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REVIEW

Novel cancer therapy targeting microbiome

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Abstract: In the human intestinal tract, there are more than 100 trillion symbiotic bacteria, which form the gut microbiota. Approximately 70% of the human immune system is in the intestinal tract, which prevents infection by pathogenic bacteria. When the intestinal microbiota is disturbed, causing dysbiosis, it can lead to obesity, diabetes mellitus, inflammatory bowel disease, rheumatoid arthritis, multiple sclerosis, autism spectrum disorder and cancer. Recent metabolomics analyses have also made the association between the microbiota and carcinogenesis clear. Here, we review the current evidence on the association between the microbiota and gastric, bladder, hepatobiliary, pancreatic, lung and colorectal cancer. Moreover, several animal studies have revealed that probiotics seem to be effective for the prevention of carcinogenesis to some extent. In this review, we focused on this relationship between the microbiota and cancer, and considered how to prevent cancer using strategies involving the gut microbiota.

Keywords: dysbiosis, prebiotics, probiotics, antibiotics

Introduction

Gut microbiota

The human microbiota is a complex ecosystem of bacteria, viruses and fungi resident on or in the skin, oral cavity, lungs, intestines and vagina.[1] The human gastrointestinal tract is colonized by a complex and abundant microbial community of 10^{13} to 10^{14} microorganisms in the colon.[2,3] *Firmicutes, Proteobacteria, Bacteroidetes* and *Acinetobacteria* are major residents in normal bowels.

The commensal microbiota is a major regulator of the host immune system. Indeed, early innate immunity to *Klebsiella pneumoniae* in the lungs is regulated systemically by the commensal gut microbiota via Nod-like receptor (NLR) ligands.[3] Segmented filamentous bacteria (SFB) not only induce cells that produce immunoglobulin A (IgA) and intraepithelial lymphocytes (IELs), but also promote host defense reactions and the accumulation of T helper type 17 (Th17) cells, which produce interleukin (IL)-17.[4,5] Moreover, *Clostridium* enhances the differentiation and proliferation of regulatory T (Treg) cells.[6,7]

In addition to these functions, the microbiota has a role in the synthesis of vitamins and short-chain fatty acids from dietary fiber such as acetic acid, propionic acid and butyric acid. Although acetic acid and amino acids do not have a role in the differentiation and induction of Treg cells, butyric acid has a crucial role.[8] Additionally, short-chain fatty acids bind to G protein-coupled receptors and regulate obesity.[9] Numerous clinical studies have revealed that disruption of host–commensal interactions (dysbiosis) can lead to a variety of diseases and conditions,[10–22] including cancer,[16] chronic intestinal inflammation,[20,23] autoimmunity[22] and impairment of the self-protection mechanisms against bacteria, viruses and parasites.[10,12,24–32]

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Lofgren et al demonstrated that germ-free INS-GAS mice were slower to develop atrophic gastritis and gastric cancer than specific pathogen free (SPF) INS-GAS mice.[33] This result suggest that the gastric microbiota contributes to gastric cancer.

Microbiota and cancer

Several studies have shown that the colonic microbiota is associated with the development of colorectal cancer. In a chemically induced mouse model of colorectal cancer, transplantation of the fecal microbiota from colorectal cancer patients to germ-free mice increased susceptibility to colonic tumorigenesis.[34]

The hypotheses regarding the microbiota-related mechanisms of carcinogenesis in colorectal cancer include the following: the alpha-bug hypothesis, driver-passenger hypothesis, biofilm hypothesis and bystander effect hypothesis.[35] The alpha-bug hypothesis posits that specific pathogenic bacteria induce colorectal cancer. For example, enterotoxigenic *Bacteroides fragilis* (ETBF) secretes *Bacteroides fragilis* toxin (BFT), which decreases E-cadherin levels. This loosens the attachments between intestinal epithelial cells and results in exposure to many antigens.[36] Moreover, decreased E-cadherin promotes intracellular migration of β-catenin and accelerates carcinogenic-related signaling such as Wnt signaling. The driver-passenger hypothesis postulates that other bacteria, that is, passenger bacteria that adapt to the tumor environment produced by the driver bacteria, proliferate, leading to carcinogenesis. *Fusobacterium nucleatum* has an antagonistic effect against probiotics and has a role as a tumor-associated bacterium or oncobacterium.[37,38] The biofilm hypothesis suggests that biofilm, produced by the gut microbiota, is associated with colorectal cancer carcinogenesis, which involves lack of E-cadherin or activation of signal transducers and activator of transcription (STAT)-3. Lastly, the bystander effect hypothesis involves gut microbiota-produced metabolites that induce colorectal cancer carcinogenesis.

Deoxycholic acid and lithocholic acid, secondary bile acids produced from bile acids by intestinal bacteria, induce DNA damage and contribute to carcinogenesis.[39] In mice that are prone to developing cancer, mice with diet-induced and hereditary obesity develop significantly more liver cancer than mice on a normal diet.[40] Moreover, deoxycholic acid-induced DNA damage in hepatic stellate cells in the liver interstitium become senescent and secrete many inflammatory cytokines and proteases (senescence-associated secretory phenotype, SASP). These promote carcinogenesis and form a microenvironment that further promotes carcinogenesis. IL-1β promotes liver cancer carcinogenesis. Intriguingly, in obese mice administered oligosaccharides that inhibit deoxycholic acid and ursodeoxycholic acid production (which promotes external release of bile acids), the incidence of liver cancer and hepatic stellate cell senescence are remarkably decreased. Moreover, lipoteichoic acid, which is a component of Gram-positive bacterial walls and a ligand of Toll-like receptor 2 (Tlr2), increases in liver cancer and upregulates cyclooxygenase-2 (Cox-2) expression.[41] Increased Cox-2 expression induces the overproduction of prostaglandins. An antagonist of prostaglandin E2 receptor 4 (EP4) has been shown to decrease liver tumors in obese mice.[42] In addition, the EP4 antagonist also decreases programmed death-1 (PD-1)-positive CD8-positive T and Treg cells.

Several studies showed that bladder microbiome was related to urothelial cell carcinoma pathogenesis or progression.[43] Bladder microbiome act as a noninvasive biomarker and can be a target of immunotherapy agents such as intravesical bacillus Calmette-Guerin.

Oral microbiota and pancreatic cancer

The human oral cavity is colonized by many bacteria, including about 600 prevalent taxa at the species level.[44] Indeed, the Human Oral Microbiome Database (HOMD) includes 619 taxa in the following 13 phyla: *Actinobacteria, Bacteroidetes, Chlamydiae, Chloroflexi, Euryarchaeota, Firmicutes, Fusobacteria, Proteobacteria, Spirochaetes, SR1, Synergistetes, Tenericutes* and *TM7*. The association between the salivary microbiota and pancreatic cancer has been analyzed using the Human Oral Microbe Identification Microarray,[45] and two out of six bacterial candidates (*Neisseria elongate* and *Streptococcus mitis*) had significantly lower levels in pancreatic cancer patients than in the control group ($P<0.05$). Another prospective cohort study analyzed 361 patients with incident pancreatic cancer and 371 matched controls and revealed that *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* were associated with a higher risk of pancreatic cancer (odds ratio: 2.20, 95% confidence interval: 1.16 to 4.18). In contrast, the genus *Leptotrichia* and its phylum *Fusobacteria* were associated with a lower risk of pancreatic cancer (odds ratio: 0.87, 95% confidence interval: 0.79 to 0.95).[46]

Gut–lung axis and lung microbiota

Lung cancer is a disease with poor prognosis, and the development of further preventive strategies is important. The concept of the "gut–lung axis" involves immune cells (such as T and B cells) that are activated by the gut microbiota, carried to the lungs by lymphatic or hematogenous spread, activate lung immune cells, and induce respiratory diseases such as asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis and respiratory infection.[47–50]

It has been reported that the lung microbiota and oral microbiota are involved in lung carcinogenesis.[51–53] Salivary *Capnocytophaga, Selenomonas, Veillonella* and *Neisseria* were significantly altered in patients with squamous cell carcinoma (n=10) and adenocarcinoma (n=10) compared with control subjects (n=10).[52] In another study, although the sample size was small (n=8/group), the bacterial diversity in sputum samples was significantly different between lung cancer patients and control subjects (P=0.038).[54] Lung cancer cases had more *Granulicatella* (6.1% vs 2.0%; P=0.0016), *Abiotrophia* (1.5% vs 0.085%; P=0.0036) and *Streptococcus* (40.1 vs 19.8%; P=0.0142) than the control subjects.[54] Another study revealed that *Granulicatella adiacens* had a higher abundance in sputum samples of four patients with lung cancer compared to six control subjects.[55] Analysis of bronchoalveolar lavage fluid (BALF) from 20 patients with lung cancer and eight control subjects revealed that the levels of two phyla (*Firmicutes* and *TM7*) were significantly increased in the patients with lung cancer (P=0.037 and 0.035, respectively).[56] Moreover, a study analyzed bronchoscopic specimens from 24 patients with lung cancer and 18 healthy controls and revealed that the genus *Streptococcus* was significantly more abundant in the lung cancer patients and, for predicting lung cancer, the area under the curve (AUC) of *Streptococcus* was 0.693 (sensitivity =87.5%, specificity =55.6%).[51]

Cancer prevention

The following treatment methods are being studied for controlling intestinal bacteria: improvement of gut microbiota dysbiosis, administration of prebiotics, which regulate the gut microbiota, administration of probiotics, which activate T cells, and administration of antibiotics.[57] When high-fat diets were administered to *K-ras*^{G12Dint} mice, tumors were formed in the small intestine, which was due to dysbiosis rather than obesity.[58] *B. fragilis*-specific CD4-positive Th1 cells enhanced the anti-tumor effect of cytotoxic T-lymphocyte antigen (CTLA)-4 antibody.[59] In addition, *Bifidobacterium* spp. increased the expression of immune-associated genes on spleen or lymph node dendritic cells and induced anti-tumor CD8-positive cells.[60] *Bifidobacterium lactis* decreased the incidence of colorectal tumor in a mouse model[61] and rat model[62] of azoxymethane (AOM)-induced colorectal cancer, by inducing apoptosis or suppressing NF-κB signaling. Probiotics consisting of a mixture of *Lactobacillus rhamnosus* GG and *Lactobacillus casei* Shirota suppress the development of aflatoxin-induced liver cancer in rats.[63] The probiotic product VSL#3, which is composed of *L. casei, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus delbrueckii* subsp. *bulgaricus, Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis* and *Streptococcus salivarius* subsp. *thermophilus*, suppressed trinitrobenzene sulfonic acid (TNBS)-induced colitis-related colorectal cancer in rats.[64] VSL#3 also suppressed the development of diethylnitrosamine (DEN)-induced liver cancer by improving the gut microbiota and suppressing the release of endotoxin from the intestines to the blood.[65] Probiotics consisting of a mixture of VSL#3, *L. rhamnosus* GG and *Escherichia coli* Nissle 1917 suppressed the growth of a xenograft of the liver cancer cell line Hepa1-6 by decreasing Th17 cells and suppressing cytokine production.[66] When antibiotics were administered to *Apc*$^{Min/+}$*Msh2*$^{-/-}$ mice, the development of colorectal cancer was significantly suppressed.[67]

Clinical trials of probiotics

A prospective cohort study that followed 45,241 participants for 12 years revealed that participants who ingested yoghurt produced by *Streptococcus thermophilus* and *Lactobacillus delbrueckii* subsp. *bulgaricus* had a lower risk of developing colorectal cancer than participants who did not ingest the yoghurt (hazard ratio: 0.62, 95% confidence interval: 0.46 to 0.83).[68] A case-control study comparing 304 female breast cancer patients aged 40–55 years old with 662 subjects matched for age and residential area revealed that those who drank beverages containing *L. casei* Shirota >4 times/week were less likely to experience breast cancer relapse than those who did not (odds ratio: 0.65).[69] Moreover, a randomized controlled trial of postoperative bladder cancer patients showed a significantly higher 3-year relapse-free survival rate in the epirubicin plus *L. casei* Shirota group than the epirubicin-only group (74.6% vs 59.9%, P=0.0234).[70] Patients with colon cancer that received probiotics,

Bifidobacterium lactis Bl-04 and *Lactobacillus acidophilus* NCFM had an increased abundance of butyrate-producing bacteria, especially *Faecalibacterium* and *Clostridiales* spp in the tumour, non-tumour mucosa and faecal microbiota, resulting in the reduction of colorectal cancer-associated genera such as *Fusobacterium* and *Peptostreptococcus*.[71] Recent study showed that a probiotic combination containing *Bifidobacterium infantis, Lactobacillus acidophilus, Enterococcus faecalis* and *Bacillus cereus* reduced the physiological disorders induced by gastrectomy.[72] Another randomized, double-blind, placebo-controlled trial showed that probiotics reduced the severity of oral mucositis induced by chemoradiotherapy for patients with nasopharyngeal carcinoma.[73] However, in cancer patients and immunosuppressed patients, caution is required because probiotic administration may lead to bacteremia directly caused by the probiotic bacteria.[74]

Observations and conclusions

Based on the results of animal experiments, probiotics seem to be effective for the prevention of carcinogenesis to some extent. However, there are few randomized controlled trials in humans, and further studies are necessary.

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