrity in patients with radiation enteritis [89] as well as increasing the species diversity of intestinal flora [90].

5. Outlook

The relationship between gastric cancer and intestinal flora is complex and multidimensional, which is becoming clearer with the maturation and wide application of 16rRNA technology. In addition to Hp, many non-HP microorganisms can indirectly or directly participate in the occurrence, development, prognosis, and therapeutic response of gastric cancer. The discovery of this relationship can, to a certain extent, provide a direction for tumor prevention and treatment, offer new ideas for the diagnosis of gastric cancer besides digestive endoscopy and traditional markers, and also bring the possibility of early gastric cancer discovery, and even provide a new research direction for the treatment of tumors, which will ultimately improve the survival rate and the quality of survival of patients. However, there are still three urgent problems in the existing studies. First, the gastric microbiota and its metabolites have not yet been identified as the main indicators of GC development, and the mechanism of microbial effects on GC needs to be more thoroughly investigated. Second, most of the current clinical studies analyze the intestinal flora of a single gastrointestinal tumor as a whole, ignoring the interactions and physiological properties of the local microbiota of the gastrointestinal tract, *i.e.*, most of the studies analyze the bacterial flora of the gastric cancer itself, and do not subdivide the site of GC into cardia, gastric sinus, and gastric body cancers for the analysis of the local microbiota. Thirdly, due to the dynamic changes of intestinal flora during the long-term progression of GC and the diversity among individuals affected by heredity, dietary habits, regional environment, etc., the results of the studies lacked standardization.

In the future, we need to further explore the specific mechanism of the role of intestinal flora in the occurrence and development of GC, as well as how to utilize this relationship to provide new ideas and methods for the prevention and treatment of gastric cancer. On the one hand, we can transplant the needed bacteria from fecal bacteria in a rational and scientific way and counteract the harmful intestinal metabolites, bacterial products, and bacterial toxins produced by other microorganisms. Second, we can analyze the intestinal flora of gastric cancer according to anatomical classification, find the highly specific flora in GC, and study the pathogenic mechanism of microorganisms through transcriptomics, proteomics, and other ways. Third, we will expand the clinical sample size and conduct large-scale prospective cohort studies. Through these studies, we hope to use them

as potential biomarkers and reflective predictors for gastric cancer patients, develop new therapeutic strategies (e.g., targeted microbial therapy), and bring new hope for the survival and prognosis of gastric cancer patients.

Abbreviations

GC: Gastric Cancer
HP: Helicobacter *pylori*
FMT: Fecal Microbiota Transplantation

Authors' Contributions

Yanqing Guo, Qiangqiang Zhang, Tashi Nyima, and Yan Hu contributed to the conception, design, and drafting of the manuscript. All authors approved the submission of the final version of the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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