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An Overview of the Role of Microbiomes in the Severity of Colorectal Cancer

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Abstract:

Microbiome means microbes coexisting with the host, regardless of the species, in a part of the body of an organism called microbiome. Nowadays, changes in gut microbiota are considered as a potential therapeutic approach for the prevention or treatment of colorectal cancer (CRC).
Studies have shown that dietary habits and lifestyle play a role in modulating the gut microbiota.
Intestinal microbiota plays a role in converting food components into oncometabolites. Some studies showed that Shigella, Citrobacter and Salmonella bacteria are more abundant in the early stages of cancer compared to healthy people. The aim of this study is to review the role of microbiomes in the development of colorectal cancer and the metabolites produced by microbiomes in the development of colorectal cancer.

INTRODUCTION

During the past few decades, the importance of the microbiome on human health and disease has been increasing. Microbes, which are even more numerous than our own cells, live on the surface and inside our bodies and can protect humans from pathogens and on the other hand regulate immunity and tolerance. The immune system also plays a role (1).

It also helps in digesting many foods that we cannot digest ourselves. However, if their balance is disrupted by antibiotics, immune system disorders or other disorders. They can lead to disease. The focus of microbiomes has largely been on the bacterial diversity of the microbiome.

Because they constitute the largest proportion of living organisms and lead to microbiota. Bacteria exist alongside a variety of microorganisms such as fungi, single eukaryotes and some worms, as well as different families of viruses. All components can affect health and disease with each other and the host.

The clearest interaction occurs between the bacterial and archaeal microbiota and the eukaryotic host.

Studies on animals without microbiota have shown that the lack of microbiota leads to metabolic and immune differences compared to normal animals. In general, the impact of the microbiome on humans can be summarized in two areas. releasing energy and nutrients from food and activating the immune system to promote the host; Due to the fact that bacteria are part of the microbiome, it has attracted the most attention.

The quantity and diversity of microbial species in the intestine increases longitudinally from the stomach to the colon, and the colon microbiota is the most dense and metabolically active community (2).

Although microbiota composition is influenced by genetics (3). Although microbiota composition is influenced by genetics and may be considered relatively stable over time in healthy adults, there is great variability in microbiota composition among individuals. This change is caused by various external environmental factors such as diet, exposure to chemicals and antibiotic/drug use (4).

Alterations of gut microbiota may be used as potential therapeutic approaches to prevent or treat CRC(5). Probiotics such as Lactobacillus and Bifidobacterium inhibit the development of CRC by inhibiting inflammation and angiogenesis and increasing intestinal barrier function through the secretion of short-chain fatty acids (SCFAs) (6). The interplay between lifestyle, host genetics, and gut microbiota is well documented in the prevention and treatment of CRC. Future studies are needed to understand the interaction between the gut microbiota and the host to influence and prevent CRC (7).

The clinical benefits of probiotics in CRC are still unclear. Metagenomic approaches combined with metabolomics and immunology will soon open a new way to treat CRC. Dietary interventions may be suitable for modulating the growth of beneficial microbiota in the gut(7) (Figure 1)

The intestinal microbiome consists of different species of bacteria, fungi, protozoa and viruses (8). Bacteria belonging to Firmicutes and Bacteroidetes predominate in the gut (9).

Gut microbiota plays a role in host physiology such as nutrition, metabolism and immunity (10).

Dysbiosis of the intestinal microbiome plays a role in various human diseases (11).

The gut microbiome is involved in inflammation and biosynthesis of chemical carcinogens such as N-nitroso compounds that cause cancer (12). It is estimated that about 70% of the human microbiome resides in the large intestine (13).

Dietary habits and lifestyle play a role in modulating the intestinal microbiota (14).

People exposed to antibiotics early in life may develop colorectal adenomas later in life (15). Gut microbiome dysbiosis is associated with the development of colorectal cancer (CRC). Gut microbiota plays a role in the metabolic conversion of dietary components into oncometabolites and tumor suppressor metabolites, which in turn affect CRC development (16).

Colorectal cancer (CRC) is classified into two categories: colitis-associated colorectal cancer (CAC) and diffuse colorectal cancer (SCC) (17). Subjects with inflammatory bowel disease converted to CAC. Gut microbiota may contribute to the initiation and development of CRC (17). Ninety-nine percent of gut bacteria cannot be cultured. Ribosomal RNA sequencing from stool or tissue of CRC patients can be used for taxonomic classification of bacteria by DNA isolation from stool samples or tumor tissue samples of CRC patients. 16S rRNA sequencing is able to identify bacterial species at the genus level (18).

The role of the gut microbiome in host cell physiology

Human microbiota colonization has been reported

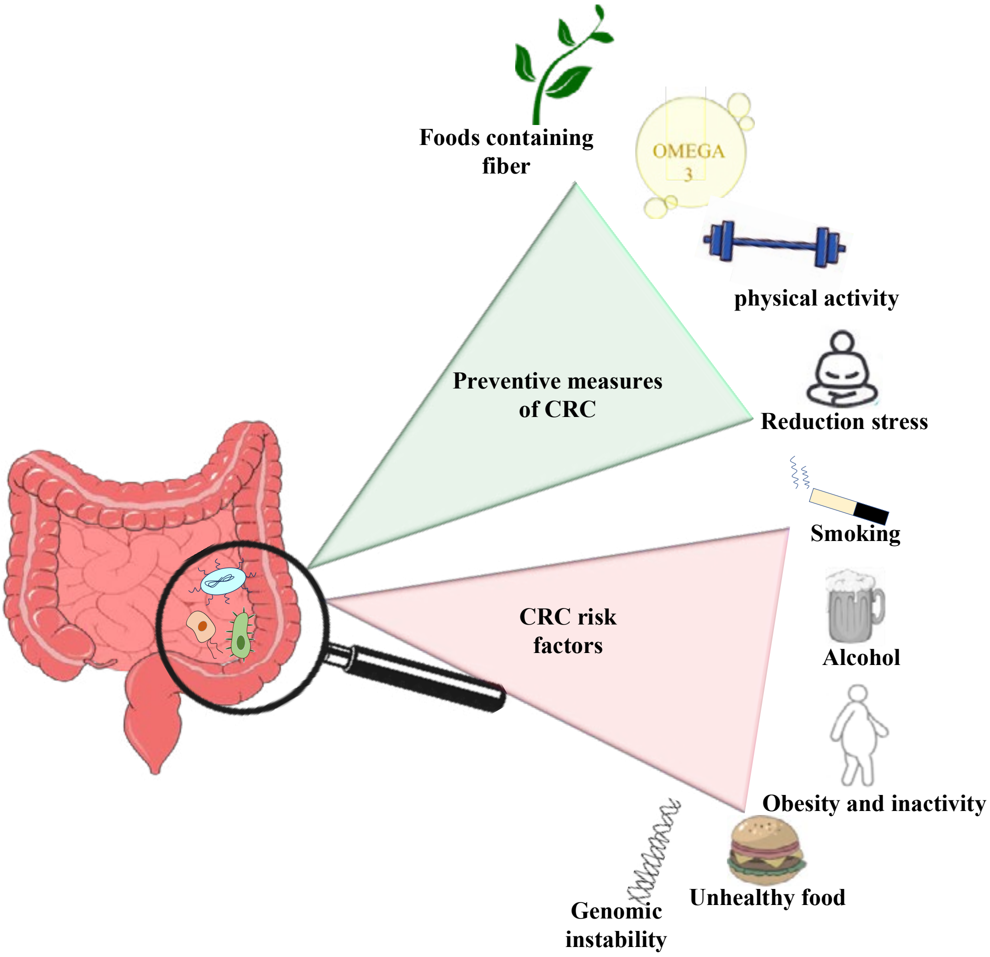

Fig1. Risk factors for CRC and preventive factors for CRC. The type of lifestyle, food pattern can affect the microbial diversity of the gut microbiome as well as the increase and decrease of CRC factors.

in the gastrointestinal tract, oronasopharyngeal cavity, skin, and genitourinary tract. The human body has 10^{14} bacterial cells, which is 10 times more than the number of cells in the body (19). In humans, the colon showed the highest microbial density and species diversity (10^{11} cells per gram of feces). Facultative anaerobes reside in the mucosa of the large intestine, while strict anaerobes reside in the lumen of the colon due to different oxygen tensions (20). A decrease in oxygen tension in the large intestine favors the growth of more bacteria and Firmicutes, followed by Actinobacteria and Veromicrobia(21).

The large intestine is considered a suitable place for bacterial growth due to its high pH, nutrients and low concentration of bile salts and pancreatic secretions (22). Lipopolysaccharide (LPS) of Gram-negative bacteria induces an innate immune function that prevents inflammation (23). Anaerobes such as Bacteroides, Eubacterium, Bifidobacterium, Fusobacterium, Peptostreptococcus, and Atopobium are abundant in the gut, while facultative anaerobes such as Lactobacilli, Enterococci, Streptococcus, and Enterobacteriaceae represent a microbiome of the gut.

Intestinal microbiota plays an important role in host mucosal homeostasis and regulation of epithelial barrier function in the intestine (24, 25). The composition of the host microbiome in the gut is regulated by diet, medications, and other lifestyle factors such as smoking, alcohol drinking, and physical activity (18). The normal intestinal microbiota plays a role in the degradation of nutrients, prevention of colonization of pathogenic bacteria, differentiation of epithelial cells and development of immune cells in the intestine (26). Gram-negative bacteria and Gram-positive Firmicutes predominate in the gut.

Short chain fatty acids (SCFAs) such as acetate, propionate and butyrate are produced by Bacteroidetes, Bifidobacterium, Clostridium, Lactobacillus, Provetella and Propionibacterium. Butyrate induces the anti-inflammatory activity of macrophages and dendritic cells. It also causes the release of anti-inflammatory cytokine IL-10 from the differentiation of Tregs and T cells. Foods rich in probiotics and prebiotics increase the levels of bifidobacterium and butyrate-producing bacteria that play a role in gut homeostasis (9).

IL-33 and TGF-β induce IgA secretion from B cells. Intestinal IgA protects against intestinal microorganisms and toxins. IL-33 blocks IL-1α-dependent CAC development through activation of the IgA-microbiota axis. Antimicrobial siderophore-binding protein lipocalin 2 (LCN2) inhibits the growth of colitogenic microbiota in the intestine (27). Gut microbes have NAD(P)H dehydrogenase (azoreductase), nitroreductase, β-glucuronidase, β-glucosidase, and 7-α-dehydroxylase, which cause cancer (28). In a healthy colon, the majority of microbial metabolism is via saccharolytic fermentation pathways. Bacteria are mainly involved in propionate production while Firmicutes are mainly involved in butyrate production (29). Butyrate showed anti-inflammatory effects by inhibiting the activity of histone deacetylase, reducing the secretion of pro-inflammatory cytokines and activating regulatory T cells expressing FOXP3 (30) . Proteolytic fermentation by Firmicutes and Bacteroides spp are involved in the production of phenols, indoles, amines and ammonia; Proteobacteria are involved in the production of N-nitroso compounds from dietary proteins in the large intestine (31, 32) .Butyrate, mainly produced in the gut by Faecalibacterium prausnitzii and Eubacterium rectale, is involved in cell proliferation, differentiation and programmed cell death in colonic cells (33).

Clostridium species are responsible for the secretion of the anti-inflammatory cytokine interleukin-10 (IL-10) in the intestine through increasing the activity of Treg cells (34). Ursodeoxycholic acid (UDCA, ursodiol), which is a metabolic byproduct of intestinal bacteria, inhibits the expression of cyclooxygenase-2 (COX-2) in CRC cells. It also inhibits deoxycholic acid (DCA) regulation of epidermal growth factor receptor (EGFR) and Raf-1 kinase activity in colon cells (35). The epithelium of the colon is covered by mucin, which prevents the entry of pathogenic bacteria. Akkermansia muciniphila, which showed an inverse association with obesity and metabolic disorders, resides in the nutrient-rich environment of human mucin (36).

Gut microbiome changes associated with colorectal cancer

One hypothesis proposes that oncogenic bacteria such as enterotoxigenic Bacteroides fragilis (ETBF) cause CRC through direct interaction with colonic epithelial cells and changes in microbiota composition at the colorectal site. Enterotoxigenic Bacteroides fragilis (ETBF) is considered to be protumorogenic (37).

Another hypothesis states that some bacteria cause changes in the local environment of the tumor and allow the establishment of bacteria such as Fusobacterium nucleatum in the tumor microenvironment (38).

Sulfidogenic bacteria such as Fusobacterium, Desulfovibrio, and Bilophila wadsworthia have been shown to be associated with the development of CRC through the production of hydrogen sulfide, leading to the induction of genomic instability (39).

In the stool samples of CRC patients, the microbial changes in the mucosal layers are different (40). Shigella, Citrobacter and Salmonella bacteria were more frequent in the early stages of colorectal cancer compared to healthy people (41). E. coli showed a higher prevalence in CRC mucosa tissue (42). F. F. nucleatum, Bacteroides clarus, Roseburia intestinalis and Clostridium hathewayi are usually common and identified in CRC (43). Peptostreptococcus anaerobius showed higher frequency in CRC (44). Bacterial biofilms play an important role in the development of CRC (45). In table 1 lists some bacteria that have antitumor activity and some bacteria that cause CRC.

The role of dietary pattern containing fiber and unsaturated fatty acids on CRC

Studies have shown that foods containing fiber have a positive effect on the metabolic activity of the digestive system (57).

In another study, it was found that dietary fiber has an inverse relationship with the incidence of colon cancer. No difference was observed among different sources of dietary fiber intake against CRC prevention (58). In a cohort study, consumption of whole grains was associated with a slight reduction in the risk of CRC. Recently, it has been found that the fermentation of soluble fibers such as lignan and B-glucan to SCFA (short chain acids) by intestinal microbiota plays an important role in cancer prevention. Dietary fiber intake is also associated with the presence of butyrate-producing bacteria in feces (59, 60). Lower amounts of SCFA in feces as a result of lower consumption of fibrous foods and lower amounts of Clostridium, Eubacterium species were found in subjects at risk of CRC compared to healthy subjects (60).

A possible mechanism that could explain dietary fiber in the prevention of CRC could be that fiber reduces carcinogenic substances due to decreased transit time and increased stool volume, which can reduce the interaction of fecal mutagens with the colon mucosa (61). In general, the dietary pattern containing high fiber not only prevents the disorders and adverse function of the intestinal microbiota, but can also stimulate the production of bacterial metabolites with anti-CRC activity, such as butyrate. In addition, in patients with CRC, receiving a dietary pattern with fiber was associated with better survival. However, more clinical and preclinical studies are necessary for these dietary interventions including high fiber intake to prevent CRC.

Various studies have defined the effect of omega-3 unsaturated fatty acids in the diet on the intestinal microbiota. Unsaturated fatty acids are able to increase the ratio of beneficial bacteria to pathogenic bacteria in the digestive system (62). This category of fatty acids has been widely studied due to their role in the protective effect of CRC carcinogenesis mainly through the mechanisms that regulate the apoptosis of colonocytes. It can also change cell cycle components and affect the immune system and modulate the expression of CRC-related genes.

DISCUSSION

Colorectal cancer is the third most common cancer in men and the second most common cancer in women.

Table 1. Microbiomes with antitumor activity against CRC and the microbiome that can lead to CRC.

Microbiomes with antitumor activity against CRC	Ref	Microbiome that can lead to CRC.	Ref
prausnitzii	(33)	Bacteroides fragilis	(37)
Lactobacillus reuteri	(33)	Helicobacter pylori	(46)
Saccharomyces boulardii	(47)	Streptococcus gallolyticus	(48)
Bacillus polyfermenticus	(47)	Escherichia coli (E. coli)	(42)
Clostridium leptum	(50)	S. bovis	(51)
Propionibacterium spp.	(52)	Fusobacterium nucleatom	(53)
Bifidobacterium longum	(54)	Desulfovibrio	(55)
Propionibacterium freudenreichii	(50)	Bilophila wadsworthia	(55)
Lactobacillus plantarum	(50)	Bacteroides clarus	(43)
Eubacterium rectale	(33)	Roseburia intestinalis	(43)
Lactobacillus/ Bifidobactrium	(56)	Peptostreptococcus anaerobius	(44)

It is the fourth leading cause of death in the world (63). CRC is a multifactorial disease in which genetic and environmental risk factors are involved. Smoking, alcohol consumption, obesity and diabetes, and dietary factors such as a diet high in processed foods, animal fat, and red meat are known risk factors for CRC. Genetic and epigenetic changes of tumor suppressor genes, proto-oncogenes and DNA repair genes cause the transformation of normal colonic epithelium to CRC (64). In addition to the effect of genetic factors, environmental factors can also be effective in causing colorectal cancer, such as the dietary pattern containing animal fatty acids, animal fatty acids cause the growth of bacteria that produce carcinogenic products such as polyamine hydrogen sulfide, DCA, lithocholic acid (LCA) and reactive oxygen species (ROS) are active, and diets rich in sugar also play a role in the growth of these bacteria (55, 65, 66).

Butyrate of intestinal microbes causes the secretion of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α), which damage intestinal epithelial cells and can be known as risk factors for CRC (67). fragilis and Enterococcus faecalis are responsible for the production of enterotoxins (eg, fragilisin) and reactive oxygen species that cause oxidative DNA damage and inflammation in intestinal epithelial cells (68).

CONCLUSION

During the last few decades, the importance of microbiomes on human health has been investigated. These microbes play a role in the regulation and tolerance of the immune system, most studies on microbiomes have been conducted on intestinal microbes because the highest concentration of bacterial population is located in the large intestine.

The diversity of intestinal microbiota is genetic, but external environmental factors such as diet, exposure to chemicals and other environmental factors, and the use of antibiotics are effective in changing intestinal microbiota.

Also, consuming foods containing saturated fatty acids and sugar leads to the proliferation of bacteria that produce carcinogenic products.

In total, the studies show that the separation of genetic factors and genes involved in the development of this disease and especially familial CRC; The type of intestinal microbiota and the food pattern and lifestyle of a person play a role in causing this condition. It should be noted that dietary pattern plays a role in the proliferation of microbiota that produce carcinogenic products.

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Author contributions

Conceptualization, R.R.; All authors reviewed the manuscript.

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Availability of Data and materials

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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