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Mini-Review

Gut Microbiota and Colorectal Cancer

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Key Words
'Alpha-bug' model · Colorectal cancer · 'Driver-passenger' model · Gut microbiota · 'Intestinal microbiota adaptions' model

Abstract

Background: Colorectal cancer (CRC) is a leading cause of cancer-related mortality worldwide whose incidence has increased rapidly in recent years. There is growing evidence that the complex gut microbiota community plays an important role in the development of intestinal tumorigenesis. ***Summary:*** This review aimed to explore the correlation between gut microbiota and CRC as well as to identify the pathogens and their metabolites that affect CRC and the potential models of gut microbiota action. It promotes our understanding of the correlation between gut microbiota and CRC. ***Key Message:*** Our knowledge of the risk factors associated with gut microbiota for CRC development, as well as of the mechanism how intestinal bacteria act on colorectal tumorigenesis, has improved, leading to a better understanding of the correlation between gut microbiota and CRC. ***Practical Implications:*** The intestinal microbiota community has a close relationship with CRC by influencing the mechanism of the body and by regulating the physiological function of the colorectum and even the entire digestive system. Gut microbiota have been linked to CRC based upon their toxic and genotoxic metabolites production by fermentation of dietary ingredients. These metabolites could bind specific intestinal cell surface receptors and subsequently affect intracellular signal transduction. The mechanisms by which gut microbiota affect CRC development include the 'Alpha-bug' model, the 'driver-passenger' model and the 'intestinal microbiota adaptions' model. This review promotes our understanding of the correlation between gut microbiota and CRC.

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Introduction

Colorectal cancer (CRC) is a leading cause of cancer-related mortality worldwide whose incidence has increased rapidly in recent years [1]. It is often the case that complex causes lead to malignant tumorigenesis. Infectious agents, such as bacteria or viruses, are associated with several types of cancer [2]. These cancers tend to have a high level of exposure to microbes in tissues. Several direct associations between microbes and cancer have ben identified over the past 30 years, including *Helicobacter pylori* and gastric cancer, human papillomavirus and cervical cancer, or hepatitis B virus and liver cancer [3, 4]. There is growing evidence that the complex gut microbiota community plays an important role in the development of intestinal tumorigenesis [5–8]. In this review, we will explore the risk factors associated with gut microbiota in the development of CRC, as well as the relationship between gut microbiota and CRC.

Overview of Human Gut Microbiota

There are about 100 trillion bacteria in the human intestine, of varying and elaborate structures, which constitute the intestinal microbiome [9]. The human gut microbiota are dominated by facultative anaerobes, including *Lactobacilli*, *Enterococci*, *Streptococci* and *Enterobacteriaceae*, and by strict anaerobes, including *Bacteroides*, *Eubacterium*, *Bifidobacterium*, *Fusobacterium*, *Peptostreptococcus* and *Atopobium* [10]. There are more than 500 different species that may be present in the commensal microbiota of normal intestines [11]. This large group of bacteria are referred to as intestinal symbiotic bacteria, because of their mutualistic and interdependent relationship with the human body during the long period of co-evolution [12].

Some specific strains of bacteria have been classified as pathogens for cancer, such as *Streptococcus bovis*, *H. pylori*, *Fusobacterium nucleatum* and *Enterococcus faecalis* [2, 13–16]. In addition, some strains of bacteria, including *Lactobacillus acidophilus* and *Bifidobacterium longum*, may inhibit colorectal tumorigenesis [17, 18]. The intestinal microbiota community has a close relationship with CRC by both influencing mechanism of the body and regulating the physiological function of the colorectum and even the entire digestive system [12, 19].

Gut Microbiota and Their Metabolites in the Promotion of CRC

Gut microbiota have been linked to CRC based upon their toxic and genotoxic metabolites production by fermentation of dietary ingredients. These metabolites could bind specific intestinal cell surface receptors and subsequently affect intracellular signal transduction.

Enterotoxigenic Bacteroides fragilis

Enterotoxigenic *Bacteroides fragilis* (ETBF) acts during the initiation phase of CRC by producing *B. fragilis* toxin [20]. In addition to its direct genotoxic effect, *B. fragilis* toxin stimulates intestinal epithelial cell shedding and gamma-secretase-dependent E-cadherin cleavage [21]. This cleavage increases the permeability of the intestinal barrier and triggers β-catenin/Wnt signaling transduction in intestinal epithelial cells, which contributes to the proliferation and oncogenic transformation of CRC [22]. ETBF triggers colitis and induces colon tumorigenesis in multiple intestinal neoplasia (Min) mice via activation of signal transducer and activator of transcription 3 (STAT3) and T helper type 17 T cell responses [23].

Sulfate-Reducing Bacteria

Sulfate-reducing bacteria are anaerobic microorganisms that can obtain energy by oxidizing organic compounds or molecular hydrogen (H_2) while reducing sulfate (SO_4^{2-}) to hydrogen sulfide (H_2S). These organisms ‘breathe’ sulfate rather than oxygen in a form of anaerobic respiration. The sulfate-reducing bacteria mainly consist of the *Deltaproteobacteria*, including the orders of sulfate-reducing bacteria, including *Desulfobacterales*, *Desulfovibrionales* and *Syntrophobacterales*, which account for the largest group of sulfate-reducing bacteria [24]. The second largest group is found among the *Firmicutes*, including the genera *Desulfotomaculum*, *Desulfosporomusa* and *Desulfosporosinus*. Other studies have shown that H_2S produced by sulfate-reducing bacteria is toxic to intestinal epithelium cells [25]. Further, Attene-Ramos et al. [26] found that even low concentrations of H_2S can cause significant DNA damage in human cells.

Fusobacterium nucleatum

In 2012, *F. nucleatum* was identified as a potential pathogen of CRC in an analysis of the gut microbial structures of CRC tissues versus matched normal tissues from the same subject [2, 16]. A dominant enrichment of *Fusobacterium* spp. sequences associated with CRC tissues has been observed, using 16S rDNA and metagenomic analyses. *Fusobacterium* spp. act as invasive anaerobes in oral infections as well as in appendicitis and inflammatory bowel disease [16, 27]. Recent studies have provided experimental support for *F. nucleatum*-mediated induction of colonic tumorigenesis. Apc(Min/+) mice showed a significant increase in colon and small bowel tumors after continuous exposure to *F. nucleatum* [28]. Data revealed that *F. nucleatum* could change the tumor microenvironment of colonic tumors, inducing an increase in myeloid-derived immune cells and upregulating inflammation-associated genes. The data also showed a gradient abundance of *F. nucleatum* in feces among healthy and tumor patients. These results suggested that *Fusobacterium* detection might not be a sufficient biomarker for identifying patients at high risk of CRC [28, 29].

Reactive Oxygen Intermediates

Reactive oxygen intermediates are chemically reactive molecules containing oxygen, including often superoxide, hydrogen peroxide, hypochlorous acid, singlet oxygen and hydroxyl free radicals. Growing evidence suggests that reactive oxygen intermediates play a part in the development of CRC by inducing oxidative DNA damage [30]. Huycke et al. [31] observed that the intestinal symbiotic bacterium *E. faecalis* produced extracellular superoxide and hydrogen peroxide, leading to intestinal epithelial cell DNA damage in vivo and in vitro. *E. faecalis* also demonstrated the ability to induce dysplasia and carcinoma in IL-$10^{-/-}$ mice, results that could not be observed in germ-free mice [32]. Based on these studies, we speculate that reactive oxygen intermediates play an important role in CRC by inducing colonic epithelial cell DNA damage in the process of inflammation.

Bile Acid and Secondary Bile Acid

Gut microbiota play an important role in the metabolism of bile acid in human intestines. Certain bacteria transform bile acid to secondary bile acid via 7α-dehydroxylation [33]. Secondary bile acids, especially deoxycholic acid (DCA), are thought to be genotoxic, having the effect of promoting colon tumorigenesis [34]. DCA caused intestinal epithelium DNA damage that might lead to apoptosis, and triggered apoptosis in a p53-independent manner [35]. Many studies have proved that DCA is associated with CRC: high concentrations of fecal DCA increase the risk of CRC [36].

How Do Gut Microbiota Affect the Development of CRC?

The 'Alpha-Bug' Model

Sears and colleagues [23, 37] proposed the 'Alpha-bug' model after clarifying the capacity of ETBF to induce colonic tumors in Min mice. The 'Alpha-bug' hypothesis integrates the single intestinal bacteria and gut microbiome community views of microbial tumorigenesis. 'Alpha-bugs' was defined as certain intestinal commensal bacteria that produce epithelium gene mutations directly as well as indirectly.

ETBF rapidly triggers the exclusive activation of STAT3, which is a member of a family of transcription factors mediating T cell lineage development, serving as key regulators of tumorigenesis [38]. Additionally, STAT3 activation is required for the induction of Th17 immune responses, which might promote cancer in cooperation with the modified colonic epithelium [23]. This model suggests that ETBF promotes colonic tumorigenesis by modifying the epithelium and mucosa immune function as well as the intestinal microenvironment. The modification of the colon epithelium includes the activation of certain signal transduction pathways [38–40], and epithelium DNA damage, which promotes CRC through releasing the toxin by ETBF [41] or the release of reactive oxygen intermediates by inflammatory cells [42].

'Alpha-bugs' bacteria may enhance carcinogenesis by their permanent presence and by selective 'crowding out' of cancer-protective intestinal bacteria. There are several candidate 'Alpha-bugs', including ETBF, *Streptococcus gallolyticus* (also known as *S. bovis*), superoxide-producing *E. faecalis* and *Escherichia coli* [31, 43–45].

The 'Driver-Passenger' Model

Recently, high-throughput sequencing technology has allowed us to explore the gut microbial structures of healthy and diseased body sites. Several experimental data sets support a possible role for gut microbiota in CRC [2, 7, 16, 46]. Based on this, Tjalsma et al. [47] firstly proposed a bacterial counterpart of the genetic 'driver-passenger' model of CRC, which will be incorporated into the genetic paradigm of CRC progression. The 'driver-passenger' model is different from the 'Alpha-bug' model. The 'driver-passenger' model suggests that 'driver' bacteria initiate CRC and that these 'driver' bacteria are then replaced by 'passenger' bacteria; either one can promote CRC development. First, certain intestinal symbiotic bacteria drive epithelium cell DNA damage (termed bacterial drivers). Second, colorectal tumorigenesis is mediated by alterations to the intestinal microenvironment, which are conducive to the proliferation of certain opportunistic pathogens or probiotics (termed bacterial passengers) [47], such as *Fusobacterium* spp. [2, 16], *S. bovis* [48, 49] and *Roseburia* spp. [46].

To summarize, bacteria of the 'driver-passenger' model have distinct roles in CRC and imply differences in their temporal association with the colonic mucosa. This correlates with alterations of gut microenvironment during CRC progress. Furthermore, recent studies of gut microbiota reported the higher and lower representation of certain bacteria in tumor tissue, stating that although bacteria drivers are underrepresented, they may be present in low, but sufficient, abundance. The colonization of bacteria drivers in tumor tissue is likely to depend on strain-specific virulence characteristics. The propensity for colonization may depend on the specific genotype and expression profile of certain strains.

The 'Intestinal Microbiota Adaptions' Model

The development of CRC results through a lengthy process from normal tissue to hyperplasia, adenoma and, eventually, carcinoma [50]. During this process, the intestinal microbiota maintain a dynamic balance, termed 'adaptions' [51]. 'Intestinal microbiota adaptions' is dependent on the stability and resilience of the human gut microbiota [52]. Resilience is the amount of stress or disturbance that can be tolerated before a system is modified towards a different equilibrium state [52].

Under healthy conditions, gut microbiota maintain homeostasis with the human body and the intestinal microenvironment. This balance may be disrupted if the microbiota microenvironment is stimulated by factors in vivo or in vitro. The composition of the gut microbiota becomes modified according to the host's physiological state. Factors including heredity, diet and environment contribute to the function of pathogens, inducing CRC occurrence. At the same time, the growth of a tumor leads to changes in the intestinal mucosal barrier function and local tumorigenesis microenvironment, which are conducive to shifting the equilibrium state of the intestinal microenvironment. Some bacteria will thrive in the new intestinal microenvironment, while other bacteria unsuitable for survival decrease or even disappear, reflecting the fact that gut microbiota are affected by the occurrence of CRC. Despite highly diverse intestinal microbiota composition, the core functional profiles are quite similar in different subjects. When cancer-promoting bacteria are dominant, the environment will be conducive to the occurrence and development of CRC; in contrast, when cancer-inhibiting bacteria are dominant, colorectal tumorigenesis will be blocked [47]. However, more research is required to reveal the correlation between changes in the intestinal microenvironment and microbiota homeostasis.

Conclusions

Over the last decades, CRC as a common, deadly human disease has been a hot topic in both preclinical and clinical medicine studies. Several clinical studies and experimental models have linked the gut microbiota with the occurrence of CRC. Gut microbiota may play a role in CRC development by influencing the body's mechanism and by regulating the physiological function of the colorectum and even the entire digestive system. Therefore, further studies are needed to determine the association of the gut microbiota and the host immune system with CRC tumorigenesis. This will lead to a deeper understanding of the mechanism of the gut microbiota's effect on CRC and the shift in microbiota homeostasis under the influence of tumors.

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