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Intestinal Flora and Gastrointestinal Tumors

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Abstract

Intestinal flora is a large and complex micro-ecosystem, and the growth and proliferation activities of different flora will have an important impact on the occurrence and development of gastric cancer and colorectal cancer as well as related treatment. This article reviews the latest research progress on the relationship between intestinal flora and gastric cancer and colorectal cancer.

Keywords

Gastrointestinal Tumors, Intestinal Flora, Gastric Cancer, Colorectal Cancer

1. Introduction

Gastrointestinal tumors mainly include gastric cancer and colorectal cancer, which are the second most common cancers in the world and seriously affect human life and health [1]. Intestinal flora is a large and complex micro-ecosystem, and the growth and proliferation activities of different flora will affect the normal physiological function of the host. Studies have shown that the gastrointestinal microbiota and its metabolites play an important role in the occurrence and development of gastrointestinal tumors. Therefore, this paper reviews the relationship between intestinal flora and gastric cancer and colorectal cancer.

In this review, we focus on the impact of gut microbiota on the occurrence and development of gastrointestinal tumors, and discuss the relationship between two common gastrointestinal tumors (gastric tumors and colorectal tumors) and gut microbiota. We conclude by highlighting the emerging approaches and future directions for harnessing microbiota to improve cancer treatment, and we discuss potential strategies for exploiting microbiota in the future.

2. Effects of Intestinal Flora on Gastrointestinal Tumors

Intestinal flora can contribute to the development of tumors by altering the host

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genome. First, bacteria that reside in the gastrointestinal tract can directly cause DNA damage through the DNA toxins they express, which can cause damage to genetic material. Cuevas-Ramos *et al.* [2] found that *Escherichia coli* containing "pks" genome can secrete a polyketide peptide gene toxin Colibactin, which can destroy the DNA interstrand cross-linking of eukaryotic cells, leading to double-strand breaks and chromosome instability, causing DNA damage and thus destroying the stability of the host genome. He *et al.* [3] also found that *Campylobacter jejuni* can secrete a cell-killing dilating toxin to destroy the double-stranded structure of DNA, thus promoting the occurrence of rectal tumors. In addition to directly causing DNA damage, pathogenic *Escherichia coli* in the gut can destroy the mismatch repair mechanism of DNA and exacerbate genomic instability [4]. Santos *et al.* [5] also found that *H. pylori* increased the stability of gene expression and promoted the occurrence of tumors by regulating the expression of miRNA related to DNA mismatch repair pathways in host cells.

Intestinal flora can contribute to tumor development by inducing a tumor-promoting inflammatory environment in the gastrointestinal tract. Lopès *et al.* [6] found that *E. coli* that can produce colicin can reduce CD3+ and CD8+ T cells and increase colon inflammation, thus promoting the occurrence of cancer. Similarly, in colon cells, enterotoxigenic fragile *Bacillus* produces fragile *Bacillus* toxins that promote tumor-driven myeloid cell recruitment by initiating a pro-inflammatory signaling cascade of STAT3-nuclear factor-κB (NFKB) to produce cytokines such as interleukin-17 (IL-17) and interleukin-23 (IL-23) [7]. Nucleobacterium and monomonas also produce toxins that can initiate inflammatory responses and recruit immune subsets, jointly promoting hyperplasia of the gastrointestinal tract [8] [9]. In addition, *Helicobacter pylori* can also promote gastro-gastrointestinal inflammatory hyperplasia by expressing its cytotoxin-associated gene A (CagA) [10].

The by-products of intestinal flora metabolism may also contribute to the development of intestinal tumors. Nguyen *et al.* [11] found that secondary bile acids, a secondary metabolite of intestinal flora, can stimulate IL-3 expression in human colorectal cancer cells by activating Erk8/1 MAPK and inhibiting STAT2 activity. Flynn *et al.* [12] also found that long-term exposure to deoxycholic acid can promote the occurrence of colon cancer prelesions. Some metabolites, such as acetate and butyrate, play a carcinogenic role by promoting epithelial-mesenchymal cell metaplastic transformation and/or cell proliferation [13].

In addition to promoting the development of gastrointestinal tumors, intestinal flora can also affect the immune pattern within developed tumor lesions by altering local cytokines and immune cell profiles. However, these effects are highly dependent on the environment, as different gut microbiota can differentiate distinct types of local immune responses that may favor or inhibit tumor growth. In many cases, tumoral microbiota drives tumor progression by promoting immune tolerance. On the one hand, gut microbiota can suppress anti-tumor immunity and activation of NOD1 by peptidoglycan contained in the cell wall of

gut microbiota has been shown to induce myeloid-derived suppressor cell-driven immunosuppression in colorectal cancer in an arginase-1-dependent manner [14]. On the other hand, intestinal flora can also promote anti-tumor immunity. Kim *et al.* [15] found that toll-like receptor 6 (TLR-6) signaling secreted by lactobacillus prevents inflammation and affects the composition of microbiota during inflammatory-induced colorectal cancer. Overacre-Delgoffe *et al.* [16] also found that the implantation of *Helicobacter pylori* into the colon and rectum of mice did not change the local intestinal flora environment, but it could promote the proliferation of cytotoxic lymphocytes and thus inhibit the growth of tumors.

3. Intestinal Flora and Gastric Cancer

Helicobacter pylori is a spiral-shaped, slightly anaerobic, gram-negative bacterium with very demanding growth conditions. A large number of previous studies have confirmed that it has a very important relationship with the occurrence and development of stomach diseases, especially gastric cancer. The direct effect of *H. pylori* on carcinogenesis is mainly exerted by two virulence factors: VacA and CagA. VacA is a high relative molecular mass polymeric postrenormalization protein present in all Hp strains, and its tolerance in the human stomach is achieved through the formation of pores on the epithelial membrane (and subsequent excretion of urea, allowing Hp to catalyze urea hydrolysis to prevent stomach acid) and inhibition of macrophages and T cells [17]. CagA [18] is a strain-specific protein that is a marker of increased risk of peptic disease and gastric cancer (also known as bacterial oncoprotein), inhibits apoptotic pathways in epithelial cells, and causes morphological abnormalities, including cell distribution and elongation, and loss of cell polarity.

Helicobacter pylori also indirectly promotes cancer by altering the composition of the stomach microbiome. In previous basic studies, the stomach of healthy patients was thought to be sterile, however, with the development of single-cell rRNA genes and DNA sequencing, it has been found that the stomach contains a complex microbial ecosystem composed mainly of bacteria from Proteus, Firmitella, actinobacillus, bacterioides, and Fusobacteria [19]. The gastritis caused by *Helicobacter pylori* is mainly caused by gastric antrum or gastric corpuscle. In antrus-dominated gastritis, increased gastrin secretion caused by *Helicobacter pylori* leads to more gastric acid production, which makes patients more susceptible to duodenal ulcers but can protect them from stomach cancer. In corpuscular gastritis, *Helicobacter pylori* inhibits acid production through inflammatory mediators, resulting in progressive loss of gastric glands and ultimately atrophic gastritis. Reduced gastric acid secretion allows other microorganisms to proliferate in the stomach [17]. How the altered flora works with *H. pylori* to induce cancer is not fully understood. One hypothesis is that some of these microorganisms (nitrosating bacteria, a type of bacteria responsible for the oxidation of ammonium to nitrite during nitrification, which enables nitrosa-

tion) may convert nitrogen compounds in gastric juice into potentially carcinogenic N-nitroso compounds (NOCs) [20], including *E. coli*, Lactobacillus, spirulina nitrite, Clostridium, Vesterella, Haemophilus, and Staphylococcus, which can all produce NOCs. Lertpiriyapong *et al.* [21] using an INS-GAS mouse model (in which insulin promoters regulate overexpression of gastrin), it was demonstrated that *H. pylori* infection and co-colonization of other intestinal flora have a higher propensity to cause gastrointestinal intraepithelial neoplasia (GIN), underscoring the importance of the gastric microbiota in the development of gastric cancer. However, there is no consensus on which bacteria dominate and may be involved in causing cancer, there is no general consensus. Jo *et al.* [22] showed that the number of nitrosifying bacteria in gastric cancer patients without *H. pylori* infection was twice that of the other three groups, but it was not significant, which supported the hypothesis that NOCs played a role in cancer occurrence. Five potential cancer-promoting bacteria were identified: Lactobacillus, Shigella, spirulina nitrate, Burkholderia and Lactobacillus. Among them, Spirillum nitrate was found in all GC patients, but not in patients with chronic gastritis [23]. However, these findings have been inconsistent across relevant studies. Schulz *et al.* [24] and Coker *et al.* [25] found through swallowing that some oral symbiotic bacteria in saliva are sources of gastric microflora. Compared with patients with atrophic gastritis or intestinal metaplasia, the abundance of oral bacteria was significantly higher in GC patients. By neural network analysis, the oral peptostreptococcus, Parvoomonas minima, angiotensor streptococcus and *Bacillus carinii* were the most important. A scoring system for oral microbiota detection was established for GC screening, with a sensitivity rate of 97% and a false positive rate of 7.7% [26]. Eun *et al.* [27] and Wang *et al.* [23] found more diverse microflora in gastric cancer patients, and significantly increased bacterial content in patients infected with *Helicobacter pylori*. These two studies proved that there was a positive correlation between the two, contrary to other research results. It is possible that this difference is due in part to a combination of factors that affect the gut microbiota, including sex, age, ethnicity, and *H. pylori* infection. However, since the decrease in bacterial diversity is associated with the development of colorectal cancer, it is reasonable to speculate that the decrease in bacterial diversity may also be related to the development of gastric cancer.

In view of the important role of *H. pylori* in the occurrence and development of gastric cancer, eradication of *H. pylori* infection in the stomach has become an important idea for the prevention and treatment of gastric cancer. The study of Jo *et al.* [22] showed that eradication of *H. pylori* could prevent the increase of nitrosifying bacteria in the previously infected group. However, a randomized controlled trial that enrolled 1630 *Helicobacter pylori* carriers and followed them for 7.5 years did not find any benefit from radical treatment of *helicobacter pylori*, and further subgroup analyses showed that eradication of *helicobacter pylori* significantly reduced the incidence of GC in patients without precancer-

ous lesions such as gastric atrophy, intestinal metaplasia, and gastric dysplasia. The results indicated that *H. pylori* had a limited role in carcinogenesis at a specific time point. On the other hand, the role of other gastric microflora in the occurrence and development of gastric cancer has also become a research hotspot [28].

4. Intestinal Flora and Colorectal Cancer

There are about 40 trillion bacteria in the gut, which play a role in digesting food components, synthesizing essential vitamins, stimulating and regulating the immune system, eliminating pathogens, removing toxins and carcinogens, supporting intestinal functions, etc. The imbalance of its flora will also affect the occurrence and development of colorectal cancer. Weisburger *et al*. [29] used N-methyl-N0-nitro-n-nitroso-n-nitrosamine-induced germ-free rats to demonstrate for the first time the relationship between intestinal flora and colon tumors. Colon cancer occurs as a prodromal symptom of adenomas and serrated polyps. A recent case-control study evaluated selected fecal bacteria in several groups of patients with various colon polyps between 2015 and 2018 with healthy controls from an ethnically diverse Iranian population using standard screening colonoscopy and absolute quantitative real-time polymerase chain reaction techniques. The number of *Clostridium nucleatum* was higher than that of Faecobacter, *Bacillus bovis*, *Bacillus fragilis* enterotoxigenes and porphyromonas. The number of Lactobacillus, Rosinia and Bifidobacterium was lower. The expression was higher in patients with tubular adenoma and villi/tubular lobe polyps than in healthy controls and in patients with proliferative or sessile serrated polyps (SSP) [30]. Sze *et al*. [31] found that after treatment, the microbiota of colon cancer patients returned to normal and was closer to that of normal colon patients than that of colorectal adenoma patients. Numerous studies have been conducted to determine the carcinogenicity of various bacteria, and Alozle *et al*. [32] found that B. St. Petersburgolytica was closely associated with the development of colorectal cancer after the onset of bacteremia. According to Corredoira *et al*. [33], there was a higher incidence of colorectal tumors in patients with bacteremia infected with St. Petersburg cholystica who underwent colonoscopy. Geis *et al*. [34] found that *E. fragilis* is highly expressed in the gastrointestinal tract of colorectal cancer and may induce inflammation through helper and regulatory T cells. Nucleobacteria, *Escherichia coli*, and *Bacillus fragilis* have also been sporadically reported in colon cancer cases [35]. Although there are a large number of studies on the pathogenic role of bacteria in colorectal cancer, there is no bacterial group closely related to the occurrence and development of colorectal cancer, or the occurrence of colorectal cancer is the result of the joint action of concentrated bacteria, and more studies are still needed to confirm.

Several mechanisms have been proposed to explain the involvement of intestinal flora in colorectal cancer. These mechanisms mainly involve interactions

between host factors (high-fat diet, obesity, etc.), oxidative stress, DNA toxicity, antigen-presenting cells of dendritic cells (antigen-presenting cells) or macrophages, and T cell-mediated adaptive immune responses [36]. The gut microbiota can induce inflammation, especially chronic inflammation, which plays an important role in the development of tumors. *Escherichia coli* may promote colorectal cancer in interleukin-deficient mice treated with azomethane, a carcinogen in the colon. Other mechanisms may include activation of the inflammatory nuclear factor-κB (NFKB) signaling pathway and T-cell-mediated adaptive immune responses, which have been linked to Fusobacterium excess with colorectal adenomas and cancer [37]. Macrophage barrier defects in intestinal microbiota flora may be associated with colon cancer [38]. Cancer growth may also be promoted by the proinflammatory environment created by the gut microbiota, which is associated with reduced natural-killer cell cytotoxicity [39]. Current evidence suggests that biological disorders may cause CRC through inflammation or T-cell-mediated immune responses, but the origin of inflammation is unclear. Host factors should also be considered, a recent study reported that the gut microbiota flora may mediate inflammation associated with gastrointestinal cancer in obese patients [40], and a study by Yang *et al.* [41] found that a high-fat diet can promote colorectal tumors. The specific mechanism by which intestinal flora promotes the occurrence of cancer is still unclear. The study of inflammatory cells has been considered as the main pathogenic mechanism, but the role of other factors in colorectal cancer cannot be ignored.

Treatments that target the gut microbiota, such as fecal microbiota transplants, probiotics, and synbiotics (multiple probiotics that act together) also known as fecal microflora transplantation, fecal microflora transplantation from a healthy donor can restore a patient's normal gut microbiota [42]. A 2015 systematic review by Rossen *et al.* found that fecal microbiota transplantation is highly effective against *Clostridium difficile* infection, promising to treat ulcerative colitis and significantly improve insulin sensitivity in male patients with metabolic syndrome. In theory, fecal microbiota transplantation can restore colorectal cancer-associated dysbiosis and reduce microbiota-induced inflammation, proliferation, and precancerous responses, as well as genotoxicity; however, it has not been well studied in colorectal cancer [43]. Regarding the use of probiotics or synbiotics in colorectal cancer, most studies have been conducted in animal models or in vitro. In 2007, Mai *et al.* [44] found that a high-olive oil diet combined with freeze-dried fruit and vegetable extracts changed the overall composition of intestinal microflora and reduced the development of intestinal adenomas in ApcMin mice. That is, this intervention provides an additional anti-tumor effect to the carcinogenic effect. However, as for the effect of probiotics on colorectal cancer, a large number of studies have only revealed their potential prospects, and there is no clear evidence [45]. Whether the normalization of intestinal microflora can increase the survival rate of patients is worthy of further study.

5. Prospects

Gastrointestinal flora, as a large and complex microscopic ecosystem, plays a very important role in maintaining the normal physiological state of the human body. Due to the diversity, structure and complexity of its metabolites, the gastrointestinal flora plays a very important role in the digestive system, the circulatory system and even the nervous system. Understanding the regulation of flora and metabolite is of great value and significance in scientific research and clinical practice, and it has always been a research hotspot in the treatment of various diseases including gastrointestinal tumors.

Conflicts of Interest

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

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