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Gut Microbiota and its impact on the inflammation-dysplasia-cancer sequence

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Abstract
The understanding and explanation of inflammation-dysplasia-cancer sequence is challenging. The gut microbiota is an important factor for the intestine wall. The changes in bacteria quality and/or quantity (dysbiosis) may begin the colon inflammation. This paper reviewed the gut microbiome risk factors which may lead to colon cancer.

Running title: Gut microbiota and inflammation-dysplasia-cancer sequence

Keywords: gut microbiota, inflammation-dysplasia-cancer sequence, colon cancer, colorectal cancer, dysbiosis, colon cancer risk factors

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Introduction

The influence of the gut microbiota on the development of human diseases is one of the most talked about topics these days. Firstly, colon cancer (CRC) is the most important of these problems. It is the second highest leading cause of death worldwide. It is also the third most common cancer in the world. Studies show that this disease is more typical for developed countries. CRC is 1.5 times more common in men than in women, with most cases occurring after the age of 50 [1] In 2023, in USA approximately 153.000 individuals will be diagnosed with CRC and 52.550 will die from the disease, including 19.550 cases and 3750 deaths in individuals younger than 50 years [2]. There were new diagnoses of CRC in 4366 females and 4978 males polish patients in 2020 [3].

The human intestinal tract comprises microbes ranging from 1013 to 1014. It encompasses circa 10 times more bacteria in it than cells and contains more than 100 times as many genes as in the human genome [4]. The intestinal flora consists of bacteria, as well as many other species of archaea, fungi, protozoa and viruses [5]. They play an important role in maintaining a normal physiologic environment, including energy metabolism, interacting with the normal gut barrier system, promoting the survival of epithelial cells, and, importantly, protecting our body against other external or opportunistic pathogens [6]. Colonization of the human gut with microbes begins immediately at birth, upon passage through the birth canal where fetuses are exposed to a variety of microorganisms [7]. There are several factors that influence colonization, the most important ones include the following gestational age, mode of delivery (vaginal birth vs assisted delivery), diet (breast milk vs formula), pregnant women sanitation level and antibiotic exposure [8]. After the first year of life, the intestinal microbiota starts to resemble that of a young adult. Their composition is relatively simple and characterized by low diversity with relative dominance of species from the phyla of Proteobacteria and Actinobacteria [5,7].

Over time, the microbiota becomes more like an adult microbiota. Firmicutes, Bacteroidetes, Proteobacteria and Actinobacteria phyla make up 90% of the intestinal flora in an adult. The gut microbiota can be divided into beneficial bacteria and opportunistic bacteria (responsible for infections). Lactobacillus, Bifidobacterium, Enterococci, and Propionobacteria are some of the beneficial microbes, while the opportunistic groups include Bacteriodes, Bacilli, Clostridia, Enterobacteria, Actinobacteria, Peptococci, Staphylococci, and Streptococci. [9]. The intestinal flora disorders are involved in various human diseases such as dysbiosis (imbalance between the beneficial and opportunistic microbes), which is associated with IBD and CRC.

In this article, the purpose is to explore the relationship between a gut microbiota role in inflammatory and colorectal cancer – the inflammation-dysplasia-cancer sequence.

Gut microbiota

The gut microbiota consists of commensal and pathogenic bacteria residing inside the gastrointestinal tract [10]. Over the past few decades, the causes of colorectal cancer have been studied, but limited attention has been paid to the intestinal microbiome influence on it. The gut microbiome plays an important role in the absorption of nutrients and minerals but also in the synthesis of various enzymes, vitamins and amino acids and the production of short-chain fatty acids (SCFAs) [10]. Acetate, propionate and butyrate are the by-products of fermentation of intestinal microflora. Their role is important for the undisturbed work of the intestine, they provide energy to epithelial cells, improve the integrity of the epithelial barrier, provide immunomodulation and protect against pathogens [11].

Several studies have shown that gut microbiome changes, which can be induced by individual eating habits, stress, disease, or changes in environmental factors may be followed by various inflammatory bowel diseases. Ultimately, this process may contribute to the development of CRC. The gut microbiome has been shown to be associated with controlling the effectiveness of cancer treatments and the toxicity of therapeutic agents. Therefore, therapeutic agents such as probiotics, which can support the gut microbiome, are expected to be among the most effective approaches to help fight CRC [6].

Dysbiosis can cause changes in bacterial metabolic activity or microorganism distribution in the intestines, as well as other organs, including the brain [12,13]. Symptoms associated with dysbiosis when the central nervous system is involved could include changes in patient's behaviour, cognitive functions, emotions and as well as nociception. The gut microbiota interacts with the host's immune system, the disorders in the gut can trigger the activation of inflammatory signalling pathways and thus affecting the whole body immune function. Immune stimulation by bacteria can cause continuous inflammation leading to changes known as dysplasia with a low degree of malignancy at first, but after years tumours can develop. On the other hand, inflammation cannot induce CRC without microbiota or compounds of bacterial origin [14]. Dysbiosis of the intestinal microflora is involved in a number of autoimmune and inflammatory diseases including IBD, multiple sclerosis, type I diabetes and rheumatoid arthritis [14].

Inflammation

The intestine is the main site of contact between the human body and foreign antigens. This process is associated with several types of lymphoid organs, collectively referred to as gut-associated lymphoid tissue (GALT), which is the largest collection of lymphoid tissue [15]. Thus, the immune system has an impact on the colon and is involved in protecting and regulating bowel functions. The gut microbiota

is closely linked to the immune system in such a way that it can cause or prevent inflammation. These processes may be associated with anti-inflammatory mechanisms that stimulate the regulatory cells of the immune system to inhibit inflammation [16].

Bacterial flora of the intestine is responsible for regulating the permeability of the intestinal barrier. However, there are situations in which some species of bacteria increase this permeability in response to foreign signals. As a result, metabolites associated with the microbes that enter the bloodstream, the body defends itself by producing pro-inflammatory cytokines and other metabolites, leading to an inflammatory reaction [16]. Similarly, cells within the gut epithelial tissue deliver bacterial metabolites to immune cells, promoting inflammation on both a local and systemic scale. The persistence of this condition may lead to subacute or chronic inflammation, which may subsequently cause the development of diseases such as IBD, diabetes or cardiovascular disease [16].

Inflammatory bowel disease

IBD, a heterogeneous chronic and relapsing inflammatory illness of the digestive system, is traditionally classified into ulcerative colitis (UC) and Crohn's disease (CD) [5]. Many factors contributing to the IBD development are both genetic and environmental factors. The most important among them are stress, sleeping habits, antibiotic use, hygiene level, diet, and smoking) affect the digestive system in different ways. IBD is mainly associated with intestinal dysbiosis, the decline of some species as Bacteroidetes and Firmicutes. Studies have proven that patients with CD and UC have less Faecalibacterium prausnitzii and Roseburia. In contrast, patients with CD possess more Proteobacteria, Neisseriacaea corrodens, Pasteurellaceae, Veillonella parvula and Escherichia coli (E. coli) [17]. IBD patients show an increase in the number of Proteobacteria, including E. coli however there has not been much evidence present on this. On the other hand, Rizzatti and other authors have proposed two mechanisms that may explain the relationship between an oxygen hypothesis and the presence of nitrates. Normally, the colon maintains an anaerobic environment through oxygen reduction, but during inflammation, oxygen availability increases, promoting dysbiosis and the growth of Proteobacteria. In addition, the nitrate produced during inflammation provides an advantage to the growth of E. coli, making it dominant in the large intestine [5].

Colon cancer

Patients with IBD (including UC and CD) are at higher risk of CRC developing. Data from 19 studies, which were conducted at a 10-year interval, show the risk of developing CRC in 10 years at 1.6%, in 20 years at 8.3%, and in 30 years at 18.4% (18). On subgroup analysis, patients with CD have an increased risk of CRC (relative risk (RR), 2.59; 95 percent confidence interval) but not of rectal cancer (RR, 1.46) [19]. Epidemiological data have shown that the effect on the intestinal microflora depends on several factors such as overweight, obesity, high-fat diet, smoking and also high alcohol consumption. These factors play a significant role in colon carcinogenesis [5,20]. Many studies have confirmed that changes in the gut microbiome can induce inflammation, DNA damage or changes in metabolites production from microorganisms, affect tumour progression [6].

An imbalance in the gut microbiota and heightened permeability (as described above) of the intestines can lead to inflammation in the colon, potentially contributing to the development or advancement of CRC [21]. Individuals diagnosed with CRC exhibited diminished levels of bacterial diversity and abundance in comparison to individuals without any health conditions [22]. Unfortunately, a single group of microbiota associated with CRC has not yet been identified.

Different types of microbiome bacteria

1. *Streptococcus bovis* (*S. bovis*) is the second leading cause of endocarditis caused by streptococci and accounts for 10-15% of all cases of bacterial endocarditis [23]. Patients infected with S. bovis of biotype I have a significantly higher risk of developing CRC compared to those with S. bovis biotype II. These studies indicate that infection caused by S. bovis biotype I, now known as S. gallolyticus, is strongly associated with CRC, with a prevalence ranging from 33% to 71%., which is significantly higher than the normal occurrence of CRC (10% to 25%) in the general population [24]. The relationship between inflammation and the development of colon cancer was established. There is a correlation between the pro-inflammatory properties of S. bovis proteins and their ability to promote cancer. S. bovis has been identified as actively contributing to the development of CRC, potentially through a sequence of tumour formation or progression that is driven by inflammation. This process may be related with the involvement of interleukin (IL)-1, cyclooxygenase-2 (COX-2), and IL-8 [6].

2. *Fusobacterium nucleatum* (*F. nucleatum*) is one of the most prominent strains associated with the development of CRC tumours [25]. Studies conducted by Xiangcang Ye and other researchers have revealed that colorectal tumours exhibit varying levels of expression for proinflammatory cytokines such as IL17A, IL21, TNF, and CCL20. Notably, CCL20 is consistently highly expressed in CRC patients at all stages who have an abundance of *F. nucleatum* [26].

3. *Enterococcus faecalis*. The presence of *Enterococcus faecalis* (*E. faecalis*) infection leads to DNA damage in enterocytes through the production of

extracellular superoxide. It has been observed that the *E. faecalis* population is significantly higher in patients with CRC compared to healthy individuals. Peroxide is a highly mutagenic substance that causes DNA breaks, point mutations and protein-DNA cross-linking, thus contributing to chromosomal instability and increasing the risk of CRC [27].

4. *Enterotoxic Bacteroides fragilis* (ETBF) is a type of bacterium that produces the toxin *B. fragilis* (BFT), which causes diarrhoea and non-specific colitis. These findings indicate that fragilysin, a toxin produced by *B. fragilis*, is the first known bacterial toxin to activate TCF-dependent β-catenin nuclear signalling in intestinal epithelial cells. It has been suggested that *B. fragilis* may contribute to the oncogenic transformation of colon cells [28]. This particular strain of bacteria may play a role in promoting cancer development in the colon by increasing the activity of signal transducer and transcription activator 3 (STAT3) and stimulating the immune response of Th17 [29].

5. *Peptostreptococcus anaerobius* (*P. anaerobius*) triggers an immune microenvironment that promotes inflammation and facilitates the formation of tumours in the intestine. *P. anaerobius* interacted with TLR2 and TLR4 increases intracellular levels of reactive oxidative species (ROS) in colon cells [30]. This interaction stimulates cholesterol synthesis and cell proliferation, leading to dysplasia of the colon cells [6].

6. Persistent *Salmonella* infections and colonization can lead to a chronic inflammatory state, heightening the susceptibility to chronic cholecystitis and various gastrointestinal disorders, which may include the development of cancers [6].

7. *Shigella* is widely recognized as the primary cause of diarrheal diseases. This bacteria has the ability to increase a patient's vulnerability to CRC by inducing a prolonged inflammatory response, thus promoting the development and progression of CRC. Moreover, recent research shows an overabundance of *Shigella* in the microbiome associated with the mucous membrane of patients diagnosed with adenoma [31].

8. *Campylobacter jejuni* (*C. jejuni*), a bacterium, generates a genotoxin known as cytolethal distending toxin (CDT) that possesses DNAse activity and leads to the formation of DNA double-strand breaks. While *C. jejuni* infection has been demonstrated to stimulate inflammation in the intestines, the strain *C. jejuni* 81-176 specifically promotes colorectal cancer development and triggers alterations in both microbial composition and transcriptomic responses. Importantly, these effects are dependent on the production of CDT by the bacterium [32].

9. *Sulfate-reducing bacteria* (SRB) is naturally present in the gut microbiota, but elevated quantities of these bacteria can potentially contribute to the development of colitis. This is likely due to the production of hydrogen sulphide (H2S) [33]. Research has indicated that there is a higher presence of SRB in the faeces of patients with CRC in comparison to healthy individuals [6]. Sulphide, which is harmful to colon cells, hampers the oxidation of butyrate, leading to the weakening of the protective barrier of colon cells. Additionally, it can cause DNA damage by generating reactive oxygen species (ROS) [34].

This paper is a continuation of our study in both the microbiome [35] and CRC [36]. We continue our work on this subject.

Conclusions

The CRC is induced by different factors – one of them seems to be dysbiosis. This is too early to point at one specific bacteria which is responsible for initiation of the tumour. The process should be multivariate and more research needs to be conducted in order to get a better overview as well as understanding about factors related to CRC.

Ethical approval
The study was a descriptive one. No human or animals were a subject of examinations.

Acknowledgments
Not applicable.

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Conflict of interest
The authors declare no conflict of interest.

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