УДК 616.348-002.44:616.345.018.73-009.6
https://doi.org/10.20538/1682-0363-2022-1-121-132

Ulcerative colitis: focus on colonic mucosal resistance

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ABSTRACT

In recent decades, following cooperation between scientists in various specialties, new unique data on the pathogenesis of ulcerative colitis have been obtained. The role of an impaired immune response to antigens of gut microbiota in genetically predisposed individuals under the effect of certain environmental factors was proven. Assessing the interaction between the colonic mucosa and gut microbiota will help to understand the mechanisms of ulcerative colitis and develop new treatment strategies for the disease.

This review presents modern views on the pathogenesis of ulcerative colitis with a focus on the imbalance between local protective and aggressive factors of the gastric and intestinal mucosa. The structure and role of the epithelial barrier both under normal conditions and in ulcerative colitis are considered in detail.

The aim of this review was to summarize the data on resistance of the colonic mucosa and its damage in ulcerative colitis.

Keywords: ulcerative colitis, microbiota, epithelial barrier, mucin, tight junction proteins, epithelial cells, immunoglobulins A

Conflict of interest. The authors declare the absence of obvious or potential conflicts of interest related to the publication of this article.

Source of financing. The study was supported by the Grant of the President of the Russian Federation for state support to leading scientific schools (SS -2558.2020.7) (agreement No. 075-15-2020-036 of 17.03.2020) “Development of health-preserving technology for a gastroenterological patient with a comorbidity on the basis of adherence management”.

For citation: Livzan M.A., Bicbavova G.R., Romanyuk A.E. Ulcerative colitis: focus on colonic mucosal resistance. *Bulletin of Siberian Medicine.* 2022;21(1):121–132. https://doi.org/10.20538/1682-0363-2022-1-121-132.

Язвенный колит: в фокусе резистентность слизистой оболочки толстой кишки

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РЕЗЮМЕ

В результате кооперации ученых различных специальностей в последние десятилетия получены новые уникальные данные о патогенезе язвенного колита, доказано участие нарушенного иммунного ответа по отношению к антигенам собственной кишечной микрофлоры у генетически предрасположенных лиц под воздействием определенных факторов внешней среды. Оценка взаимодействия слизистой оболочки толстой

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кишки и микробиоты кишечника поможет понять механизмы развития язвенного колита и разработать новые стратегии лечения.

В обзоре мы представляем современные взгляды на патогенез язвенного колита, сосредоточив внимание на нарушении равновесия между местными факторами защиты и агрессии слизистой оболочки желудочно-кишечного тракта. Подробно рассматриваем строение и роль эпителиального барьера как в норме, так и при язвенном колите.

Целью обзора является обобщение данных литературы о резистентности слизистой оболочки толстой кишки и ее повреждении при язвенном колите.

Ключевые слова: язвенный колит, микробиота, эпителиальный барьер, муцин, белки плотных контактов

Конфликт интересов. Авторы заявляют об отсутствии явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Публикация подготовлена ОмГМУ за счет финансирования по гранту Президента РФ для государственной поддержки ведущих научных школ (НШ-2558.2020.7) (соглашение № 075-15-2020-036 от 17.03.2020) «Разработка технологии здоровьесбережения коморбидного больного гастроэнтерологического профиля на основе контроля приверженности».

Для цитирования: Ливзан М.А., Бикбавова Г.Р., Романюк А.Е. Язвенный колит: в фокусе резистентность слизистой оболочки толстой кишки. *Бюллетень сибирской медицины.* 2022;21(1):121–132. https://doi.org/10.20538/1682-0363-2022-1-121-132.

INTRODUCTION

Modern lifestyle has a significant impact on the microbial composition of the intestine and leads to a change in the diversity of the gut microbiota in ulcerative colitis (UC), decrease in the resident flora, and a rise in the number of opportunistic and pathogenic bacteria. A combination of aggressive factors (imbalance of the gut microbiota composition, the presence of aggressive gut metabolites) leads to impaired intestinal permeability and disruption of its mucosal barrier. This is normally determined by the state of tight junctions, as well as the amount and quality of mucin that protects the epithelium.

The dynamic interaction between the anatomical and functional elements of the mucoepithelial barrier in the gastrointestinal tract (GIT) is arranged in such a way that, on the one hand, they create a semipermeable barrier that provides absorption and transport of nutrients, and, on the other hand, they regulate passage of proinflammatory molecules, microorganisms, toxins, antigens, and pathogens from the luminal to the internal environment of the body and provide development of immune responses to penetration of pathogenic agents, as well as immune tolerance in relation to food components and commensal bacteria.

The functioning of the protective mucosal barrier is based on the unity of physical, biochemical, and immunological interactions of its structures [1]. Given complex organization and regulation of the intestinal mucosal barrier, it is necessary to determine the most essential protective elements in the pathophysiology of UC.

PRE-EPITHELIAL PROTECTION

Pre-epithelial protection (mucous bicarbonate barrier) is a layer of mucous gel in combination with substrates secreted by the surface epithelium. Previously, the pre-epithelial mucus layer was characterized only by the ability to move chyme through the digestive tract due to its moisturizing and lubricating effects, as well as to protect the epithelium from the aggressive effects of antigens, acids, and enzymes. With the advent of modern research methods, scientists began to study such characteristics of the intestinal mucosal barrier as its composition, secretion, and destruction, as well as the role of various external factors in changing its permeability, structure, and chemical composition [2]. Most scientists agree that an increase in the thickness of the mucus layer is associated with an increase in its protective functions, but there is also an opinion that a thick layer of parietal mucus is a favorable environment for opportunistic and pathogenic bacteria [3].

The main components of the pre-epithelial protection are mucins, or highly glycosylated glycoproteins, which, due to their specific properties, protect

the internal environment of the body from bacteria and damaging agents [4]. Mucins are divided into 2 types: membrane-bound (transmembrane) (MUC1, MUC3, MUC4, MUC13, MUC15, MUC17, MUC20, and MUC21) and secreted (secretable, gel-forming) (MUC2, MUC5AC, MUC5B, MUC6, and MUC20). This component of the mucosal barrier is represented in the small intestine by a single, loose, and permeable layer, and in the large intestine – by a denser, double layer [5]. The double layer of the colonic mucus is subdivided into a dense inner layer that is firmly attached to the epithelial cells and is impermeable for bacteria. This layer is composed of transmembrane mucins and is called glycocalex. An increase in the permeability of this layer facilitates easier penetration of bacteria in the epithelial cells.

Transmembrane mucins MUC3, MUC4, MUC12, MUC13, and MUC17 are expressed in both unchanged and altered mucous membranes. Membrane-bound mucins act as sensors of the luminal environment in the interaction between the host and the microbe [6]. Transmembrane mucins consist of two subunits: a large extracellular subunit and a smaller subunit, which consists of extracellular, transmembrane, and cytoplasmic domains. The extracellular subunits of these mucins rise above the plasma membrane to a height of about 1 μm [7]. The main transmembrane mucins of the mucosal barrier are MUC3, MUC12, and MUC17. MUC1 is synthesized during the development of pathological conditions, for example, cancer and infectious diseases of the GIT [8]. MUC1 functions as a regulator of the Toll-like receptor (TLR)-initiated innate immune response, which is an example of cellular signaling by transmembrane mucins [9]. There is conflicting evidence from research findings on MUC16. In most works, the authors indicated its absence in the colon [10] in both healthy and sick patients, while J. Yamamoto-Furusho et al. indicated the expression of MUC16 and MUC20 in the colonic mucosa, which was associated with histologic remission in patients with UC [11].

The gel-forming mucins MUC2, MUC5AC, MUC5B, and MUC6 are the main components of the mucous layer which provide its viscoelastic properties. MUC2 is the major universal mucin which is secreted in all parts of the GIT and plays the key role in keeping microbes at a distance from the epithelial surface. MUC2 regulates intestinal homeostasis and tolerance to food components through dendritic cells and intestinal epithelial cells, and the MUC2 receptor complex suppresses inflammatory responses in dendritic cells [12].

In inflammatory bowel disease (IBD), impairment of mucin synthesis and subsequent emergence of mucosal barrier dysfunction are observed [13]. A decrease in glycosylation and sulfation [14], as well as an increase in sialylation, reduce the effects of mucin in patients with UC and prevent maintenance of an effective intestinal barrier function, especially in relation to bacterial translocation [15]. Healthy colonic mucus is sufficiently sulfated, which provides increased resistance to bacterial and enzymatic degradation. The study by D. Boltin et al. demonstrated that sulfation occurred to a lesser extent in patients with UC [16]. In addition, in the colon affected by UC, a decrease in the number of goblet cells, MUC2 expression, and mucus layer thickness in comparison with the control group of healthy people was noted [17]. In this pathology, a decrease in the content of sulfates in MUC2 is identified, but a compensatory increase in the expression of this mucin in the active phase of the disease leads to an overall unchanged level of sulfates in the colon [18].

MUC1 and MUC5AC, which usually cannot be found in the colon of healthy people, were identified in the scrapings from the resected part of the colon in patients with UC [19]. In patients with UC, a specific increase in MUC1 expression and a decrease in MUC2 expression at the sites of crypt abscesses and erosive ulcerative lesions were observed [20]. A decrease in the expression of the *MUC9* [21] and *MUC20* genes and increased expression of the *MUC16* gene [22] were also noted both in the active phase of the disease and at the remission stage in UC patients compared with the control group. Sialylation and sulfation increase tissue resistance to degradation. An increase in sialylation of mucin oligosaccharides was detected in rectal biopsies of patients with UC [23].

In a large-scale study by S. van Der Post et al., the basic composition of the intestinal mucosal barrier was identified. It consists of gel-forming and transmembrane proteins that form the mucosal barrier in healthy people and in patients with UC in remission. Several of these proteins were reduced in UC patients, including the major structural compo-

nents, MUC2 and IgGFc-binding protein FCGBP, as well as other goblet cell products, including calcium-activated chloride channel regulator 1 (CLCA1) and zymogen granule protein 16 (ZG16). Scientists suggest that the disease may be preceded by insufficient replenishment and increased destruction of goblet cells in response to sequential microbial attacks, which initiates a new episode of UC [24].

In the unchanged gastric and intestinal mucosa, the localization of mucins coincides with the distribution of trefoil peptides. Trefoil factors (TFF1–3) are a group of peptides synthesized and secreted by the epithelium of the mucous membrane [25]. A combined effect of TFF and mucin enhances the protection of the mucous membrane from ulcerogenic agents, prevents the penetration of protons through the mucus, and increases its viscosity [26]. The structural domain of TFF is presented in the form of a clover leaf, which contributes to their resistance to proteolytic degradation [27]. Each TFF interacts with mucin differently. The most viscous mucus is in the stomach and upper duodenum (to protect against acid and enzymes), which coincides with the localization of TFF2. Formation of intercellular contacts in the epithelial layer is mediated by E-cadherin, which interacts with β-catenin, leading to destabilization of intercellular connections and possible cell migration [28]. If the cell is not attached to the matrix, it is vulnerable to apoptosis [29].

It was found that TFF3 has a pronounced antiapoptotic (anoikis-resistant) effect on enterocytes through activation of NF-κB [30] and epidermal growth factor (EGF) [31]. In the study by R. Nakov et al. [32], it was demonstrated that the level of serum TFF3 correlates with the intensity of clinical manifestations, endoscopic presentation, and the content of fecal calprotectin in patients with UC.

The mucous bicarbonate barrier is the basis for the interaction between gut microbiota and the host organism. In a healthy organism, this interaction has a form of partnership, and the pre-epithelial barrier is a favorable environment for microorganisms, which, in turn, regulate its state [33]. There is an assumption that the proportion of bacteria that destroy the mucus layer increases when the diet is poor in dietary fiber. It means that under these conditions, the mucus layer becomes an energy source for gut microbiota instead of fiber, which results in gradual destruction of the mucus layer [34].

The protective function of mucus is also determined by its interaction with the immunity. The parietal mucus layer contains a resistin-like molecule β (RELMβ), Fc-γ binding protein FCGBP, secretory immunoglobulins A, and antibacterial substances (defensins, lysozyme, and ribonuclease). Immunoglobulin A (IgA) is one of the most common antibodies in the mucosal secretion, which neutralizes pathogenic bacteria and maintains the commensal microflora through several mechanisms. The discovery of IgA at the end of the 50s of the XX century played a significant role in the development of immunology [35]. Firstly, it created the basis for transformation of early concepts of tissue immunity, elaborated by the outstanding immunologist A.M. Bezredko, a student of I.I.Mechnikov, in 1929. It was A.M. Bezredko who defined tissue immunity as formation of resistance of an individual organ to infection without formation of protective antibodies. He believed that local resistance is provided by cells accustomed to weakened or killed microorganisms.

The interest in the study of the immune mechanisms associated with IgA has not waned since its discovery. Its protective functions are realized at the surfaces of mucous membranes that are in contact with the environment. In 1993, A.V. Kononov formulated a concept of local secondary sIgA deficiency in mucous membranes during their chronic inflammation. He proposed a scheme for the morphogenesis of chronic inflammation, taking into account the interactions between local immunity, microcirculation, and epithelium [36]. Despite abundance of experimental and theoretical data, many issues concerning the nature of the interaction and the physiological function of IgA and Fc-binding ligands are still unclear and require further study.

Pattern recognition receptors (PRRs), which include Toll-like receptors (TLRs) and NOD-like receptors (NLRs), play an essential role in mucin synthesis. PRRs are activated by pathogen-associated molecular patterns (PAMPs) and microbe-associated molecular patterns (MAMPs), which leads to induction of the NF-kB family of transcription factors and development of an immune response of varying severity [37]. TLR1, -2, -4, -5, -6 (extracellular sensors) and NLR1, -2 and TLR9 (cytosolic sensors) are expressed in epithelial cells and have complementary effects, promoting both innate and adaptive immunity.

TLRs are a family of 11 transmembrane receptors that are located at the cell surface and in intracellular endosomes. The profile (level and localization) of TLR expression differs in different parts of the GIT. It was found that TLR2, -4, -5, -7, and -9 are either minimally or not expressed in the epithelium of the small intestine, and expression of TLR2, -4, and -5 can be found in the colon. At the same time, TLR3 expression is at the same level both in epithelial cells of the small intestine and in the colon [38]. Examples of MAMPs include lipopolysaccharides (found in the outer membrane of gram-negative bacteria), lipoteichoic acid (present on the wall of gram-positive bacteria), peptidoglycan (bacterial cell wall component), and flagellin (the main structural component of bacterial flagella). They all function as PRR ligands. MUC2 expression increases, when TLR is activated by lipopolysaccharides, lipoteichoic acid, and flagellin [39].

NLRP6 inflammasome, when stimulated with the TLR-2/1, TLR-4, and TLR-5 ligands, is activated in goblet cells located in the colonic crypts. NLRP6 inflammasome acts as a sensor of cellular stress, triggers an inflammatory cascade, and plays the key role in maintaining the intestinal barrier, protecting against infection, and regenerating the mucous membrane [40]. TLR-initiated cascades stimulate complex MUC2 exocytosis and mucin secretion in adjacent goblet cells via intercellular signals. The increased secretion of MUC2 may thus facilitate expulsion of bacteria from the upper part of the crypts [41]. Unlike transmembrane TLRs, NLRs are a family of innate intracellular receptors [42]. Activation of NOD1 and NOD2 by such ligands as bacterial peptidoglycans ultimately leads to activation of NF-kB transcription factors and triggers immune responses [43].

EPITHELIAL PROTECTION

Epithelial protection requires a contiguous layer of cells including five cell types: enterocytes, goblet cells, enteroendocrine cells, Paneth cells, and undifferentiated epithelial cells. Enterocytes are the most common type of cells, forming an effective barrier to protect the internal environment and controlling selective absorption of ions, nutrients, and other components from the luminal environment. Goblet cells are located between enterocytes; they are responsible for secretion of mucus. Enteroendocrine cells produce gastrointestinal hormones, peptides, and neurotransmitters [44]. Dysregulation of the epithelial barrier with changes in paracellular permeability due to altered intercellular junctions is probably one of the primary factors in the pathogenesis of IBD [45].

The paracellular space is sealed by tight junctions (TJs), which regulate the flow of water ions and small molecules, building a dynamic intestinal barrier [46]. TJs are composed of two types of proteins: 1) transmembrane proteins, which include occludin, claudins, tricellulin, and junctional adhesion molecules (JAMs); 2) peripheral membrane proteins of zonula occludens cells (ZO-1, ZO-2, and ZO-3). Some TJs have properties of increased barrier permeability, while others form channels and pores that are selective in size and / or charge [47]. Adherens junctions and desmosomes are mainly involved in communication between adjacent epithelial cells [48]. Dysfunction of TJs leads to disruption of the intestinal barrier integrity. The intestinal barrier function is influenced by changes in pH, osmotic pressure, and cytoskeleton function [49]. TJs can be damaged by various pathogens with a subsequent increase in epithelial permeability and bacterial translocation.

Occludin and adhesion proteins regulate the integrity of TJs, and tricellulin ensures transport of macromolecules. Claudins are mainly responsible for the intestinal barrier function and are represented by a family of 27 members that modulate paracellular ion transport depending on the charge and size [50]. According to their functions, claudins can be divided into two groups: pore-forming claudin-2, -7, -12, -15, -16 and claudin-1, -3, -4, -5, -8, -14, -18, -19, which reduce the permeability of the epithelium. The expression of TJs differs throughout the GIT and depends on functional needs of its segments. At a finer structural level, it also depends on localization on cell membranes [51].

Claudin-1 and claudin-2 are capable of initiating the formation of TJ filaments on fibroblasts that lack tight junctions [52]. Claudin-2 controls transport of monovalent cations, such as Na+, to the interstitium and reduces paracellular transepithelial resistance, enhancing transepithelial water flow [53], as opposed to claudin-1, -3, -4, -5, and -8, which “tighten” the epithelium [54]. Another important property of claudin-2 is that it directly reduces the barrier function of claudin-1 and claudin-4 [50].

In UC, a decrease in the expression of claudin-1, claudin-4, and occluding and activation of claudin-2 are registered [55]. The greatest protective effect in IBD was demonstrated by claudin-1, -3, -4, -5,

and -8 [56]. In patients with UC, both in the active phase of the disease and in its remission, increased expression of claudin-2 and a decrease in the expression of occludin and ZO-1 were observed compared with the healthy controls. The expression of ZO-1 was significantly higher in patients with UC in remission, compared with patients in the active phase of the disease. Expression of ZO-1 and occludin had a negative correlation with C-reactive protein and erythrocyte sedimentation rate (ESR).

L.S. Poritz et al. [57] found an increase in the claudin-1 / occludin ratio in colon biopsies in patients with UC compared with samples from healthy controls and patients with Crohn's disease. In another study, it was demonstrated that claudin-1 was elevated in the colon of UC patients compared with the control group, but did not correlate with the severity of the disease [58]. In biopsies obtained from the sigmoid colon of patients with UC, there was a tendency to an increase in claudin-12 expression [59].

The physiological role of zonulin has not been fully established, but there is no doubt that it also regulates TJs. Excessive production of zonulin can lead to an excessive increase in the permeability of the epithelial layer [60]. The study of zonulin in the blood, as a rule, is associated with diagnosis for suspected leaky gut syndrome and increased permeability of the epithelium in the examined person. Elevated serum zonulin levels have been reported in celiac disease, non-celiac gluten sensitivity, irritable bowel syndrome, and IBD [61], compared with healthy controls. However, the study [62] demonstrated that serum zonulin is not a reliable marker of increased intestinal permeability in the examined individuals.

Finally, the third level in the complex structure of the epithelial barrier is represented by intermediate filaments, catenins, cadherins, and desmosomes. One desmosome is rather small, therefore, several desmosomes can usually be seen at the site of contact between two cells [63].

SUBEPITHELIAL PROTECTION

The subepithelial layer is represented by the lamina propria of the mucous membrane. The lamina propria contains cells of innate and adaptive immunity that secrete IgA, cytokines, chemokines, and proteases and are involved in immune defense mechanisms of the body. The subepithelial immune complex provides regulation, trophism, and kinetics of the skin epithelium and realizes nonspecific and specific immune responses. Immune cells respond immediately and synchronously to invading pathogens.

Neutrophils are some of the first cells to reach the site of inflammation and limit the invasion of microorganisms through phagocytosis [64]. Macrophages are able to determine the shape and size of possible targets, cooperate in performing functions, exhibit high proteolytic and weak antigen-presenting activity, play a primary role in maintaining tissue homeostasis, and patrol tissues [65]. Regulatory T cells play a crucial role in maintaining immune homeostasis, since they are able to suppress activation of various immune cells involved in GIT inflammation and induce immune tolerance to antigens from the diet or commensal flora [66].

Since the discovery of dendritic cells by R. Steinmann and Z. Cohn, they have been called natural adjuvants of the immune response. Due to the presence of multiple outgrowths in the cytoplasmic membrane, dendritic cells have a large surface area, which allows them to actively recognize the patterns of microbes and dead cells, soluble molecules, and other cells of the body and activate primary and secondary B-cell- and T-cell-dependent immune responses (memory cells). Mast cells are located close to the nerves and are activated by neural mediators. They are also involved in several types of neuroinflammatory responses.

Submucosal neurons control secretion and absorption of nutrients into the local circulation, while Meissner's plexus neurons coordinate smooth muscle contractions [67]. A network of millions of enteric sensory neurons, interneurons, and motor neurons is capable of producing a variety of neurotransmitters and neuropeptides [68].

When MAMPs / PAMPs are activated, an immediate inflammatory response to foreign microorganisms is initiated. This interaction helps to identify foreign molecules by antigen-presenting cells, such as dendritic cells and macrophages. The cells then migrate to the peripheral site where they present antigens to T-cells with subsequent production of proinflammatory cytokines, such as interferon-gamma (IFN-γ), chemokines, and antimicrobial peptides, to protect the intestinal barrier. Given a close relationship between inflammation and increased permeability, markers of inflammation are often considered as surrogate markers of intestinal permeability.

Therefore, the content of α1-antitrypsin is often estimated in combination with fecal myeloperoxidase and calprotectin [69] as markers of subclinical intestinal inflammation [70]. Researchers propose using α1-antitrypsin fecal clearance as one of the laboratory markers of Crohn's disease intensity [71]. Another surrogate marker for mucosal repair, serum lipocalin-2, is expressed by intestinal epithelial cells in response to proinflammatory stimuli, such as cytokines or TLR activation. Serum lipocalin-2 in combination with metalloproteinase correlates with UC intensity [72].

PHYSIOLOGICAL SIGNIFICANCE OF GUT MICROBIOTA

Under normal conditions, the GIT is inhabited by gut microbiota that maintains its integrity. Gut microbiota is in symbiosis with its host, comprises more than 100 trillion microbes, and contains at least 150 times more genes than the human genome [73]. The composition of the gut microbiota in each person is stable, individual, and adapted precisely to the person's needs. The indigenous microbial flora maintains the morphology of the gastric and intestinal mucosa.

Shotgun metagenomic sequencing of gun microbiota revealed 1,952 unclassified bacterial species in addition to 553 species previously cultivated from the human intestine [74]. Microorganisms do not just exist, but interact, build complex relationships, and are characterized by a complex hierarchical structure with various interspecies relationships. Due to their coexistence in the same territory, they compete with each other for nutritional components, parasitize, adapt to each other or, developing together, enhance each other's functions (synergy, symbiosis, antagonism, parasitism, etc.). The gut microbiota produces enzymes involved in metabolism of carbohydrates, lipids, and nucleic acids and synthesis of vitamins, short-chain fatty acids (SCFAs), antimicrobial substances, hormones, and amino acids. The gut microbiota is also involved in immunomodulation, detoxification, and evacuation function of the GIT [75].

Four types of bacteria represent the colonic microbiota: Actinobacteria, Bacteroidetes, Firmicutes, and Proteobacteria. Bacteroidetes and Firmicutes are predominant types in adults [76]. The diversity of bacteria is higher in the contents of the intestinal lumen than in the parietal mucus layer [77] due to the facultative microbiota supplied with food. The number of bacteria changes even during the day. The colon contains 70% of all microorganisms in the human ecosystem. The predominant microorganisms are obligate anaerobes and their content in this part of the digestive tract exceeds the number of aerobes by 1,000 times [78]. In addition to bacteria, the colonic microbiota of a healthy person consists of viruses, fungi, archaea, and protists, which are an equally important component of the intestinal ecosystem [79, 80]. Together with the host organism, the gut microbial community forms some kind of a "superorganism" that performs many functions.

Changes in the microbiota can cause disturbances in the intestinal motor function and sensitivity. In addition, altered composition of the gut microbiota contributes to motor dysfunction and visceral hypersensitivity [81].

The microbial flora of the colon is in direct contact with the apical membrane of colonocytes and forms microcolonies in the mucous layer, which diversity depends on the composition of the chyme. Dietary fibers, sugars, and proteins that are not digested by enzymes of the macroorganism in the small intestine are fermented by the microbiota. The main products of dietary fiber fermentation are SCFAs (acetate, propionate, butyrate) [82]. SCFAs take part in the regulation of intestinal motility, control over inflammatory responses, maintenance of glucose levels, and blood circulation in the intestinal wall. In addition, they have an anticarcinogenic effect. Physiological effects of SCFAs are related to their interaction with G-protein-coupled receptors. These include GPR41, GPR43, and GPR109A receptors, which are exposed on immunocompetent cells, colonocytes, and adipocytes [83]. Butyrate activates the GR-P109A receptor and suppresses inflammation in the colon. Acetate and propionate activate the GPR43 cell surface receptor and induce chemotaxis of neutrophils [84].

In IBD patients, on the one hand, the proportion of microorganisms with anti-inflammatory activity, such as Firmicutes and Bacteroides, decreases. On the other hand, the proportion of proinflammatory bacteria, which include the Proteobacteria type, increases. In addition, in IBD, the total number of microorganisms increases, however, their diversity, on the contrary, decreases [85]. The pathogenetic mechanisms of the Western diet that provoke the emergence of UC remain unknown. Scientists suggest a direct effect of the Western diet on the composition of the colonic microbiota and indirect effects through

production of microbial metabolites, changes in the local immune response, and impaired barrier function of the colonic mucosa [86]. Undoubtedly, the Western diet has a significant impact on the qualitative and quantitative intraspecies diversity of the gut microbiota [87].

CONCLUSION

The protective barrier in the gastric and intestinal mucosa is a dynamic structural and functional system (Figure). The first line of immune defense is aimed at preventing penetration of antigens into the mucous membrane and eliminating foreign antigens with subsequent activation of the antigen-specific immune response. Innate immunity provides a response through recognition of PAMPs and MAMPs and results in activation of acquired immunity. The two major PRR systems are TLRs and NOD molecules. In IBD, Paneth cells are found in the colon following an increased need for antimicrobial protection. Under normal conditions, these cells are present only in the small intestine. After presentation of antigens to T-helpers and macrophages, naive T cells (Th0) are differentiated into Th1 and Th2 cells. Differentiation of Th0 into Th1 is accompanied by production of proinflammatory cytokines, while differentiation into Th2 cells promotes production of anti-inflammatory cytokines.

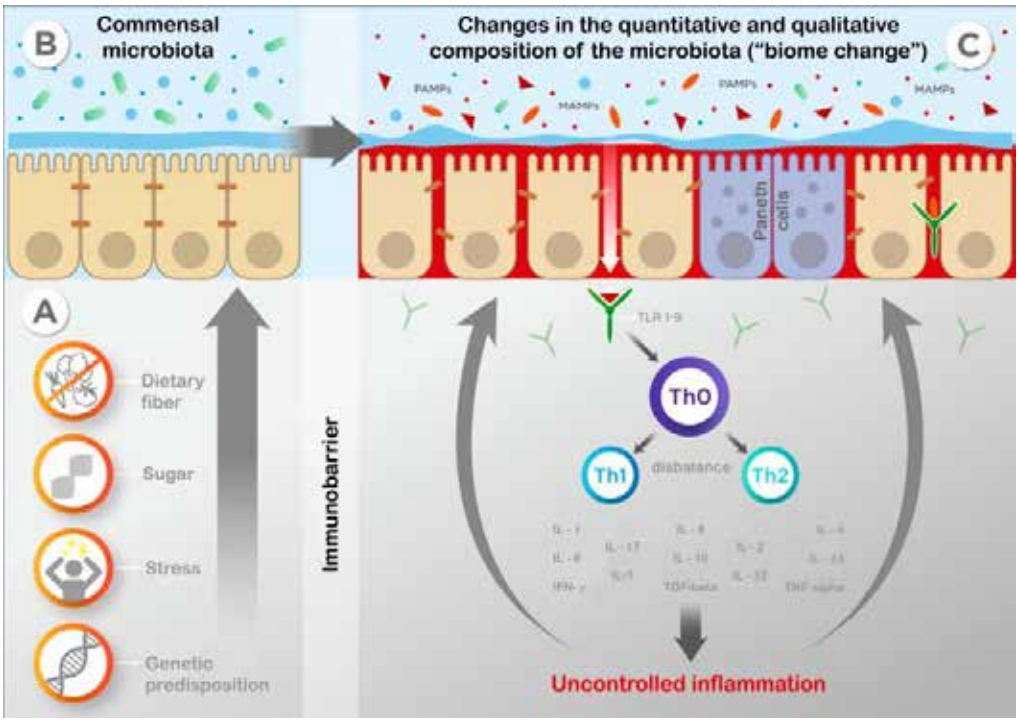

Figure. Simplified diagram of stages of colonic mucosa damage in ulcerative colitis: *B* – under normal conditions, the intestinal barrier function is determined by the state of tight junctions of the epithelium, as well as the quantity and quality of mucin that protects the epithelium. In UC, a combination of genetic factors and certain environmental factors (*A*) leads to impaired permeability of the intestinal mucosa and changes in the gut microbiota, thus impairing the intestinal barrier function (*C*)

Each level of protection has a complex logical organization. Modern research methods make it possible to study structural composition of the mucosal barrier and its interaction with the gut microbiota. Studying the structural and functional capabilities and understanding the mechanisms of coexistence and functioning of the gut microbiota and intestinal mucosal barrier are necessary for every practicing physician. New, effective methods for treating diseases that were earlier considered resistant to therapy are emerging. Further study of the interaction between the mucosal barrier and gut microbiota will help to understand the development mechanisms of chronic inflammatory diseases and develop targeted treatment strategies through restoration of barrier function and integrity.

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Received 22.03.2021;
approved after peer review 13.04.2021;
accepted 25.05.2021