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Correlation between gut microbiota dysbiosis and colorectal cancer: review

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Abstract

Introduction and Purpose:

The human gut microbiota, comprising a diverse consortium of approximately 100 trillion microorganisms, is integral to maintaining health and modulating disease processes. Its development begins at birth, influenced by maternal microbiota and environmental factors. Dysbiosis, defined as an imbalance in the gut microbial composition, has been implicated in a range of gastrointestinal pathologies, including colorectal cancer (CRC). This review endeavors

to elucidate the relationship between gut microbiota and CRC, examining the impact of specific bacterial taxa on the pathogenesis CRC.

Description of the State of Knowledge:

Gut microbiota encompasses a multitude of microbial species, with their composition differing along the gastrointestinal tract. Healthy gut microbiota performs essential functions such as pathogen protection, metabolic processes, and immune system modulation. Factors like diet and genetics significantly influence microbial composition. Dysbiosis contributes to CRC through inflammation, genotoxin production, and immune modulation. Specific bacteria, such as Fusobacterium nucleatum and Bacteroides fragilis, are associated with CRC. Mechanisms of carcinogenesis include bacterial adherence, invasion of epithelial cells, and activation of pro-inflammatory pathways.

Summary:

Understanding the gut microbiota's role in CRC highlights the importance of maintaining a balanced microbiome for cancer prevention. Dietary interventions promoting beneficial bacteria and reducing harmful species could mitigate CRC risk. Further research should prioritize the identification of microbial biomarkers for early CRC detection and the development of therapeutic strategies aimed at modulating the gut microbiota. These efforts will enhance CRC prevention and treatment modalities.

Keywords: gut microbiota; colorectal cancer; dysbiosis; bacteria

Introduction

Human gut microbiota comprises an estimated 100 trillion microorganisms, encompassing bacteria, viruses, and fungi [1,2]. Interindividual differences in the gut microbiota are consistent, initially acquired during infancy from the mother's skin, vagina, and feces, and maturing primarily within the first two years of life. Microbiota development results from interactions between host physiological processes and environmental microorganisms [3]. Establishing a diverse and balanced microbiota early in life is crucial for the development and

maturation of a functional immune system [4]. The intestinal microbiota can be classified into two categories: beneficial bacteria and opportunistic bacteria capable of causing infections. Beneficial microorganisms include genera such as Lactobacillus, Bifidobacterium, Enterococcus, and Propionibacterium, whereas the opportunistic group comprises Bacteroides, Bacilli, Clostridia, Enterobacteria, Actinobacteria, Peptococci, Staphylococci, and Streptococci [5,6]. Interestingly, alterations in the gut microbiota can result in dysbiosis, which has been linked to the pathogenesis of gastrointestinal disorders, including irritable bowel syndrome (IBS), and colorectal cancer (CRC) [2,7].

CRC remains a significant global health burden, with its incidence and mortality rates varying across regions and populations [8]. According to GLOBOCAN 2022 CRC is the third most common cancer diagnosed in men and women worldwide, with more than 1.9 million new cases per year. In addition, it ranks in second place regarding mortality, with 904 019 deaths noted in 2022 [9]. It was proven that the etiology of CRC involves a combination of hereditary and environmental risk factors [10]. The range of heritability of CRC varies from 12% to 35% [11].

As it comes to risk factors, substantial evidence indicates that alcohol consumption, smoking, higher consumption of animal-derived foods, and increased body weight elevate the overall risk of disease [12,13]. On the other hand, calcium supplements intake, whole grains, fiber, and dairy products, alongside engagement in physical activity, are regarded as protective measures [13]. It was also suggested that infection with certain bacterial species, including Fusobacterium nucleatum and Bacteroides fragilis, may elevate the risk of CRC [14,15].

This review aims to elucidate the relationship between gut microbiota and CRC, examining the impact of specific bacterial species on CRC pathogenesis.

Material and methods

The study was based on a literature review and analysis of publications available on PubMed and Google Scholar platforms. The research was conducted using a combination of keywords such as: “gut microbiota”, “colorectal cancer”, “dysbiosis” and “bacteria”. We focused on full-text articles that addressed issues related to the subject of this review.

Intestinal microbiota composition

The human gastrointestinal (GI) tract microbiota consists approximately 1500 species, distributed in more than 50 different phyla [16]. In a single individual, 150 to 170 bacterial species predominate, benefiting from the nutrient-rich, warm environment of the gut while performing protective, metabolic, and structural functions [17,18]. It was reported that the gut microenvironment primarily supports the rise of bacteria from seven predominant phyla: Firmicutes, Bacteroidetes followed by Actinobacteria, Fusobacteria, Proteobacteria, Verrucomicrobia, and Cyanobacteria. This makes up to 90% of the total bacterial population in humans [19]. Most species within the Bacteroidetes phylum belong to the genera Bacteroides and Prevotella. In the Firmicutes phylum, species such as Clostridium clusters IV and XIVa, including genera Clostridium, Eubacterium, and Ruminococcus, are predominant. Additionally, the human gut has been reported to contain the hydrogen-consuming methanogen Methanobrevibacter smithii and the halophilic archaea Haloferax alexandrinus and Haloferax massiliensis [20].

The GI tract is functionally and anatomically divided into the stomach, small intestine, and large intestine (LI). Each compartment's distinct microenvironment and physiochemical barriers selectively favor the growth of specific microbiota. Previously, the stomach was assumed to be sterile and resistant to bacterial development due to a bactericidal barrier, bile acid reflux, thick mucus layer, and gastric peristalsis [21]. In 1981, the Lancet revealed the presence of numerous acid-resistant bacterial strains in the stomach, including Streptococcus, Neisseria, and Lactobacillus. Robin Warren and Barry Marshall discovered Campylobacter pyloridis in 1982, which was then renamed Helicobacter pylori. More than 65% of stomach phylotypes originated in the mouth. These mouth-derived bacteria, such as Veillonella, Lactobacillus, and Clostridium, were discovered to be acid-resistant and transitory [21,22]. In a healthy human stomach, five major phyla are typically present: Firmicutes, Bacteroidetes, Actinobacteria, Fusobacteria, and Proteobacteria, with predominant bacterial genera including Prevotella, Streptococcus, Veillonella, Rothia, and Haemophilus [23].

The small intestine is separated into three sections: the duodenum, the jejunum, and the ileum. Bile acids, pancreatic secretions, and antimicrobial agents characterize the duodenum milieu, in which quicker food transit and lots of oxygen restrict bacterial density ($10^{3–4}$ CFU/ml) and variety. In the duodenum, Firmicutes and Actinobacteria are the predominant phyla. The jejunum primarily supports the growth of Gram-positive aerobes and facultative anaerobes, such as Lactobacilli, Enterococci, and Streptococci [24].

In the large intestine, anaerobes outnumber aerobes by a factor of 100 to 1000. Bacterial density reaches up to 10^12 colony-forming units (CFU) per milliliter, with Firmicutes and Bacteroidetes being the dominant phyla [25]. The ratio of these two phyla can vary at different life stages and under various pathophysiological conditions, serving as a predictive marker of health and disease [26]. In the LI lumen, bacterial genera such as Bacteroides, Bifidobacterium, Streptococcus, Enterobacteriaceae, Enterococcus, Clostridium, Lactobacillus, and Ruminococcus predominate, whereas Clostridium, Lactobacillus, Enterococcus, and Akkermansia are associated with the mucosa. Additionally, certain pathogens, including Campylobacter jejuni, Salmonella enterica, Vibrio cholerae, Escherichia coli, and Bacteroides fragilis, may be present in the LI in lower abundances [27].

Functions of microbiota

The formation of the human gut microbiota begins during early stages of pregnancy. It is essential for maintaining normal physiological functions of the host, but also synthesizes various metabolic products that can exert either beneficial or detrimental effects on human health through host interactions. The gut microbiota establishes and reproduces on the surface of the intestinal mucosal surfaces, forming a stable ecosystem that prevents the infiltration of pathogenic germs [2].

The gut microbiota fulfills a multitude of crucial functions within the human body. It supports protection against pathogens by colonizing mucosal surfaces and producing various antimicrobial substances, thereby enhancing the immune system [28]. Furthermore, it has a vital function in digestion and converting nutrients into biologically active compounds. The bacteria are capable of metabolizing indigestible carbohydrates such as cellulose, hemicelluloses, resistant starch, pectin, oligosaccharides, and lignin to create short chain fatty acids (SCFAs) including acetic, propionic, and butyric acids [29]. Firmicutes, Bacteroidetes, and some anaerobic gut bacteria are the primary producers of these metabolic products [30]. Moreover, regulates the proliferation and differentiation of epithelial cells, modulates insulin resistance and secretion [31,32]. The gut microbiota plays an essential part in preserving human health, affecting not just the GI tract but also other organs such as the brain, liver, and pancreas [33,34]. It influences the gut-brain axis, thereby affecting the patients' psychological and neurological functions [35]. Therefore, gut microbiota plays a pivotal role in maintaining intestinal physiology and overall health.

Factors affecting gut microbial composition

Diet

The intestinal microbiota is integral to health and disease, with its composition influenced by both environmental and host genetic factors. There are several factors that significantly influences the regulation of gut microbiota. This is due to promoting the growth or decline of certain microbial species, as well as by modifying the metabolites produced within the gastrointestinal environment [36]. From birth, dietary inputs are pivotal in forming the infant gut microbiota, adapting to shifts in nutrient availability [18]. Furthermore, feeding methods profoundly impact the microbial composition of infant gut microbiota [37]. Interestingly, infants fed with breast milk tend to have a higher prevalence of Actinobacteria and lower levels of Firmicutes and Proteobacteria. Conversely, infants who are formula-fed tend to show an increase in populations of Clostridia, Streptococci, Bacteroides, and Enterobacteria [38].

As it comes to animal-based diet, research has demonstrated that dietary habits significantly influence gut microbiome diversity. Evidence suggests a link between dietary-induced alterations in bacterial composition and specific diseases, particularly those characterized by chronic low-grade inflammation, such as type II diabetes [39,40]. Diets high in animal proteins are associated with elevated levels of Bacteroides spp., Alistipes spp., and Bilophila spp., alongside a reduction in beneficial bacteria, including Lactobacillus spp., Roseburia spp., and Eubacterium rectale [40]. Mouse studies have revealed that high-fat and high-sugar diets caused a decrease in Bacteroidetes, while increasing Firmicutes and Mollicutes [41]. Zhang et al. reported significant reductions in lactic acid and Enterococcus in mice fed high-fat diets [42]. Further investigations in rodent models confirmed shifts in gut microbiota, particularly increased levels of Enterobacteriaceae, Escherichia, Klebsiella, and Shigella in high-fat diet groups [43]. Recent research indicates that diets rich in animal and saturated fats can significantly impact gut microbiota composition. These dietary patterns are associated with increased levels of lipopolysaccharides (LPS) and trimethylamine-N-oxide (TMAo), alongside a reduction in short-chain fatty acids (SCFAs) [40,44].

However, high levels of Prevotella species have been associated with plant-based diet [45]. It was confirmed in the study conducted by De Filippo et al., which compared the fecal microbiota of children of Burkina Faso and children living in Italy. First group consumed a diet low in fat and animal protein but high in starch, fiber, and plant protein, and showed an exclusive presence of Prevotella in their gut microbiome. In contrast, European children, whose

diet was high in animal protein, sugar, starch, and fat, and low in fiber, did not exhibit this microbial profile [46]. Bacteroides, a principal enterotype and genus within the Bacteroidetes phylum, presents opposite dietary responses when compared to Prevotella. Its higher levels have been linked to long-term consumption of diets that are high in animal proteins and saturated fats [47].

Interestingly, gluten free diet (GFD) may also influence the gut microbiota composition. It has been shown that one month of GFD diet in healthy adults was associated with decrease in Lactobacillus and Bifidobacterium populations, while the increase in E. coli and Enterobacteriaceae was noted. This led to reduction of beneficial gut bacteria and may be linked with bacteremia episodes [48]. In addition, healthy volunteers in study conducted by Bonder et al. presented a decrease of Roseburia and increase in abundance of *Victivallaceae* and Clostridiaceae [49].

Genetics

Host genetics play a crucial role in determining species richness, individual taxa abundances, and variability in pathogen susceptibility. The association between the microbiome and genes linked to the host's innate immune system was shown, where pattern recognition receptors detect intestinal microorganisms, thereby influencing microbiome composition and microbiome-associated diseases [50]. Zoetendal et al. found that monozygotic twins, even when living apart for years, exhibited high microbial profile similarity. In contrast, marital partners living together with similar diets did not show such similarity [51]. In addition, higher heritability in phyla such as Firmicutes, Actinobacteria, Tenericutes, and Euryarchaeota was reported, whereas the highly abundant Bacteroidetes phylum exhibited low heritability [52].

Interestingly, the expression of 6000 genes in the colonic epithelia was in correlation with the gut microbiota. Researchers identified 12 allele-specific single-nucleotide polymorphisms (SNPs) associated with the gut microbiota, 8 of which were linked to diseases such as CRC, Type 2 diabetes (T2D), and obesity [53]. Turpin et al. discovered that that approximately one-third of fecal bacterial taxa exhibit heritability. Furthermore, 58 SNPs were identified in 1098 individuals, correlating with the relative abundance of 33 bacterial taxa. Four loci were validated in a second cohort of 463 subjects and were associated with Rikenellaceae, Faecalibacterium, Lachnospira, and Eubacterium [54]. The composition of the gut microbiota is influenced by the secretor status based on the ABH antigens and and Lewis histo-blood group antigens expression in the mucosa. In a study of 71 healthy individuals, 14 non-secretors

exhibited significantly reduced diversity and richness of bifidobacteria, specifically B. bifidum, B. adolescentis, and B. catenulatum/pseudocatenulatum. Conversely, several bacterial genotypes were more prevalent, and the richness of dominant bacteria detected by PCR-DGGE was higher in non-secretors compared to secretors These findings highlight that ABH secretor status may be a key host genetic determinant of intestinal microbiota composition [55]. Further evidence supports the substantial contribution of host genetics to the gut microbiome. High similarity in heritable taxa and functional gene categories among pigs, humans, and mice was observed, which indicated a consistent mechanism of host genetic influence on the gut microbiome across mammalian species [56].

Gut microbiota dysbiosis and CRC

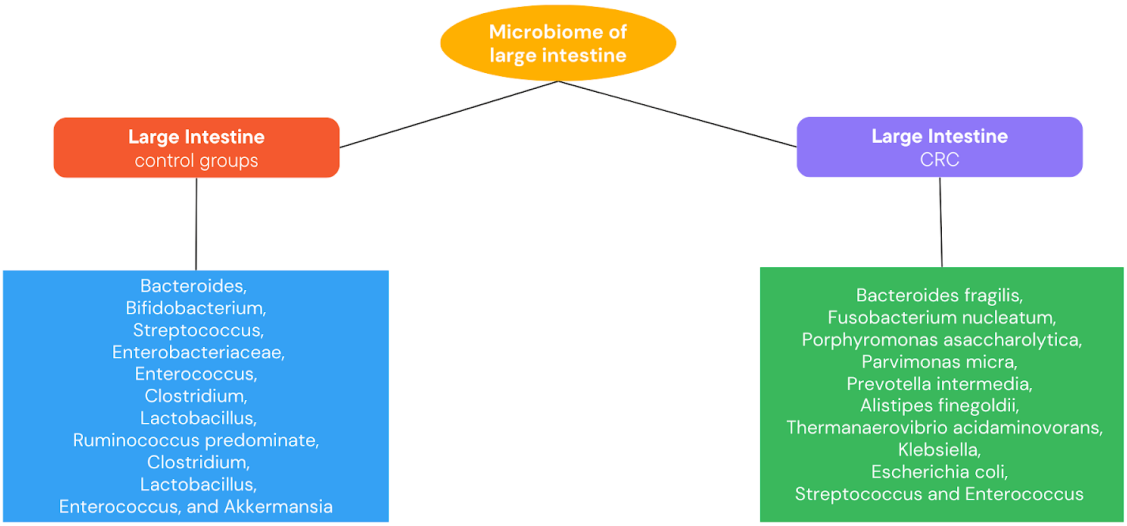
Dysbiosis, characterized by compositional and functional alterations of the gut microbiome, contributes to the pathogenesis of various diseases, including obesity, diabetes, neurodegenerative disorders, and cancers [57-62]. Notably, bacterial infections can induce carcinogenesis. Studies have demonstrated that Helicobacter pylori colonization leads to persistent inflammation and gastritis, which can progress to gastric malignancy. Research has shown that H. pylori promotes tumorigenesis through the activation of the β-catenin signaling pathway [63]. Conversely, the eradication of H. pylori reduces the risk of gastric cancer, underscoring its role in early gastric carcinogenesis [64].

Several factors impacting gut microbiota are associated with the development of CRC, such as obesity, a diet filled with fats, smoking, and regular alcohol consumption [8]. Studies conducted on mice with modified immune and inflammatory reactions suggest that an imbalance in the gut microbiota alone might be enough for stimulating the development of cancer [65,66]. These findings indicate that the immune system plays a crucial role in the interactions between gut microbiota and CRC. Besides the influence of specific pathogens on carcinogenesis, the high redundancy of gut microbiota at the metagenomic level suggests that an imbalance in the microbial community could potentially promote the growth of cancer cells [67].

CRC has been associated with specific bacterial populations. Recent analyses of fecal metagenomic samples from CRC patients have identified CRC-enriched bacteria, including Bacteroides fragilis, Fusobacterium nucleatum, Porphyromonas asaccharolytica, Parvimonas micra, Prevotella intermedia, Alistipes finegoldii, and Thermanaerovibrio acidaminovorans, which may serve as potential diagnostic bacterial markers across different populations [68,69].

Moreover, Streptococcus bovis, Helicobacter pylori, Enterococcus faecalis, and Clostridium septicum are among the other bacterial species contributing to CRC [70-72]. In addition, CRC microbiota exhibits higher species richness and reduced abundance of potentially protective taxa such as Roseburia [73,74]. Numerous studies prove that individuals predisposed to CRC exhibit a higher abundance of secondary bile acid-producing microbial species and a reduced presence of butyrate-producing bacteria [75].

Fig. 1. Schematic representation of the intestinal microbiome (large intestine) in patients with CRC compared to control groups.



Interestingly, colorectal carcinogenesis has several suggested pathways, some of which may be dependent on species. These processes involve the generation of genotoxins produced by bacteria, changes in microbial metabolism, modification of the host's immunological responses and inflammatory pathways, initiation of oxidative stress, and control of anti-oxidative defenses [76]. The significant role of chronic inflammation as a risk factor for CRC has been underscored. Microbial metabolites can penetrate compromised colonic epithelial barriers, leveraging the host's immune response to induce inflammation, thereby promoting tumorigenesis [75,77]. Another researches indicates that genus of obligate anaerobic *Fusobacterium* including *F. mortiferum, F. nucleatum*, and *F. necrophorum* play pivotal role in contributing to tumourigenesis through an inflammatory mechanism [78,79].

FadA is a crucial virulence factor for Fusobacterium nucleatum that facilitates cellular adhesion and invasion. It stimulates the β-catenin signaling pathway and causes CRC [80]. Additionally, many Escherichia coli strains linked with CRC have acquired virulence factors, specifically the afa and eae adhesins, which improve their ability to attach to and penetrate the intestinal epithelium [81,82]. Toxins might potentially trigger the development of CRC by influencing signaling pathways that originate from the host. Certain strains of Helicobacter pylori generate CagA or VacA, which have been linked to higher levels of inflammation and increased incidences of cancer [83]. The majority of the Gram-negative bacteria implicated in CRC produce cytolethal distending toxin (CDT), which is categorized as a bacterial genotoxin. CDT presents nuclease activity that triggers a DNA-damage response, leading to cell cycle arrest [84]. Additionally, CDT promotes gut colonization and increases pro-inflammatory molecules such NF-κB, tumor necrosis factor (TNF)-α, IL-6, and cyclooxygenase (COX) 2, all of which contribute to carcinogenesis [85].

Summary

It was demonstrated that the gut microbiota associated with CRC differs significantly from that of healthy individuals. It is important to note that cancer progression is influenced not only by the prevalence of individual microbial species but also by the overall metabolic pathways and functions of the microbiota. Potentially, gut microbiota may provide opportunities to identify patients likely to respond to treatment, enhance existing therapies, and develop novel therapeutic approaches.

Disclosure

Author's contribution:

Conceptualization, ZC; methodology, ZC, DD, AB; software, AB, AC, PW; check, AC, DD and BC; formal analysis, BC, AB; investigation, ZC, DD, AC; resources, PW, ŁG; data curation, PW, KS; writing - rough preparation, ZC, DD, AB; writing - review and editing, ŁG, FG, KS; visualization, BC, FG; supervision, BC; project administration, ZC;

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