Intestinal Microbiomes In Gastrointestinal Cancer

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Abstract. The intestinal flora, a crucial system of microorganisms in the human body, is crucial to the immune system, metabolism, and inflammatory response of the body. The intestinal flora is one of them, and as a crucial element of the gastrointestinal microecology, it has a significant impact on the development and spread of gastrointestinal cancer as well as its management. The study of intestinal flora has become more in-depth recently as a result of the quick advancement of high-throughput sequencing technology, and the role of intestinal flora in the development and prognosis of gastrointestinal cancer is becoming increasingly obvious. In this article, the key topics covered include the links between Helicobacter pylori and gastric cancer, as well as the relationship between Fusobacterium and colon cancer, and discusses the mechanism by which intestinal microbes affect the treatment of gastrointestinal cancer. The link between gut microbiota and gastrointestinal cancer was further clarified, and the regulation of gut microbiota was proposed as a new management method for the clinical gastrointestinal cancer treatment.

Keywords: Intestinal Microbiomes; Gastrointestinal Cancer; Cancer Treatment.

1. Introduction

The role of some bacteria in carcinogenesis has been well established, including Helicobacter pylori (H. pylori), which causes stomach cancer, and Fusobacterium, which causes colon cancer. More over 50% of the population all around the world has infection of Helicobacter pylori . H. pylori has been closely associated with a wide range of gastrointestinal illnesses ever since its discovery. One of the recognized risk factors for stomach cancer has been shown to be Helicobacter pylori infection. The third most common cancer and the fourth most common cause of cancer-related death is colorectal cancer (CRC)[1]. One of the most abundant bacterial species in the tissues of colorectal cancer is fusobacterium. In this review, we will discuss how Helicobacter pylori contributes to the development of gastric cancer by causing inflammation of the stomach mucosa and altering the epigenome of vital tumor suppressor genes, and Fusobacterium promotes colorectal cancer by recruiting bone marrow-derived immune cells and releasing Fad protein to achieve anti-tumor immunosuppression and promote tumor angiogenesis. Gastrointestinal microbes not only promote the occurrence and development of gastrointestinal cancer but also affect the treatment and postoperative recovery of gastrointestinal cancer surgery. We will further discuss the treatment of gastrointestinal cancer from the microbial changes after gastrointestinal surgery, and the effects of chemotherapy drugs and radiotherapy drugs on microbes.

2. Helicobacter pylori and stomach cancer

Gastric cancer is the biggest reason for cancer-related deaths worldwide.Chronic infections, caused by Helicobacter pylori, all play a role in the development of stomach cancer[2]. There are two main ways that H. pylori infection can lead to the development of gastric cancer: the bacteria can affect the cells indirectly by causing inflammation, or they can affect gastric epithelial cells directly by causing protein modification and gene mutation[3].

2.1. Helicobacter pylori mediated gastric mucosal inflammation and gastric cancer

Studies have revealed a link between the severity of gastritis and a patient's chance of developing stomach cancer in cases when Helicobacter pylori is present in the stomach[3]. In chronic gastritis mucosa caused by Helicobacter pylori, T cells are numerically superior to other immune cells, such as granulocytes/monocytes and plasma cells. Gastric epithelial cells, dendritic cells (DCs), and macrophages recognize and present H. pylori-derived antigens, creating a complex cytokine milieu that promotes the differentiation of different T cell lineages, including Th1 cells (characterized by IL-12, 18, TNF-a, IL-1β), Th2 cells (IL-4, IL-5, IL-10), Th17 cells (IL17A, F, IL-23) and Treg cells (TGF-β1, IL-10)[4].

They mutually induce and regulate a complex network of T cells to maintain the balance of the immune system. When cytokines regulate and induce imbalance in the balance of the immune system, it will lead to immune system dysfunction and reduce the body's resistance. H. Pylori-induced gastritis is characterized by enhanced production of various proinflammatory cytokines in the gastric mucosa, which are believed to play an important role in the development of cancer. TNF-α, IL-1β, IL-6, IL-7, and IL-8, increase their expression in Helicobacter pylori mediated gastritis,which has been proved[5, 6].

Among them, IL-1β and TNF-α enhanced NF-κB activation activity. The induction of NF-κb activity by H. pylori strains carrying 40kb gene cluster named cag pathogenicity island (cagPAI) was 10.8 times higher than that of cagpai-negative strains, due to the fact that the majority of the cagPAI-encoded products are part of the bacterial type 4 secretion system (T4SS), which translocates the bacterial effector CagA from H. pylori into the cytoplasm of the host cell and binds T4SS to a number of plasma membrane receptors in host cells to trigger signaling that activates NF-κB[7].

Studies have found that NF-κB can activate FLICE inhibitor protein (FLIP), which inhibited apoptosis induced by Fas-associating protein with a novel death domain(FADD). FADD is a Fas-associating protein with a death functional region. When Fas binds to the corresponding ligand FasL (CD95L), the Fas receptor trimerizes and is activated. The activated Fas receptor binds to FADD and then interacts with caspase-8, 10 to activate caspase-8, 10, forming a death-inducing signal complex. Then a series of caspase-3, 6, 7 and so on are activated to promote the apoptosis of the cells where Fas protein is located. Therefore, NF-κB signaling cascade accounts as one of important triggers in inflammation-induced gastrointestinal malignancies. Secondly, because advanced gastric cancer cells express a high level of connective tissue growth factor (CTGF), which activates NF-κB and down-regulates E-cadherin to encourage gastric cancer invasion and metastasis, NF-κB, the key signaling player in the process of gastric cancer invasion and metastasis.[8]. Cytokines/chemokines, growth factors, cIAPs that prevent apoptosis, the angiogenesis regulator vascular endothelial growth factor (VEGF), matrix metalloproteinases (MMP)-2, and others are examples of NF-κB-driven gene products.[2]. These NF-κB-driven gene products all promote the occurrence of gastric cancer.

2.2. Helicobacter pylori causes stomach cancer by influencing epigenetics

Gastric cancer caused by Helicobacter pylori is a typical inflammatory malignant tumor[9]. Helicobacter pylori can induce epigenetic modification of critical tumor suppressor genes during the development of gastric cancer. There are many different types of epigenetic alterations, but the most prevalent ones include DNA methylation, point mutation, deletion, duplication, and recombination. The most frequent type of gene silencing thought to contribute to the development of cancer is methylation, which takes place in CpG islands, which are regions of gene promoters that are rich in the nucleotide cytosine-guanine[10].

Major tumor suppressor genes frequently experience promoter hypermethylation during H. pylori-induced chronic gastritis and gastric carcinogenesis[9]. For instance, in gastric cancer cell lines, genome demethylation revived FOXD3 expression. The invasion of gastric cancer cells were greatly reduced by transgenic overexpression of FOXD3[11]. Hypermethylation brought on by H pylori infection, however, can free tumor suppressors from FOXD3-mediated transcriptional regulation. The expression of the gene encoding the DNA repair protein O6-methylguanine DNA

methyltransferase (MGMT) is reduced by hyper-methylation of its promoter in individuals with H pylori gastritis, which may upset the balance between cell death and survival and cause gastric cancer[12].O6-methylguanine can be repaired by methyltransferase (MGMT), an enzyme, in order to stop transition mutations from occurring during DNA replication. Therefore, reducing MGMT levels can increase mutations in gastric epithelial cells, thereby promoting the occurrence of gastric cancer. In addition to the above two genes, several other tumor suppressor genes such as RUNX3, Trefoil factor family 2, E-cadherin and p16 also undergo aberrant methylation-induced silencing[13-15].

3. Fusobacterium and colorectal cancer

3.1. Fusobacterium in microenvironment

Some researcher found that adenoma tissue contained more Clostridium bacteria than surrounding non-adenomatous tissue, and that fecal samples from adenoma patients also contained more Fusobacterium compared to the healthy group[16]. Another of their experiments demonstrated that in mouse models of colorectal cancer, mice infected with Clostridium had higher tumor burdens, tumor-associated macrophages in tumor tissue, and bone marrow-derived CDb11 cells were more abundant[17]. Similar research from Coussens revealed that tumor-associated macrophages were 7.8 times more prevalent in the tumor tissue of mice fed Clostridium than they were in the control group, and interestingly, the content of CD4T cells in the tumor tissue of mice fed to the Clostridium group was also significantly reduced. Previous research has demonstrated that CDb11 cells are able to speed up the production of blood vessels to promote tumor development [18].Tumor-associated macrophages can also promote tumor development by secreting growth factors and mediator[19]. Angiogenesis of tumor tissue is regulated by many factors, of which angiogenic factor (VEGF) is one of the important factors. Interestingly, the researchers found that Clostridium was able to upregulate VEGF expression by infecting epithelial cell[20]. Previous experiments have shown that in the colorectal cancer tissue microenvironment. Fusobacterium often plays a key role in promoting the development of cancer,especially in promoting angiogenesis.

3.2. Virulence factors

Current studies have shown that Clostridium spp. is strongly associated with colorectal cancer. An in vitro experiment found that the adhesin FadA of Clostridium spp. upregulated the expression of annexin A1 through E-cadherin, thereby stimulating the growth of colorectal cancer cells. annexin Annexin A1 is a regulator of Wnt/β-catenin signaling, which is associated with the activation of cyclin D1 and is crucial for controlling the cell cycle, is regulated by annexin A1. At the same time, the study also found that there is a positive feedback regulatory mechanism between adhesin FadA and annexin A1 in cancer cells, which is significantly different from normal tissue cell[21]. Similarly, Guo et a[22]. found that the Clostridium nucleus induces colorectal cancer through the FadA-dependent activation of the E-cadherin/β-catenin pathway, while Clostridium also promotes DNA damage and cell proliferation so that the cell cycle does not stay in the S phase. Additionally, a meta-analysis research involving 4150 CRC patients revealed that overexpression of cyclin D1 was linked to both distant metastases and a worse overall survival rate.

In summary, the adhesin FadAs of Clostridium are a virulence factor that promotes the progress of colorectal cancer, which is often closely associated the metastasis of colorectal cancer and poor prognosis

4. Interaction between gastrointestinal tumors and microorganisms after treatment

4.1. Microorganisms' changes after gastrointestinal cancer surgery

The intestinal flora has the functions of promoting the intake of nutrients by the digestive system, regulating the immunity of the body and resisting the invasion of pathogenic microorganisms. The type and number of intestinal microflora are affected by different factors, such as the secretion of gastric acid, intestinal motility, gastrointestinal surgery, etc. Among them, cancer surgery is the trickiest factor. First of all, due to the decreased gastric acid secretion and gastrointestinal motility disorder after surgery, the microbial balance will be broken in the gastrointestinal tract. Secondly, the administration of broad-spectrum antibiotics after surgery may inhibit the function of normal flora, leading to the proliferation of drug-resistant harmful microflora, with the occurrence of symptomatic gastrointestinal episodes, such as the excessive passage of gas, foul smell of flatulence, belching, heartburn, abdominal noises, abdominal bloating, and abdominal pain[23]. Thirdly, surgical trauma may alter the permeability of the intestinal mucosa, which not only causes local inflammation but also leads to the disorder of gastrointestinal flora, which in turn aggravates inflammatory respons[24]. Moreover, surgery also affects the number of intestinal microflora, as reported, the relative abundance of intestinal Bifidobacterium and Lactobacillus acidophilus decreased, while the Escherichia coli and Streptococcus usually increased after colon resection in colorectal cancer patient[25]. Therefore, gastrointestinal surgery poses great challenges for microflora stabilization.

4.2. Gastrointestinal microorganisms affect chemotherapy efficacy

Chemotherapy, the most common treatment for gastrointestinal cancer, also has an impact on the intestinal microflora. For example, Viaud et al. have demonstrated that intestinal microflora could participate in the potentiation of immune response triggered by cyclophosphamide[26]. In detail, after the destruction of the intestinal mucus layer by cyclophosphamide, specific gram-positive bacteria can transport to the secondary lymphoid organs, promoting the production of "pathogenic" helper T cells 17 (pTh17) and eliciting Th1 immune responses. pTh17 cells can activate granulocytes, natural killer cells (NK cells), and other immune cells by secreting cytokines IL-17, IL-6, TNF-α, etc. and the activated immune cells can promote anti-tumor efficacy by phagocytosing or lysing cancer cells, which improve the therapeutic effect of cyclophosphamide. However, in germ-free mice and in mice administrated with antibiotics to kill gram-positive bacteria, the enhanced immune response disappeared, suggesting that the intestinal microflora play an important role in anti-tumor adjunctive therapy.

Similar results have also been reported in other studies, for example, Iida et al. found that intestinal bacteria can induce myelin cells to release reactive oxygen species(ROS), while this effect significantly reduced in the antibiotic-treated mouse group[27]. The increased level of ROS can induce apoptosis by eliciting a cytotoxic effect, leading to significant cell death in cancer cells. Through this pathway, intestinal bacteria can improve the efficacy of oxaliplatin against cancer. Moreover, Scott et al. investigated that the gut microbiome can assist 5-FU to induce cancer cell death. 5-FU, an anti-metabolite chemotherapy drug, can inhibit the function of thymidylate synthase and interrupt the synthesis of cellular DNA. The researchers found that the gut microbiome can also restrict the function of nucleoside diphosphate kinase NKD-1, further inhibiting cellular DNA synthesis, thereby promoting autophagy and apoptosis of cancer cells, which further enhances the therapeutic effect of 5-FU[28]. As a result, it is clear that the intestinal flora is crucial to the adjuvant therapy for anti-tumor treatment.

However, researchers also discovered some adverse effects of intestinal microflora on chemotherapy. Gelle et al. reported that the pig mycoplasma metabolizes gemcitabine (2-deoxy-2,2-difluorodeoxycytidine) into inactive 2,2-difluorodeoxyuridine, which leads to undesirable drug resistance. In addition to mycoplasma, a number of bacteria can also induce gemcitabine resistance. For example, γ-proteobacteria, a gram-negative bacillus, can help the synthesis of cytidine deaminase,

while gemcitabine works by inhibiting the activity of nucleotide reductase to interrupt DNA synthesis. Therefore, gamma-proteobacteria will reduce the therapeutic effect of gemcitabine[29]. This phenomenon has also been discovered in mouse colon cancer models conducted by Voorde, et al. and they found gemcitabine resistance can be eliminated by administration of ciprofloxacin due to the killing bacteria effect[30].

4.3. Effects of radiation therapy on microorganisms

Radiation therapy plays a pivotal role in almost all cancer treatments, however，numerous bacteria are radiation-sensitive and can alter the microbiota's makeup, which may have an impact on the therapeutic results and perhaps induce some adverse reactions. Numerous investigations have demonstrated that diarrhea after radiation therapy is mainly related to the imbalance of the gut microbiome[31]. Specifically, patients without radiation enteritis have a higher diversity of gut microbiota than patients with post-radiation enteritis. In addition to the diversity, the number of microbiota can also be affected. In patients with enteritis, the abundance of bacilli, bacilli, mycobacteria, and Verlococcus was low, while the abundance of Clostridium, Clostridium, Gram fiber and Prevobacteria was relatively high. Generally, these intestinal microbiotas had a lower Pachychycetes/Bacteroides ratio[32]. Moreover, after pelvic-abdominal radiation therapy, an increased level of bacilli and actinomycetes and a decreased level of Clostridium Clostridium in the feces can be found in radiation enteritis patients[33]. Taken together, radiation therapy may cause intestinal flora disorders, which in turn induce some side reactions, such as the occurrence of radiation enteritis, diarrhea, vomiting and so on. Therefore, we should keep these intestinal microflorae in order to prevent adverse reactions during radiotherapy.

In general, intestinal microflora can have both better and worse effects on chemotherapy against cancer. We can grasp the related advantages to improve cancer therapy and also we should take action to avoid the bad impacts through the combination of antibiotics or other strategies.

5. Conclusions

The stability of microbes in the gastrointestinal tract is crucial for keeping body in a healthy state. Abnormal colonization of maleficent bacterias, such as Helicobacter pylori, can induce gastritis and even progressively lead to the occurrence of gastric cancer; Abnormal proliferation of maleficient bacterias, such as Clostridium SPP also shows potential to induce colorectal cancer and even accelerate the course of the disease, etc. Apart from that, in patients with gastrointestinal cancer, whether surgical resection, chemotherapy or radiotherapy, the prognosis will be affected by gastrointestinal microbes. Gastrointestinal microbes can help improve therapeutic efficacy through synergistic immune activation or ROS responses, while also participating in drug metabolism, thereby reducing efficacy. But in most cases, the inflammation and diarrhea caused by intestinal disorders after the above-mentioned therapeutic intervention can further interfere with the prognosis of cancer diseases. In general, gastrointestinal microbes play key roles in the occurrence and progress t of gastrointestinal cancer, and it is necessary to conduct more in-depth studies to explore more effective therapeutic strategies for gastrointestinal cancer.

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