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Assessment of the Human Metabolome as a Method for Molecular Diagnostics of Colorectal Cancer: Prevention and Therapy

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Abstract—The analysis of the metabolome is a key point for understanding the dynamic processes occurring in the organism. Under normal conditions, the concentration of certain compounds in tissues is determined by their role in metabolic processes and, as a rule, varies within small limits. However, with pathology, the metabolic profile of the affected tissue can change dramatically. By studying the dynamics of the composition and concentration of metabolites, one can understand the molecular basis of the occurrence of many diseases, or at least identify their biomarkers. This review focuses on the relationship between intestinal flora and colorectal cancer; however, the exact mechanism of the intestinal flora that causes this type of cancer is still unclear. Data from the literature indicate the role of metabolites of probiotic cultures: cleavage products of proteins, carbohydrates (in particular lactose), peptide bacteriocins, antioxidants, and compounds that function as neurotransmitters and neurohormones. These substances act as signaling molecules within the microbial consortium and at the same time affect the host as a whole. Microorganisms favorable for human health (lactobacilli, bifidobacteria and lactic streptococci) used as probiotics form a natural immune defense, accelerate the process of regeneration of the epithelium, and also take an active part in the process of phagocytosis, showing high efficiency in the treatment of various diseases of the gastrointestinal tract. Thus, it is important to maintain a balance between these microorganisms and opportunistic bacteria. They may also be used as probiotics in the prevention and early detection of colorectal cancer.

Keywords: metabolome, metabolites, colorectal cancer, lactobacilli, probiotics, diagnostics

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INTRODUCTION

Metabolic profiling of the tissues and blood serum of experimental animals, that are experimental models of human diseases, contributes to understanding of the mechanisms of biochemical processes occurring in the body in normal and pathological conditions, which can be further used for the diagnosis, prevention and treatment of various diseases (Piruzyan, 2005; Zelentsova et al., 2019).

The health or disease state of a person depends on exogenous and endogenous microorganisms, which together form the human microbiome. The intestinal microbiota plays a significant role in the host organism. Changes in the composition of the microbiome are associated with various pathologies, for example, obesity, diabetes, several types of cancer, diseases of the intestines, cardiovascular system pathology, and kidney pathology (Le Chatelier et al., 2013).

The penetration of bacteria through the intestinal wall leads to an increase in the number of microorganisms or their metabolites in the bloodstream, which leads to the activation of the immune system. This impact is critical, especially in tissue, because modulation of inflammation or repair processes can affect the severity of the resulting injury (Andrianova et al., 2020). In addition to influencing the immune system, the gut microbiota may interact with the kidneys through the production of various compounds, in particular short-chain fatty acids (SCFAs). These acids, represented mainly by acetate, propionate and butyrate, are the main products of the enzymatic breakdown of complex polysaccharides by colon bacteria. Certain SCFAs are very important for healthy gut function. SCFAs renew and nourish intestinal enterocytes, being an energy substrate for them. Also, SCFAs help maintain an acidic pH, thereby inhibiting opportunistic and pathogenic microorganisms and maintaining a normal healthy biocenosis.

We present a review of studies on such changes in the composition of the intestinal microbiota that affect the incidence and progression of colorectal cancer (CRC), which is a malignant tumor from the epithelial tissue of the sigmoid (colon) intestine and rectum.

CRC is the third most common cancer and the second leading cause of cancer death worldwide (Hou et al., 2021). CRC incidence and mortality rates are increasing every year. This is due to changes in lifestyle and

dietary habits, suggesting a relationship between the state of the human gut flora and the development of CRC. In the pathogenesis of colon cancer, damage to the intestinal mucosa as a result of prolonged exposure to mechanical, toxic, and allergic factors is essential, which leads to disruption of the motor and secretory functions of the intestine (Ahmed and Umar, 2018). The currently available screening test options have a number of disadvantages. Commercial tests based on stool condition show low sensitivity and a high false positive rate, which negatively affects the percentage of early detection of carcinogenesis. Standard colonoscopy has a low popularity due to invasiveness and discomfort. As a result, a promising direction in the diagnosis of CRC is the study of the metabolome and intestinal microflora leading to the ability to identify microbial populations associated with this pathology and choose effective ways to treat this disease. It is assumed that the metabolomic profile of intestinal tissues can be used to diagnose not only CRC, but a number of different diseases, and choose the best way to prevent and treat them (Piruzyan, 2005; Tilg et al., 2018).

GUT MICROBIOTA IN COLORECTAL CANCER

The microbiome is a complex microecosystem in the gut that consists of intestinal flora, epithelial cells of the mucous membranes, food probiotic components, and small molecules, including hormones, enzymes, mucus, and bile salts (Klimko et al., 2020). Probiotics are beneficial bacteria that normally live in our body, while prebiotics are compounds that become food for these bacteria. The main probiotic strains are *Lactobacillus acidophilus*, *L. rhamnosus, Bifidobacterium*, and *Streptococcus thermophilus*. Along with the above, the intestinal flora contains pathogenic bacteria, including *Enterococcus faecalis*, *Enterotoxigenic bacteroides fragilis*, *Streptococcus constellatus*, *Clostridium*, and *Streptococcus agalactiae*.

Chemical environmental carcinogens, food xenobiotics, excessive use of antibacterial drugs, improper use of laxatives, and other factors significantly affect the state of the intestinal microflora, causing quantitative and qualitative disturbances in the ratios between different microbial populations (Konev, 2005). Dysbiosis develops, characterized by a violation of the ratio of microbial populations in various parts of the intestine, and increased reproduction of opportunistic flora. It has been shown that the microbiota profiles in CRC patients differ from those in healthy people, and bacterial phylotypes differ depending on the location of the primary tumor. However, compositional variations of the microbial profile are not limited to tumor tissue and differ even in the case of proximal and distal colon cancer (Kim et al., 2020). Using CRC model objects, it was shown that driver bacteria cause inflammation, and increased cell proliferation, and enhance the production of genotoxic substances that promote mutations associated with the adenoma–carcinoma sequence. Experimental data in animal models also point to a link between the gut microbiota and the development of CRC (Wang et al., 2017).

One of the hallmarks of cancer is metabolic dysregulation. In view of this, metabolomics is the optimal approach for studying the metabolic mechanisms of oncogenesis (Nannini et al., 2020). Metabolic fingerprinting, combining pyrosequencing with gas chromatography–mass spectrometry, is used to identify differences in the profiling of intestinal flora and fecal metabolites between healthy people and patients with CRC. It was shown (Ohara et al., 2010) that dysbiotic changes of varying severity, such as a decrease in normal flora and colonization by opportunistic bacteria, were found in all patients with CRC. The number of bifidobacteria was reduced in 82.7% of patients; lactobacilli, in 71.1%; lactic acid bacteria, in 53.8%; enterococci, in 48%; and *Escherichia* with normal fermentation, in 50%. An increase in hemolytic *E. coli* was found in 11.5% of patients. An increased number of opportunistic microflora occurred in 48% of CRC patients. The following in particular stand out: *Klebsiella pneumoniae*, was found in 13.5% of patients; *Enterobacter* spp., in 7.6%; *Proteus* spp., in 1.9%; *Citrobacter* spp., in 3.8%; yeast-like fungi of the genus *Candida*, in 7.6%; *Staphylococcus aureus*, in 5.8%; *Pseudomonas aeruginosa*, in 3.8%; *Acinetobacter*, 1.9%; and *Clostridium*, in 1.9% (Ohara et al., 2010).

It is known that SCFAs, the main metabolites formed as a result of microbial fermentation of insoluble dietary fibers in the intestine, can directly activate G-protein coupled receptors, inhibit histone deacetylases, and serve as energy substrates for linking dietary patterns and gut microbiota, thereby improving gut health (Hou et al., 2021).

The fecal microbiota of patients (with a mean age of 52.5 years) was analyzed, which included healthy people and patients with CRC (Wang et al., 2017). Analysis of microbial DNA in human faeces was performed by pyrosequencing to specifically detect the V4 region of bacterial ribosomal 16S RNA on isolated genomic DNA. The following bacterial phyla were found in the fecal microbiota of CRC patients and healthy individuals: Verrucomicrobia, Tenericutes, Synergistetes, Proteobacteria, Fusobacteria, Firmicutes, Cyanobacterium, Chlorobacteria, Bacteroidetes, Actinobacteria, Acidobacteria, Crenarchaeota and Euryarchaeota. This study did not find significant differences in the fecal intestinal microbiota of patients with CRC and healthy individuals at the level of bacterial phyla. Nevertheless, significant differences in intestinal fecal microbiocenosis at the level of genera and species were revealed. In patients with CRC, compared with the intestinal biocenosis of healthy people, the following genera predominate: *Clostridium* spp., *Fusobacterium* spp., *Streptococcus* spp., and *Peptostreptococcus* spp. Many species from these genera have proteolytic and lipolytic activities.

However, in patients with CRC, the following types predominate: *Citrobacter farmeri*, and *Akkermansia muciniphila*, which is a mucin-degrading bacterium that can lead to the development of CRC if predisposed (Azcárate-Peril et al., 2011).

In the fecal biocenosis of healthy people, the following genera and species predominate: *Megamonas hypermegale*, *Anaerosporobacter* spp., *Enterobacter* spp., *Dorea formicigenerans*, *Adlercreutzia* spp., *Faecalibacterium* spp., *Dialister* spp., *Prevotella* spp., *Roseburia* spp., *Ruminococcus* spp., *Pseudobutyrivibrio* spp., and *Bacteroides* spp. Many of these microorganisms are part of the main composition of the microbiota and are SCFA producers. In patients with CRC, compared with the profile of healthy individuals, an increased content of SCFAs was found in particular: acetic, valeric, butyric, and isovaleric acids. The concentration of isobutyric acid is higher in the fecal metabolite profile of healthy individuals, and the concentration of propionate is almost the same. It is believed that SCFAs, especially butyric acid, have anti-cancer effects: they protect against the onset and progression of CRC (Wang et al., 2017). Most of the microorganisms inhabiting the intestines are of the glycolytic type and belong to the phyla Firmicutes, Bacteroidetes, and Actinobacteria. When protein residues of food enter the large intestine, the main source of nutrition—the prebiotic substance—is replaced by a protein substance, which leads to bacterial proteolysis with the formation of end products—cresol, indole, hydrogen sulfide, skatole, mercaptans, etc.

These products are toxic to intestinal enterocytes. Next, there is a change in the ratio of bacterial phyla—Firmicutes/Bacteroidetes and Bacteroidetes/Actinobacteria, alkalization of the internal environment of the colon, and an increase in the number of opportunistic pathogens and pathogens with proteolytic activity—representatives of the genera *Clostridium* spp., *Bacteroides* spp., *Proteus* spp., *Fusobacterium* spp., *Peptostreptococcus* spp., *Akkermansia* spp., etc.

If changes in the microbiome are not amenable to compensatory adaptation, this can lead to the development of pathologies. Therefore, the identified changes in the populations of the intestinal microflora in patients with CRC suggest the feasibility of using drugs to restore normal microflora at all stages of treatment and rehabilitation of patients (Ohigashi et al., 2011; Zhang et al., 2012).

Clostridium difficile, being part of the normal human intestinal microbiota, are both toxigenic and non-toxigenic (Gerding et al., 2015). *Clostridium* produce the largest amount of toxins compared to other bacteria, which can lead to various pathologies (Popoff and Bouvet, 2009). The genetic characteristics of toxigenic clostridia indicate the possibility of horizontal transfer of toxin genes (Gantois et al., 2006). There is increasing evidence that lactobacilli and bifidobacteria, which are part of the gut microbiota, exhibit antimicrobial activity and are involved in protecting the gastrointestinal tract (GIT) of the host. Therefore, it is assumed that the main mechanism by which probiotic strains exert their beneficial effects lies in the balanced production of SCFAs. The mechanisms by which gastrointestinal pathogens are combated are complex and include competitive metabolic interactions and the production of antimicrobial molecules.

THERAPEUTIC STRATEGIES FOR DISEASE TREATMENT WITH PROBIOTICS

Lactic acid bacteria can be used in the form of oral and parenteral preparations to replace potentially pathogenic microflora. Probiotic cultures are resistant to the harsh environment of the upper digestive tract. This allows them to reach the large intestine, where their beneficial effect is mainly realized. In particular, these bacteria can suppress the reproduction of harmful putrefactive and pathogenic bacteria, as well as displace pathogens that cause intestinal and nosocomial infections, that are often multi-resistant to widely used antibiotics (Stoyanova and Gabrielyan, 2017).

Antibiotics and probiotics today are not considered as completely incompatible groups of medicinal drugs or antagonists. Their joint rational use creates the prerequisites for achieving maximum results in a wide range of clinical situations. The use of probiotics is being considered as a new effective and safe alternative preventive or therapeutic strategy for the treatment of CRC. They are able to optimize various physiological functions of the host organism and can be used in people with suppressed immunity as well. The antitumor potential of probiotic strains is due to metabiotics with epigenetic, antimutagenic, immunomodulatory, apoptotic, and antimetastatic effects (Sharma and Shukla, 2016).

The main feature of probiotic strains is their ability to prevent the growth of pathogenic and opportunistic microorganisms due to the synthesis of antimicrobial metabolites such as lactic and acetic acids, peroxides, and diacetyl, but the leading place is given to specific antimicrobial substances of a protein nature called bacteriocins. Bacteriocins, even at very low concentrations, have the ability form pores in bacterial membranes.

Bacteriocin fragments have a short lifespan in the human body or environment, which minimizes the ability of strains to interact with degraded antibiotic fragments: this is a common starting point in the development of bacteriocin resistance, compared to conventional antibiotics, which are secondary metabolites (Lahtinen et al., 2011; Fiorda et al., 2017). Bacteriocins, unlike antibiotics, are completely broken down in the body, and the likelihood of complications from bacteriocins is minimal, while the use of antibiotics often has negative consequences for humans.

Bacteriocins are produced by the lactococci *Lactococcus lactis*, these are streptococci of the serological group N, which, according to their systematic position, are isolated from the genus *Streptococcus*, including pathogenic *Streptococcus*, and are named *Lactococcus*, they do not cause infectious diseases in humans and animals (Bernbom et al., 2006). There is a growing interest in bacteriocin-forming lactococci, which, due to their harmlessness, high enzymatic activity, and high antimicrobial activity, are the object of fundamental research to create new active probiotics and biological preservatives. It has been established that nisin producing strains have the function of maintaining the balance of a group of lactic acid bacteria in the intestinal tract of humans and animals. Nisin is mainly effective against gram-positive spore-forming bacteria and is ineffective against pathogens related to gram-negative bacteria and the microscopic fungi that colonize food during storage, which are the main cause of spoilage and cause disease in humans (Willey and van der Donk, 2007). The resulting volatile fatty acids are also the most important regulators of carbohydrate, lipid, and energy metabolism in the gastrointestinal tract, liver, and other tissues (Ustyugova et al., 2012; Shenderov, 2013).

It has been shown that the use of probiotic preparations based on lactic acid bacteria has a positive effect on the functioning of organs and tissues of the human body, including the immune and endocrine systems. Probiotics have anticarcinogenic, antimutagenic, and antioxidant activities, and also suppress pathogenic and opportunistic intestinal microorganisms (Stoyanova et al., 2020).

The effectiveness of lactic acid probiotic bacteria has also been proven in the prevention and treatment of antibiotic-associated diarrhea, which occurs when the composition and activity of the normal microflora of the human gastrointestinal tract is disturbed. In adults, the use of products containing *L. casei* DN 114001, a probiotic strain has been shown to be effective in preventing diarrhea (Hickson et al., 2007). In children, oral lactobacilli may prevent diarrhea or reduce the side effects associated with antibiotics such as amoxicillin (Shenderov, 1998). A positive effect of the *L. casei* DN 114001 strain has been shown during eradication therapy of *H. pylori* infection in children (Sýkora et al., 2004).

In recent years, more and more attention has been paid to the search for new strains with antimicrobial potential. An intensive search is underway for producers of antibiotic substances that are not pathogenic for humans with broad spectrum antimicrobial activity (Stoyanova et al., 2020), and producers of antibiotic substances that are strictly specific.

Known probiotics are listed below:

— *Bifidobacterium bifidum* dominates the large intestine, supports the production of vitamins in the intestine, suppresses harmful bacteria, supports the immune system response, and prevents diarrhea;

— *Lactobacillus acidophilus* improves lactose tolerance, reduces the level of *Escherichia coli* by 61%, reduces cholesterol levels, and relieves gas formation in the abdomen;

— *Bifidobacterium longum* supports liver function, reduces inflammation, and removes lead and heavy metals;

— *Lactobacillus casei* supports immunity, suppresses *Helicobacter pylori*, and helps fight various infections;

— *Bifidobacterium infantis* reduces diarrhea and constipation;

— *Lactobacillus brevis* boosts cellular immunity, enhances natural killer T-cells, and kills *Helicobacter pylori* bacteria;

— *Bacillus subtilis*—a probiotic that causes a powerful immune response, inhibits the growth of harmful bacteria, in particular salmonella, and inhibits other pathogenic microorganisms;

— *Lactobacillus bulgaricus*—a probiotic strain that fights harmful bacteria that invade the digestive system, neutralizes toxins, and naturally produces its own antibiotics;

— *Lactobacillus rhamnosus* maintains bacterial balance, and helps fight urinary tract and gastrointestinal infections.

Probiotics are involved in increasing the level of the host's immune defenses and thus reduce the frequency and duration of infections, greatly alleviate antibiotic-associated diarrhea and alleviate acute diarrhea of various causes. Probiotics have also shown great potential for the treatment of CRC (Ohigashi et al., 2011; Zhang et al., 2012; Raman et al., 2013). Lactobacilli have a pronounced antagonistic activity and the ability to adhere, which provides an important role for these microorganisms in maintaining colonization resistance. Due to these properties, lactobacilli inhibit the growth and reproduction of foreign microflora coming from outside, prevent the engraftment of foreign microflora, and block the receptors of mucous membrane cells from adhesion of potentially pathogenic bacteria. Lactobacilli and the structural components of these cells can have a pronounced effect on the immune system through stimulation of monocyte migration, activation of phagocytic activity, and induction of delayed-type hypersensitivity (Solov'eva et al., 2010). The use of dietary supplements with a probiotic effect can be considered as one of the most physiological and clinically significant ways to correct dysbiotic disorders in diseases of the gastrointestinal tract, including CRC.

CONCLUSIONS

The data considered here allow us to conclude that the metabolomic profile of the intestine can not only aid in diagnosis of human diseases, in particular colorectal cancer, but also in choosing the best way to prevent and treat the disease. Such studies expand the boundaries of understanding the phenomenon of human health in the aspect of endoecology and open up prospects for the development of biotherapy (Shenderov, 2017). Ultimately, the results of the research serve as the basis for the development of preventive and therapeutic approaches for the treatment of many diseases associated with an altered gut microbiome (and its metabolites) in an era of increasing antibiotic resistance.

COMPLIANCE WITH ETHICAL STANDARDS

The authors declare they have no conflicts of interest.

This article does not contain any research involving humans and animals as research objects.

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