THEORETICAL ANALYSIS OF THE INTESTINAL MICROBIOTA INFLUENCE ON COLORECTAL CANCER DEVELOPMENT

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ABSTRACT

Background. ColoRectal Cancer (CRC) is one of the most common malignant tumors: about a million new cases are diagnosed annually in the world. In Ukraine, the incidence of CRC is 20.5 per 100,000 population. The ratio of mortality and morbidity indicates significant shortcomings in the diagnosis, treatment and prevention of CRC.

Aim. To study theoretical scientific developments regarding the influence of intestinal microbiota on the development of colorectal cancer.

Materials and Methods. In the course of writing the scientific article, a number of modern literary sources and the latest data from scientific Web databases were studied of Science, Scopus, Google Scholar and PubMed, methods of systematic and comparative analysis of the specified problem were applied. Medical and statistical data of scientific publications on morbidity and treatment results in different countries of the world were studied.

Results. According to world statistics, CRC is the third most common in men (10.0% of the total number of malignant neoplasms) and the second most common in women (9.2%). Approximately 45.0% of CRC patients die despite treatment. A high percentage of emergency operations is recorded in elderly patients with chronic accompanying pathology, which is the cause of a large number of postoperative complications ([24.0–80.0] %) and mortality ([11.0–36.0] %). The incidence of CRC in Ukraine is the highest among a number of countries and indicates significant deficiencies in the diagnosis and treatment of patients, as well as in the prevention of this disease. Intestinal microbiota plays an important role in the development of colorectal cancer. Disruption of the functioning of the intestinal microbiota also leads to the development of a significant number of infectious, metabolic, oncological, neurological and endocrine diseases.

Conclusion. The analysis of literary sources and clinical studies of domestic and foreign authors allows us to assert that the microbiota, influencing the immune system, plays an important role in the induction and progression of colorectal cancer.

Keywords: *mortality, morbidity, treatment.*

Introduction

ColoRectal Cancer (CRC) is one of the most common malignant tumors: about a million new cases are diagnosed annually in the world. The highest incidence of CRC is recorded in Australia and New Zealand (44.8 per 100 thousand male and 32.3 per 100 thousand female population), the lowest – in West Africa (4.5 and 3.8 per 100 thousand population, respectively). Almost 55.0% of CRC cases occur in more developed regions of the world, however, in many countries, the lower prevalence of detected cancer may be due to the absence or incomplete coverage of the population by statistical observation. It is well known that there are significant differences between the shares of the population whose monitoring is reflected in cancer registries between high- and low-income countries [1–5].

For a long time, the occurrence of CRC was associated with a genetic predisposition, but later it was proven that in most cases, CRC occurs episodically and irregularly. Not only absorption of useful substances takes place in the intestines. It is also responsible for the formation of a normal immune response to stimuli. The normal state of the microbiota plays a major role in the stability of its work.

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Microbiota is a term used to characterize the microbiocenosis of individual organs and systems of the human body.

Makkouk A. & Weiner G.J. (2014) examined the etiological factors of colorectal cancer. The authors report that in addition to genetic mutations and inflammation, the list of these factors includes epigenetic factors, nutritional changes, dysfunction of the immune system, and microbiota, that is, the population of microorganisms (bacteria, archaea, fungi, protozoa, and viruses) that inhabit all parts of our body [6].

According to Irrazabal T. et al. (2014) multiple effects of the intestinal microbiota are associated with the diversity of the composition of microorganisms. Since mutations of the genes of the cells of the colonic epithelium are an indispensable attribute of these effects, the microbiota is possibly associated with both the formation of genotoxic stress, which contributes to genetic and epigenetic changes of the intestinal epithelium, and the maintenance of the inflammatory state of the intestine, which together with oxidative and nitrosative stress leads to CRC [7].

Clark C.R. (2016) emphasizes that the microbiota is a community of all microorganisms that exist in a certain environment (on the skin, in the respiratory tract, intestines, etc.). In particular, the human intestinal microbiome contains a huge number of various bacteria, microscopic fungi and even viruses [8].

McDermott A.J. & Huffnagle G.B. (2013) in their research concluded that the gut microbiota is actively involved in morphogenesis, various metabolic processes and homeostasis maintenance. Observations on mice are especially revealing in this regard. Without microbiota, these animals are more sensitive to infections, they have a decrease in the vascularization of the intestinal wall, elongation of the villi of the intestinal epithelium due to atrophy of the crypts and a decrease in the rate of its renewal, a decrease in the enzymatic activity of digestion, the production of cytokines, the level of serum immunoglobulins and the number of intraepithelial lymphocytes, a decrease in the thickness of the muscle layer and the size of Peyer's patches [9].

Ha C. et al. (2014) state that colonization of the intestine of mice microbiota ensured the restoration of the mucosal immune system and induced the expression of various genes related to the absorption of nutrients, metabolism, angiogenesis, mucosal barrier function, and the intestinal nervous system. The microbiota in the intestines comes into contact with the second, after the brain, the largest pool of nerve cells in the body and with the pool of immune cells, influencing the formation of cognitive functions and the immune status of the body [10].

The above-mentioned studies conclude that the gut microbiota plays an important role in the development of infectious complications. Violation of its functioning leads to the development of a significant number of diseases (infectious, metabolic, autoimmune, oncological, neurological and endocrine), including colorectal cancer.

The **aim** of the study was to study the influence of intestinal microbiota on the development of colorectal cancer in patients.

Materials and Methods

Web databases of Science, Scopus, Google Scholar and PubMed were studied. During the development of the material, methods of systematic and comparative analysis were applied in relation to this problem.

Results and Discussion

Microbiota is a collection of microorganisms living in the human intestine. It consists of bacteria, fungi, protozoa, viruses and bacteriophages living in symbiotic relationships and having an epigenetic effect on the human body. This complex group of organisms has a significant metabolic potential, mainly due to its ability to decompose various substances. Hundreds of types of bacteria with different physiological and biochemical characteristics live in the lumen of the large intestine, in the mucus layer and on the surface of the epithelium.

Gill S.R. et al. (2006) state that the human gut microbiota is influenced by many factors, such as age, geographic location, dietary preferences and taste preferences, and physical activity. Microbiota constantly develops, grows and adapts depending on environmental factors and bacterial relationships [11].

Verdecchia A. (2007) emphasizes that the intestinal microbiota, which takes an active part in a wide range of physiological processes occurring in the large intestine, is of particular clinical interest. It is known that the intestinal microflora prevents the colonization of the large intestine by pathogenic microorganisms, stimulating the production of mucus and antimicrobial agents, strengthening the barrier between the intestinal tissues and its cavity, participating in the regulation of vital processes of intestinal cells [12].

According to Flint H.J. (2012), the composition of the human microbiota depends on a num-

ber of factors: the availability of nutrients, pH, the presence of oxygen, the influence of drugs (antibiotics), the secretion of bile acids and digestive enzymes, the integrity of the mucous membranes and the interaction with the host's immune system [13].

Ley R.E. (2006) proves that in situations where the bacterial balance in the large intestine is disturbed due to various external or internal factors, the number and variety of pathogenic bacteria increases, which in itself is the basis for the development of inflammatory changes in the intestinal wall. Thus, with disturbances in the functioning of the intestinal microflora, the risk of developing a significant number of diseases (infectious, metabolic, autoimmune, oncological, neurological, and endocrine), including colorectal cancer, increases [14].

Durban A. et al. (2011) emphasize that the microflora of the colon plays an important role in the development of infectious complications. A person exists in close contact with a huge number of microorganisms living on the skin, mucous membranes, in the oral cavity, urogenital and gastrointestinal tracts. Bacteria play a key role in many processes occurring in the colon, including fermentation of proteins and carbohydrates, transformation of bile acids and fats, metabolism of xenobiotic substances, stimulation of the immune system, and activation and disposal of mutagenic metabolites. The results of the vital activity of bacteria significantly affect the human body in many aspects - anatomical, physiological, biochemical and genetic [15].

Tkach S.M. et al. (2014) note that the microflora of the colon contributes to the development and regulation of the immune system (especially the local one), preventing the colonization of the colon by pathogenic agents [3].

According to Prakash S. et al. (2011), the intestinal microbiota stimulates the production of mucus and antimicrobial proteins, strengthening the barrier between the cavity and intestinal tissues, regulates the processes of intestinal cells (proliferation, growth, differentiation, survival and death), controls angiogenesis in the surrounding tissues [16].

Gagniere J. et al. (2016) claim that the species composition of the microbiota may vary depending on the age, lifestyle, diet and genotype of the subject. The microbiota is dominated by *Firmicutes phyla* ([30.0–50.0] %), *Bacteroidetes* (20.0–40.0 %) and *Actinobacteria* ([1.0–10.0] %). Strict anaerobes, including *Bacteroides, Eubacterium*, *Bifidobacterium, Peptostreptococci,* and *Atopobium,* constitute the main, and facultative anaerobes, such as *Lactobacilli, Enterococci, Streptococci,* and *Enterobacteriaceae,* a smaller (approximately 1000-fold) part of the microbiota of the large intestine, only 50.0% of the number of species, inhabiting the intestine [17].

Jandhyala S.M. et al. (2015) emphasize that the metabolic functions performed by the microbiota include anaerobic fermentation of carbohydrates with the formation of CO_2, H_2, CH_4, short-chain fatty acids, and such metabolites as phenolic compounds, amines, ammonia, nitroso compounds, and indoles. They can affect gene expression, proliferation and differentiation of the intestinal epithelium, mediate vitamin synthesis, ion absorption and mucus formation. Such a complex metabolic activity of the microbiota affects the obtaining of energy from the consumed food, regulates the storage of fat, and helps the absorption of substrates for both humans and the microbiota itself [18].

Wu N. et al al. (2013) conducted a comparative study of the microflora of the colon of patients with CRC and healthy people. The authors found no significant differences between samples for most bacteria, with the exception of *Fusobacteria*, which was found in greater numbers in the feces of patients with colon malignancies. Also, in the group of patients with CRC, an increased number of *Eubacteriaceae, Clostridiales, Staphylococcaceae* and *Enterococcaceae* bacteria was noted in comparison with the control group of healthy people [19].

Toprak N.U. et al. (2006) presented data in which EnteroToxigenic strains of *B. Fragilis* (ETBF) were isolated by the method of bacteriological cultivation of bacteria from feces of patients diagnosed with CRC. After that, using ethanol precipitation from cultivated colonies of *B. Fragilis* isolated DNA, with its subsequent analysis by polymerase chain reaction. According to the results of research, it was found that in patients with CRC, the percentage of detection of the ETBF strain is significantly higher than in the control group: 28.8% and 8.5%, respectively [20].

McCoy A.N. et al. (2013), found the connection of bacteria of the genus Fusobacterium with the development of KRR. When comparing groups of subjects, it was found that in the stool samples of patients with malignant neoplasm of the large intestine, Fusobacteria is present in a significantly greater number compared to patients with colon adenoma and healthy people [21].

Koropatkin N. et al. (2012) noted a decrease in bacterial diversity, an increase in the number of gram-negative bacteria of the genus *Fusobacterium* and *Porphyromonas*, which belong to pro-inflammatory bacteria in the colon of patients with CRC [22].

Boleij A. & Tjalsma H. (2012) published the results of a meta-analysis based on six independent studies (a total of 340 patients), demonstrating that in patients with a high bacterial load of *S. Gallolyticus* (biotype I) had a higher risk of developing colon cancer compared to patients who had increased growth of other *S. Bovi*. However, the main shortcoming of the presented results was that the researchers did not divide *S. Bovi* into biotypes. Thus, despite the fact that *S. Gallolyticus* infection, it can be, in its essence, an indicator of the development of colorectal cancer [23].

According to research by Klein R.S. et al. (1977) *Streptococcus gallolyticus* (formerly *S. Bovi biotype I*), is by definition a pathogenic microorganism for humans causing bacteremia, endocarditis and urinary tract infections and can provoke the development of colorectal cancer [24].

Conclusions

Thus, the analysis of literary sources and clinical studies of domestic and foreign authors allows us to state that the microbiota, influencing the immune system, plays an important role in the induction and progression of colorectal cancer. The influence of microbiota on cancer can be local, manifested at the level of the intestine itself, or systemic, realized first through an intact barrier, and then due to its violation. In turn, the immune and inflammatory responses to CRC are very complex and adapted to the stage of the cancer, the context of its microenvironment, and especially to the composition of the microbiota.

The scientific developments of scientists prove that with disturbances in the functioning of the intestinal microbiota, the risk of developing a significant number of diseases (infectious, metabolic, autoimmune, oncological, neurological and endocrine), including colorectal cancer, increases.

DECLARATIONS:

Disclosure Statement

The authors have no potential conflicts of interest to disclosure, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

Statement of Ethics

The authors have no ethical conflicts to disclosure.

Data Transparency

The data can be requested from the authors.

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