GUT DYSBIOSIS AND COLORECTAL CANCER: FROM ONCOGENESIS HYPOTHESES TO NON-INVASIVE DIAGNOSTICS

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Colorectal cancer (CRC) is one of the most prevalent malignant neoplasms that occupies the leading position in terms of cancer mortality. The main problem of CRC is that the disease is diagnosed at the advanced stages (about 50% of cases identified are stage III and IV CRC), which results in high mortality. Dysbiotic gut microbiota alterations represent one of the key risk factors of CRC. Three hypotheses of CRC emergence were formulated in order to explain the relationship between dysbiosis and carcinogenesis: “alpha-bug”, keystone pathogen, and driver–passenger hypotheses. The driver–passenger model is the most promising, it divides bacteria into “drivers” of cancer triggering inflammation and cell damage and the passenger bacteria modeling tumor microenvironment, accelerating tumor growth, and exacerbating dysbiosis. Drivers and passengers can be markers of various carcinogenesis stages. Colonoscopy involving examination of the surface of the rectum and colon is the most effective method to detect CRC, including the early stage disease. However, the wide use of this procedure is limited by the fact that it is associated with discomfort for patients and the risk of possible sequelae. Non-invasive microbiota assessment based on the driver–passenger model can become a safe and affordable alternative to the invasive diagnostics during preventive screening, since it makes it possible to improve survival rate due to involvement of a larger number of patients.

Keywords: colorectal cancer, inflammatory bowel diseases, microbiota, microbiome, diagnostics, carcinogenesis hypotheses, personalized medicine, non-invasive studies, survival

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ДИСБИОЗ КИШЕЧНИКА И КОЛОРЕКТАЛЬНЫЙ РАК: ОТ ГИПОТЕЗ ОНКОГЕНЕЗА К НЕИНВАЗИВНОЙ ДИАГНОСТИКЕ

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Колоректальный рак (КРР) — одно из самых распространенных злокачественных новообразований, занимающее лидирующие позиции по смертности от рака. Основная проблема КРР — диагностика заболевания на поздних стадиях (около 50% случаев выявляют на III и IV стадиях), что приводит к высокой летальности. Одним из ключевых факторов риска КРР являются дисбиотические нарушения кишечной микробиоты. С целью объяснить взаимосвязь дисбиоза и канцерогенеза были сформулированы три гипотезы возникновения КРР: «Alpha-bug», «Keystone pathogen hypothesis» и «Driver-Passenger». Модель «Driver-Passenger» наиболее перспективна и разделяет бактерии на «драйверы» рака, запускающие воспаление и повреждение клеток, и «бактерии-пассажиры», моделирующие микроокружение опухоли, усиливающие ее рост и усугубляющие дисбиоз. Драйверы и пассажиры могут выступать маркерами различных стадий онкогенеза. Колоноскопия поверхности прямой и ободочной кишки — наиболее эффективный метод для обнаружения КРР, в том числе на ранних стадиях заболевания. Однако повсеместное применение данной процедуры ограничивается связанным с ней дискомфортом для пациентов и риском возможных последствий. Неинвазивное исследование микробиоты на основе модели «Driver-Passenger» может стать безопасной и доступной альтернативой инвазивной диагностике в ходе профилактического скрининга, позволяя повысить выживаемость за счет вовлечения большего числа пациентов.

Ключевые слова: колоректальный рак, воспалительные заболевания кишечника, микробиота, микробиом, диагностика, гипотезы канцерогенеза, персонализированная медицина, неинвазивные исследования, выживаемость

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CRC Statistics

Colorectal cancer (CRC) is a malignant neoplasm of various parts of the colon or rectum and one of the most common types of pathological tumor processes (10% of all cancer cases) [1]. CRC ranks second or third among the most frequent causes of cancer deaths: about 1.1–2 million new cases (600–935 thousand deaths per year) [2].

Given the trends, the forecast for detecting new CRC cases in Western countries by 2030 is 2.2 million people, and by 2040, about 1.6 million deaths annually will occur among 3.2 million patients [1, 3]. The highest mortality is recorded in Eastern Europe. Among adults under 50, there is a tendency towards an increase in CRC cases, especially rectal and colon cancer, and subsequent deaths [3, 4], which, along with the overall dynamics, is causing concern.

The dynamics of CRC incidence in the Russian Federation corresponds to the global trend. For the period 2011–2021, the average annual increase in the detection of colon and rectal cancer is 2.14% and 1.47%, respectively [5]. In 2021, cancer of various parts of the intestine accounted for a total of 12.2% of all malignant neoplasms [4]. This trend can be explained not only by a true increase in incidence but also, probably, by improved screening quality [1].

Along with an annual increase in CRC cases among young people by 1–2.4%, there is a steady decrease in morbidity and mortality among people aged ≥65 years, which is associated with increased participation of the risk group in regular preventive screening and once again confirms the need to develop new strategies for early diagnosis and prevention [3, 4].

The prognosis for the course and outcome of the disease depends on the diagnosed stage. Approximately 50% of CRC detection cases occur collectively at stages III and IV of the disease, leading to high mortality in the first year after detection [1,4]. Early tumor diagnosis (at stages 0, I, or II) is accompanied by 80% survival over five years, which decreases to 10% with later diagnosis [6].

Most CRC cases are sporadic, and only 20–30% are caused by hereditary syndromes [3]. The prevalence of sporadic cancer cases over hereditary ones indirectly confirms the dominance of various environmental factors as the main cause of the onset and development of carcinogenesis [2].

Risk Factors

The emergence and development of CRC is a multifactorial and multi-stage process, representing a complex interaction of environment, lifestyle, genetic, epigenetic, and other factors [2]. Among other risk factors, age, Western diet (especially consumption of large amounts of red meat), smoking, alcohol abuse, obesity, diabetes, and inflammatory bowel diseases (IBD) are highlighted [3]. Dysbiotic disturbances in the microbiota are also considered a key risk factor for CRC. Every year, the global scientific community publishes new data confirming the pathogenic and carcinogenic effects of dysbiotic microbial communities [2, 3, 6–10].

Dysbiosis stimulates the emergence and development of a cascade of various inflammatory reactions in the intestine, up to IBD, which, along with the direct impact of pathogenic and opportunistic microorganisms, is recognized as one of the main causes of CRC [2, 6]. Patients diagnosed with IBD have a higher risk of developing CRC: the probability of development is 8.3–20% [11].

Thus, a comprehensive approach to studying intestinal oncogenesis involves analyzing the three-way interaction between the intestinal microbiota, the mucosal immune system, and colonic epithelial cells [7, 8].

CRC Hypotheses and Microbiota

To approach understanding the potential mechanism of carcinogenesis influenced by the microbiota, as well as the development of dysbiotic disturbances in this process, three models were successively proposed: "Alpha-bug", "Keystone pathogen hypothesis", and "Driver-Passenger".

"Alpha-bug" Model

This model was based on a hypothesis that emerged as a result of studies on the enterotoxigenic subtype of Bacteroides fragilis (ETBF) and was proposed by Sears CL and Pardoll DM [7]. According to this model, bacteria possessing unique virulence factors not only directly trigger chronic inflammation and carcinogenesis and negatively affect the immune system but also contribute to dysbiosis by displacing commensal bacteria with anti-tumor effects. Such bacteria were called "alpha-bugs".

In the process of developing the "Alpha-bug" model, various researchers supplemented it with the following taxa: *Escherichia coli* pks+, *Enterococcus faecalis*, *Fusobacterium spp*., *Streptococcus gallolyticus* subsp. *gallolyticus* (*S. bovis* biotype I) [2].

"Keystone pathogen hypothesis" Model

In their model, Hajishengallis G and co-authors point out several shortcomings of the "Alpha-bug" hypothesis: focusing only on individual toxigenic species, excluding the influence of commensals from consideration (i.e., lack of a comprehensive approach), analyzing oncogenesis starting from the dysbiotic stage. Their proposed model suggests considering "keystone" bacteria whose impact on the host organism is disproportionate to their numbers. These "keystone" minor bacteria affect homeostasis, microbiota composition, initiate inflammatory processes, and dysbiosis. The hypothesis complements the list of organisms included in the "Alpha-bug" model with the following species: *B. thetaiotaomicron*, *Citrobacter rodentium*, *Klebsiella pneumoniae*, *Methanobrevibacter smithii*, *Porphyromonas gingivalis*, *Proteus mirabilis* [10].

"Driver-Passenger" Model

The "Driver-Passenger" model, also proposed by Tjalsma H and colleagues, expands and unifies the first two concepts, viewing carcinogenesis as a complex process induced by driver bacteria and progressing under the influence of passenger bacteria. Drivers cause inflammation and epithelial cell damage, contributing to the onset of CRC, and create a favorable environment for the development of opportunistic and commensal passengers. Passengers are better adapted to the tumor microenvironment, promote further progression of carcinogenesis, can suppress the growth of drivers, and exacerbate dysbiotic disturbances in the microbiota [12].

The functional role of driver bacteria shows significant similarities with the characteristics of alpha-bugs and "keystone" bacteria, which expectedly suggests common candidates. Researchers propose the following bacteria: *B. thetaiotaomicron*, *Bifidobacterium bifidum*, *E. coli* (филотип B2 и pks+), *E. faecalis*, *Eubacterium rectale*, ETBF, *P. endodontalis*, *Ruminococcus gnavus*; *Citrobacter spp*., *Morganella spp*., *Salmonella spp*., *Shigella spp*.; *Enterobacteriaceae*, *Porphyromonadaceae*, *Pseudomonadaceae*, *Ruminococcaceae*.

Taxa such as Clostridium septicum, P. *gingivalis*, S. gallolyticus *subsp*. gallolyticus, *Proteus spp*., *Fusobacterium spp*., and other *E. coli* pathotypes can be singled out into a separate "driver-passenger" subgroup, as they combine properties of both groups. For example, *Fusobacterium spp*. have a high affinity for intestinal epithelial cells, especially tumor cells. *F. nucleatum* can form biofilms between itself and other species, such as *C. difficile, Candida albicans*, *E. faecalis*, *P. gingivalis*, *Streptococcus spp*. [3].

The group associated with late stages of carcinogenesis and functioning as passengers includes: Akkermansia muciniphila, *Prevotella intermedia*, *Parvimonas micra*, *Peptostreptococcus anaerobius*, *P. stomatis*, *Saccharomyces cerevisiae*; *Aspergillus spp*., *Lactobacillus spp*., *Clostridium spp.*, *Collinsella spp*., *Klebsiella spp*., *Mucor spp*., *Peptostreptococcus spp.*, *Prevotella spp*., *Roseburia spp.*, *Staphylococcus spp.*, *Streptococcus spp*., *Veillonella spp*.; *Streptococcaceae*. Both drivers and passengers show proven associations with certain stages and mechanisms of carcinogenesis, with elevated levels of various interleukins and Th17-mediated immune response, with some CRC subtypes, and with the mutational status of tumor and adenoma cells [3, 13].

Currently, the "Driver-Passenger" model is a comprehensive concept that most closely reflects the dynamic, functional, and temporal interactions within the microbial community at various stages of CRC, compared to other hypotheses. The limitations of this model lie in the heterogeneity and multifunctionality of the microbiota, whose composition and quantity vary depending on many factors, and currently do not take into account the influence of commensal archaeal species and parasitic infections [12].

Further research will help clarify microbiome-associated mechanisms of CRC development and progression to create a more universal model of oncogenesis.

Dysbiotic Disturbances of the Archaeome

Archaea are minor commensal representatives of the microbiome that metabolize various compounds produced during the anaerobic decomposition of organic substances by intestinal bacteria. Throughout oncogenesis, archaeome dysbiosis is observed: depletion of the methanogenic component and an increase in the abundance of halophilic species [14]. The role of archaea requires further study in the context of the "Driver-Passenger" hypothesis.

Parasitic Infection as a CRC Driver

Common parasitic invasions of the gastrointestinal tract include: amebiasis (*Entamoeba histolytica*), ascariasis (Ascaris *lumbricoides*), balantidiasis (*Balantidium coli*), blastocystosis (*Blastocystis spp*.), cryptosporidiosis (*Cryptosporidium sp*.), giardiasis (*Giardia lamblia*), strongyloidiasis (*Strongyloides sp.*), trichocephalosis (*Trichuris trichiura*), cystoisosporiasis (*Cystoisospora belli*), cyclosporiasis (*Cyclospora cayetanensis*), schistosomiasis (*Schistosoma sp.*), enterobiasis (*Enterobius vermicularis*). Some of these are classified as normobiota, but the vast majority of these organisms have been proven to influence the development of inflammation and dysbiosis. They secrete toxic metabolites, alter pH, compete for resources, initiate immune responses, increase intestinal wall permeability, and affect the balance between symbionts and pathogens (even after therapy). Thus, they can function as drivers, which requires further analysis [15].

CRC Diagnostics

Given CRC statistics, developing new strategies for early diagnosis and prevention is becoming an increasingly urgent task in modern medicine.

Physical examination, diagnostic imaging, endoscopic examination, biopsy analysis, and fecal occult blood testing are the main methods for diagnosing and detecting CRC. Currently, colonoscopy is the best method for early CRC detection [1]. However, the invasiveness of this procedure limits its widespread use.

In the context of the presented data, the state of the intestinal microbiota can be considered as an alternative diagnostic and prognostic marker for CRC. Microbiota analysis can help in making a decision about the need for colonoscopy, as well as in determining the stage of the disease, the possibility of unfavorable development, outcome and metastasis formation [7, 9].

CONCLUSION

Non-invasive intestinal microbiota examination based on the "Driver-Passenger" model is a convenient and safe preventive method of primary diagnosis, increasing the likelihood of a positive outcome in case of detecting dysbiotic disturbances and identifying CRC through this screening. Its widespread use in medical practice can help reduce morbidity and mortality by increasing the flow of people willing to undergo screening. The development of such non-invasive diagnostic methods is a relevant socially significant direction.

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