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Pathogenetic factors of ulcerative colitis: mainstream for 2020

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ABSTRACT

The causes of ulcerative colitis are still unknown. Scientists made important advances in understanding the pathogenesis of this disease in the 21st century. Complex involvement of an impaired immune response in relation to antigens of the intestinal microbiota in genetically predisposed individuals under the influence of certain environmental factors was revealed. The factors that disrupt the epithelial barrier and alter the composition of the intestinal microbiota trigger the onset of the disease, thereby stimulating an impaired immune response. Recent studies have discovered completely new hypotheses of its origin and development, gradually interpreting the already known pathogenetic mechanisms of the disease. In this review, we focused on the new concepts in the pathogenesis of ulcerative colitis. We examined genetic, environmental, barrier, and microbial factors. We went into detail on the structure and role of the epithelial barrier and identified specific genes that are involved in the regulation of the intestinal epithelial barrier function in ulcerative colitis. We studied the literature containing information on relevant studies in PubMed and Google Scholar citation systems, using such key words as ulcerative colitis, colon microbiota, barrier function, genetic predisposition, and predisposing factors.

Key words: ulcerative colitis, inflammatory bowel disease, microbiota, pathogenesis, predisposing factors, genetic predisposition.

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Факторы патогенеза язвенного колита: мейнстрим-2020

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РЕЗЮМЕ

Причины возникновения язвенного колита до сих пор неизвестны. Значительные успехи в понимании патогенеза этого заболевания достигнуты в XXI в. и доказывают комплексное участие нарушенного иммунного ответа по отношению к антигенам собственной кишечной микрофлоры у генетически предрасположенных лиц под воздействием определенных факторов внешней среды. Дебют заболевания провоцируется факто-

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рами, которые нарушают эпителиальный барьер и изменяют состав микробиоты кишечника, тем самым стимулируя аномальный иммунный ответ. Исследования последних лет открывают как абсолютно новые гипотезы его возникновения и развития, так и подробно расшифровывают уже известные механизмы патогенеза болезни. В представленном обзоре мы сосредоточились на новых концепциях патогенеза язвенного колита – генетических, экологических, барьерных и микробиомных факторах. Подробно представили строение и роль эпителиального барьера, обозначили специфические гены, которые участвуют в регуляции барьерной функции эпителия кишечника при язвенном колите. Поиск литературы, содержащей информацию о соответствующих исследованиях, проводился в системах PubMed и Google Scholar по следующим ключевым словам: язвенный колит, микробиота толстой кишки, барьерная функция, генетическая предрасположенность, предрасполагающие факторы.

Ключевые слова: язвенный колит, воспалительные заболевания кишечника, микробиота, патогенез, предрасполагающие факторы, генетическая предрасположенность.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

The first description of ulcerative colitis (UC) was presented by Samuel Wilks in 1859 under the title “Morbid appearances in the intestine of Miss Bankes” in the Medical Times and Gazette. In 1875, S. Wilks, together with V. Moxon, described morphological presentation of this disease [1]. Despite a long history of studying UC, the causes of this disorder still remain unknown. The generally accepted modern concept of UC development includes genetic predisposition, epithelial barrier defects, dysregulation of immune responses, intestinal dysbiosis, and environmental factors [2].

The number of patients with inflammatory bowel diseases (IBD) is increasing every year and may reach 30 million people in the world by 2025 [3, 4]. In Russia, the incidence of UC is 2–3 cases per 100 thousand people [5]. High incidence of IBD in economically developed countries is explained by a combination of such factors as improvement of socioeconomic and sanitary conditions in modern society, changes in diet, availability of endoscopic examination, and the level of awareness among both patients and doctors about this medical condition [6]. Epidemiological studies reveal an increase in the incidence of UC in regions where it was at low level before, and where the Western way of life and nutrition is gradually predominating, such as countries of Asia and South America [7].

A tremendous interest of scientists from all over the world in the study of UC has been persistent for many years and requires large investments. To date, progress has been made in understanding this disease, new hypotheses of its emergence have appeared, and the mechanisms of the pathogenesis have been gradually unveiled. For example, it has been proven that the appendectomy at a young age has protective effects against UC development, given the surgery was performed for acute appendicitis [8]. In addition, based on the results of a meta-analysis of four studies, it has been recently discovered that there is an association of IBD with Parkinson’s disease. The studies showed that the risk of developing Parkinson’s disease in IBD patients was significantly higher than in the control group [9]. Moreover, the risk of developing Parkinson’s disease in patients with UC was 30%, and in patients with Crohn’s disease (CD), it was 28%.

Recent studies have been aimed at identifying new targets of etiotropic and pathogen-specific drug therapy to increase the effectiveness of treatment. Emergence of new treatment methods, such as immunosuppressive and biological therapy, resulted in significant pathomorphosis of UC. The disease is aggravating even with appropriate treatment, resulting in development of life-threatening complications, a continuously relapsing course, and universal forms in the majority of patients. The aim of this review was to summarize the data that form the modern understanding of the pathogenetic mechanisms in UC.

GENETIC FACTORS

Genetic studies, including genome-wide association studies (GWAS), whole genome sequencing (WGS), and genetic mapping, have identified 260 susceptibility loci associated with IBD [10–13]. Conventionally, genes that are involved in the development of UC can be divided into the following groups: genes encoding an immune response; genes encoding intestinal barrier function (the so-called barrier genes); genes encoding the quantitative and qualitative composition of the intestinal microbiota. The examination of patients using modern methods of genetic testing allowed scientists to come to the following conclusions.

Firstly, most of the genetic factors were found to be common for UC and CD [14]. Genes encode both innate and adaptive immune pathways, cytokine signaling, and immune response (for example, IL23-R, IL-12, JAK2, CARD9, TNFSF18, and IL-10). In addition, many genes (70%) are associated with other autoimmune diseases, such as ankylosing spondylitis and psoriasis.

Secondly, the strongest genetic signals within UC-specific loci are associated with the human leukocyte antigen (HLA) region on chromosome six. Sixteen HLA allelic associations (mainly class II), specific for UC, were described in genetic mapping [15]. It is known that many UC-specific genes are involved in the regulation of the epithelial barrier function. Studies showed that they are associated with colon involvement in UC and CD [16]. This indicates the key role of aberrant adaptive immune responses and epithelial barrier dysfunction in the pathogenesis of UC.

A group of scientists from Belgium conducted a study in 2017 [17], which analyzed various components of the intestinal epithelial barrier in IBD patients in terms of genetic predisposition. 128 genes associated with epithelial dysfunction were selected, of which 25 were associated with the mucous layer, 34 – with tight junction proteins, 5 – with adherens junctions, 14 – with desmosomes (intercellular junctions), 4 – with hemidesmosomes (half desmosomes), 17 – with cytoskeleton, 9 – with extracellular matrix, and 20 – with regulatory proteins. Analysis of the barrier genes revealed the potential role of *MUC21*, *MUC22, GNA12*, and *HNF4A* genes and loci in the emergence of UC. In the inactive phase of the disease, a persistent change in the expression of *MUC1* and *MUC4* in biopsies of patients with IBD was found, which served as an evidence of their crucial role in the recurrence of IBD (Figure).

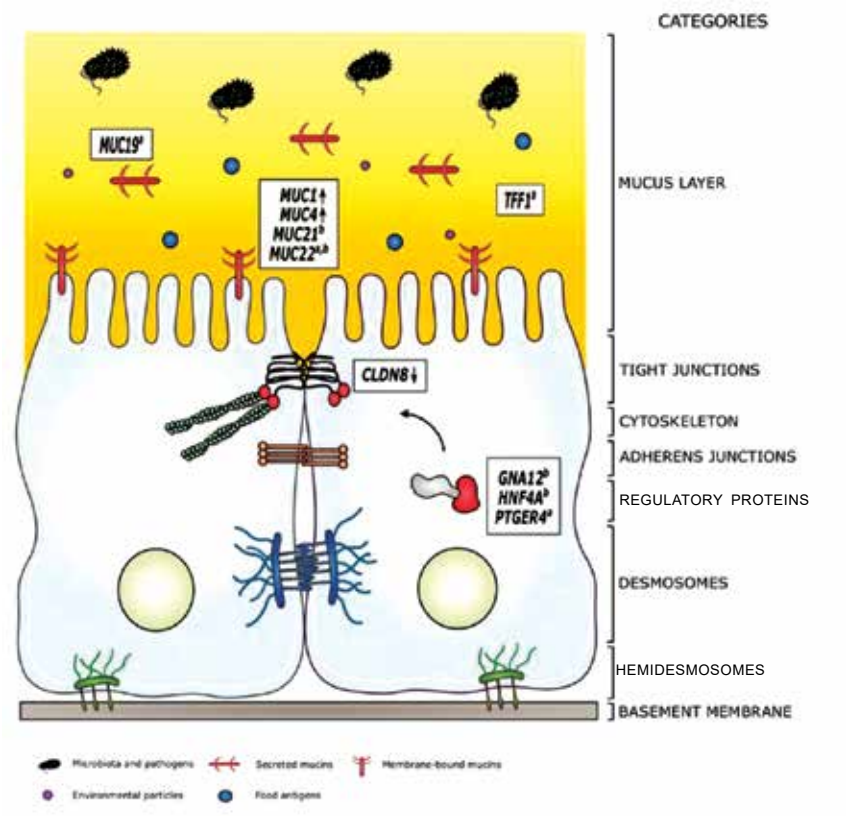

Figure. The role of epithelial barrier genes in the onset of IBD

One of the latest significant discoveries was whole genome sequencing (WGS) performed in almost 2,000 UC patients, which revealed a new and rare variant of a missense mutation (present in 0.6% of cases) in the adenylyl cyclase 7 (*ADCY7*) gene, which doubles the risk of UC development [18].

Thirdly, despite the identification of many susceptibility loci, genetics explains only 8–19% of disease heritability in IBD [19], CD being more common than UC. The concordance rate among monozygotic twins in UC is only 6.3% (compared to almost 60% in CD). Taken together, genetic factors provide a small but definite increase in susceptibility to UC. However, many patients do not have a genetic predisposition, if they are assessed using a polygenic risk score that takes into account all susceptibility loci [20].

Fourthly, non-genetic factors, in particular, epigenetics, which will be discussed below, play an important role in UC emergence [21].

EPIGENETICS

As mentioned above, genetic factors do not explain the occurrence of UC in all patients. In recent years, susceptibility to IBD has been supplemented by new data on epigenetic reprogramming. In response to external stimuli, such as nutrition, psychological stress, and physical activity, this mechanism gives commands to genes to increase or, on the contrary, weaken their activity. Thus, epigenetics studies the changes in gene activity, while the DNA structure remains the same. The main epigenetic mechanisms that control gene expression are DNA methylation, histone modification, and noncoding RNAs [22].

Changes in DNA methylation of the gene promoters are functionally involved in the regulation of gene expression in patients with IBD, mainly with UC. This provided a new look at the pathogenesis of the disease. The first studies concerning epigenetics in IBD were devoted to carcinogenesis and the development of neoplasia in patients [23]. It was proven that a higher level of DNA methylation in *AGTR1*, *WNT2*, and *SLIT2* genes was associated with an increased risk of cancer in patients with UC [24].

A number of studies in this area demonstrate that it is the DNA methylation landscape in genes that determines the severity and nature of IBD [25, 26]. Epigenetic changes are correlated with clinical features and outcomes of IBD, such as the extent of the lesion and the phenotype of the disease. For example, a higher level of *MDR1* methylation was independently associated with universe UC, severe attacks of the disease, and young age of the disease onset [27], while a higher level of *PAR2* methylation in the rectal mucosa was associated with the steroid-dependent or steroid-refractory UC [28].

Nevertheless, there are no convincing and unambiguous data of evidence-based medicine on the influence of epigenetics on the emergence and nature of IBD, since there are many technical difficulties in reproducing the sequences and heterogeneity in the analyzed population (the sampling technique and the studied material differ). For the same reasons, it is not yet possible to conduct meta-analyses on this topic.

INFLUENCE OF ENVIRONMENTAL FACTORS

An increase in the number of UC patients occurs in parallel with changes in lifestyle [29] and basic approaches to nutrition in modern society, namely, widespread use of convenience foods, high-calorie foods, taste modifiers, animal proteins, sugar and refined carbohydrates, artificial sweeteners, a variety of modern cooking and food preservation technologies, emulsifiers, and a lack of dietary fiber in the diet [30]. The general concept of UC association with nutrition is based on data of epidemiological studies and is referred to as westernization of the diet.

Westernization also concerns living conditions and lifestyle in general, for example, the impact of environmental pollution, the availability of antibacterial drugs, and a decrease in physical activity [31]. One of the theories explaining a rise in autoimmune diseases in general and UC, in particular, is the hygiene hypothesis formulated by the English epidemiologist David Strachan [32]. This concept reveals the possibility of an excessive immune response and development of autoimmune diseases following a decrease in antigenic exposure due to improvement of the sanitary conditions in the environment and widespread use of antibacterial drugs and detergents.

It was suggested that stress can initiate or induce a new attack of IBD and is a potential trigger of UC [33]. This association is supported by numerous studies that showed that stressful events in a person's life can trigger a disease [34, 35]. Psychological stressors increase intestinal permeability, weaken tight junctions, and increase bacterial translocation into the intestinal wall.

Finally, scientists have been studying the protective effect of tobacco smoking on the occurrence of UC for a long time. The likelihood of UC occurrence in nonsmokers is higher than in smokers. When giving up smoking, the relative risk of UC development increases by 4.4 times [36].

CHANGE IN THE INTESTINAL MICROBIOTA

A combination of various lifestyle factors in the era of postindustrial society has a significant impact on the microbial composition of the intestine and leads to a change in its diversity in UC. A group of scientists from the United States proved that under the influence of triggers, in particular, emulsifiers, the intestinal mucosal barrier decreases, increasing the number of microbes with proinflammatory and mucolytic activity, resulting in the development of inflammation and emergence of IBD, metabolic syndrome, and, possibly, other chronic inflammatory diseases [37].

A study in 2010 showed significant differences in gut microbiota in children living in rural communities of Burkina Faso compared to children living in Europe. Gut microbiota of African children was rich in *Bacteroides* and poor in *Firmicutes* and *Enterobacteriaceae*, while the results obtained from European children were opposite [38]. With a high probability, it can be assumed that this situation is determined by dietary habits. In Africa, foods with high fiber content prevail, and in Europe, the traditional Western diet prevails.

An important characteristic of gut microbiota of each person is its individual variability, due to genetic predisposition. Based on molecular analysis by 16s RNA sequencing, it was found that gut microbiota is represented by four known types of bacteria: *Actinobacteria*, *Bacteroidetes*, *Firmicutes*, and *Proteobacteria*. In adults, two types of bacteria are predominant: *Bacteroidetes* and *Firmicutes* [39]. Research data were published in 2017 [40], revealing a decrease in the diversity of fungal and bacterial components of microbiota in IBD patients; and in patients with UC, these changes were more pronounced than in patients with CD. Patients with UC exhibit a decrease in the proportion of microorganisms with anti-inflammatory activity that synthesize short-chain fatty acids (SCFAs), such as *Firmicutes*, and an increase in the proportion of pathobionts, which include *Proteobacteria*. Within the phylum *Firmicutes*, the proportion also changes: *Roseburia* and *Faecalibacterium* of the *Ruminococcacceae* and *Lachnospiraceae* families decrease and the content of *Ruminococcus gnavus* increases [41]. An increase in the content of opportunistic bacteria *Enterobacteraceae* and *Esherichia coli* is noted within the phylum *Proteobacteria* [42]. Other studies demonstrate an increase in the content of sulfate-reducing bacteria *Desulfo vibrio* with excessive production of hydrogen sulfide, which negatively affects proliferation, apoptosis, and differentiation of colonic epithelial cells [43].

In addition to bacteria, microbiota of the colon consists of viruses, fungi, and archaea, which are also an essential part of the intestinal microbial composition [44]. Archaea account for up to 10% of all anaerobes inhabiting the colon of a healthy person. Studies show their positive effect on human health [45], while previous studies demonstrated their proinflammatory effect via stimulating the growth of pathogenic bacteria [46]. Gut microbiota also consists of viruses. The quantitative and qualitative composition of the virome also depends on the prevailing food products in the diet, place of residence, hygiene, environmental factors, and the type of breastfeeding [47]. In a healthy person, bacteriophages persist in bacterial hosts, maintaining the constancy of the internal state of gut microbiota. Under the influence of environmental factors in genetically predisposed individuals, or following a combination of a eukaryotic virus and a genome of a macroorganism, activation of phages (in the latent period) and viruses takes place, which leads to a disturbance of the dynamic balance in the microbial composition of the gastrointestinal tract (GIT).

A number of aggression factors, such as a disturbance of the intestinal microbiome composition and the presence of aggressive intestinal metabolites, lead to dysfunction of mucosal permeability, disrupting its barrier function, which is normally determined by the state of tight junctions with the help of claudins, as well as by the content and quality of mucin that protects the epithelium [48]. When defects of the mucous membrane emerge, food and bacterial agents can penetrate into deeper layers of the intestinal wall, which then stimulate development of inflammatory and immune responses [49].

In recent years, fecal microbiota transplantation (FMT) has been performed to restore intestinal homeostasis in patients with UC. A study by P. Moayyedi et al. [50] showed that FMT induces remission in patients with active UC. A total of 70 UC patients underwent FMT or received a water enema (placebo) every week for 6 weeks. The remission rate in the FMT group was significantly higher than in the placebo group (24% versus 5%, respectively). Meta-analysis of 14 cohort and 4 randomized clinical trials (308 patients with UC) by S. Costello et al. [51] demonstrated the effectiveness of UC treatment with a clinical remission rate of 28% in patients undergoing FMT, compared to a 9% remission rate in patients receiving placebo. In addition, a clinical response was achieved

in 49% of patients treated with FMT compared to 28% of patients receiving placebo.

EPITHELIAL BARRIER

Scientists agreed that disruption of the epithelial barrier is the underlying factor in the pathogenesis of UC. Given complex organization and regulation of the intestinal mucosal barrier, it is necessary to determine which elements are most important for the pathophysiology of IBD.

The intestinal barrier function is provided by a complex of components that combine mucosal, epithelial, and immune (innate and adaptive) barriers. The mucosal barrier is a double layer. Colonic mucus contains more bacteria in the thinner outer layer than in the denser inner mucosal layer. The parietal mucosal layer contains secretory immunoglobulins A and antibacterial substances (defensins, lysozyme, and ribonuclease). The mucosal layer provides the first apical line of defense against luminal microbes and forms a sieve-like gel structure that prevents large particles and bacteria from contacting the intestinal epithelium [52].

Thanks to the almost impermeable polarized monolayer of intestinal epithelial cells, a second physical component of the intestinal barrier is formed. Enterocytes, the most represented type of colonic epithelial cells, are interconnected by intercellular junctions, represented by catenins, occludins, and claudins. Tight junctions are the main gatekeepers of the epithelial intestinal barrier, which can pass ions and small molecules up to 20 kDa. The throughput capacity of tight junctions depends on the state of proteins, mainly, claudins [53].

In addition to enterocytes, the epithelium is composed of other specialized cells with a wide range of functions, including goblet cells, which produce gel-like mucus, and Paneth cells, which secrete antimicrobial peptides that strengthen the immune barrier. M cells, which are also a part of the epithelium, capture luminal microbes and transport them to dendritic cells, which recognize the absorbed microorganisms and form an immune response [54].

In UC, dysfunction of antimicrobial peptide secretion and disruptions of tight junctions (the physical component of the barrier) are observed [55]. In active UC, key proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interferon (IFN) -γ, and interleukin (IL)-13, have a direct pathological effect on the integrity of the epithelial barrier [56]. Genome-wide association study (GWAS) reveals UC-specific susceptibility genes that regulate the epithelial barrier, mucus production, and stability of the membrane and intercellular junctions. However, the main mechanism has not yet been fully understood.

MITOCHONDRIAL DYSFUCTION

The PROTECT study (analysis of complete genomic sequencing of 206 children with a short history of UC) is highly interesting. It demonstrated a decrease in the expression of genes encoding an oxidative phosphorylation chain in mitochondria and a polymorphism of the *PPARGC1A* gene, which affects the activation of the mitochondrial function. Thus, mitochondriopathy was determined as one of the possible mechanisms in the pathogenesis of UC [57]. The role of mitochondrial dysfunction was discussed previously in the pathogenesis of this disease [58]. For the past 10 years, researchers have identified mitochondriopathy as one of the main and most poorly understood “pieces of the puzzle” in the genesis of inflammation [59]. The data obtained over the past 3 years again revive and confirm this concept in the pathogenesis of UC [60–62].

CONCLUSION

The presented literature review summarizes current research on the etiology and pathogenesis of UC (Table).

Table

Modern concepts of etiology and pathogenesis of UC

Parameter	Description
Genetics	Most genetic factors (67% of the susceptibility loci) are common for UC and CD. Sixteen HLA allelic associations have been described for UC (mainly class II). Outside the HLA region, the *ADCY7* gene has the strongest association with UC. UC-specific genes are involved in the regulation of the intestinal epithelial barrier function. Many patients do not have a genetic predisposition, according to a polygenic risk scale that takes into account all susceptibility loci (6.3% in monozygotic twins)
Environmental factors	Westernization includes urban lifestyle, environmental pollution, dietary habits, antibiotics, improved sanitation and fewer infections. Smoking is a protective factor against UC. Giving up smoking often precedes UC. Appendectomy reduces the risk of UC development, if the surgery was performed for acute appendicitis at a young age

Table (continued)

Parameter	Description
Microbiota	A decrease in gut microbiota diversity (viruses, bacteria, and fungi). Fecal microbial transplantation is effective in treating UC. It is not known whether a disturbance in the composition of microbiota is a consequence or an initiator of inflammation. Depletion of microbes with anti-inflammatory activity (*Ruminococcaceae* and *Lachnospiraceae*) and an increase in microbes with proinflammatory activity (*Enterobacteriaceae* and *Fusobacteriaceae*)
Epithelial barrier	Disruption of the epithelial barrier is a key mechanism in the pathogenesis of UC. Barrier function of the intestine is provided by a number of components that combine mucosal, epithelial (physical), and immune (innate and adaptive) barriers
Mitochondria	Mitochondriopathy is one of the mechanisms in the pathogenesis of UC. Mitochondriopathy leads to impaired energy production, increased oxidative stress, and release of molecular patterns associated with a proinflammatory response

A modern lifestyle of people with a genetic predisposition has a significant effect on the microbial composition of the intestine and leads to a change in the diversity of the intestinal microbiota in UC, a decrease in the resident flora, and an increase in the number of opportunistic and pathogenic microorganisms. A number of aggression factors, such as disturbances of the intestinal microbiome composition and the presence of aggressive intestinal metabolites, impair mucosal permeability and disturb the barrier function, which is normally determined by the state of tight junctions, as well as by the amount and quality of mucin that protects the epithelium. Food and bacterial agents can penetrate into deeper layers of the intestinal wall through the defects in the mucous membrane, which then stimulate the development of inflammatory and immune responses [63].

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