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EPITHELIAL BARRIER OF THE COLON IN NORMAL AND ULCERATIVE COLITIS

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ABSTRACT
This article is devoted to the morphofunctional evaluation of diffuse endocrine cells of the mucosa of the digestive tract. Endocrine cells of the gastrointestinal tract secrete a number of biologically active substances with a wide range of both local and systemic effects, which ultimately affect the growth and development of the organism. Morphological changes in the diffuse endocrine system of the digestive tract of the offspring of female rats with chronic liver damage have been studied by many scientists. Other authors have considered characteristic changes in the diffuse endocrine system of the digestive tract of the offspring of female rats with chronic lesions in the intestine. One of the most important in modern morphology are the questions of genesis, differentiation, structure and cytophysiology of tissues under conditions of normal functioning and under pathology. The study of these problems provides an opportunity for further development of cytology, histology, endocrinology, embryology and deeper understanding of processes occurring in clinical pathology. In this respect the questions connected with formation of endocrine apparatus of large intestine during phylo- and ontogenesis, structure and differentiation of human and vertebrate animal intestinal epithelium endocrine cells in norm, under experimental influence and some kinds of gastrointestinal tract (GIT) pathology are of great interest.

Keywords: colon, epithelial barrier, mucus, glycocalyx, mucins, tight contacts, immune system, ulcerative colitis

INTRODUCTION

The colon contains a large number of commensal bacteria and food antigens, at the same time pathogens can enter the intestine. The macroorganism needs to maintain tolerance to the former and develop an effective immune response to the latter. The epithelial barrier of the large intestine plays the leading role in this task. Disruption of epithelial barrier function leads to development of inflammatory response to normal intestinal antigens, which, according to some authors, is the initial mechanism of development of ulcerative colitis. This review is devoted to the current ideas about the structure and function of colonic epithelial barrier and its disorders in ulcerative colitis. However, until now there is no consensus on the types of endocrine cells of some gastrointestinal compartments, the ways of their genesis and regeneration.

In this regard, the large intestine is the least studied part of the digestive system. Investigations of intestinal endocrine system state in a number of pathological processes occurring in this section are

also of interest for understanding of endocrinocyte response to the effects of endogenous and exogenous adverse factors. Intestinal epithelial cells are in constant contact with a variety of foreign antigens coming with food to the so-called biological barriers, the main task of which is to maintain homeostasis of the body. Necessary for this integrity of epithelium is provided by intensive processes of cell regeneration, the study of mechanisms of regulation of which is one of the most intensively developed scientific directions. Epithelium change in the small intestine occurs quickly, as evidenced by the indicators of mitotic index (MI) and apoptosis index (IA) of the small intestine epithelium. The ratio of MI to IA is especially high in the region of crypts and lower third of villi and low in the region of lateral surfaces of villi. This gave grounds to conclude that the reproductive zone of the epithelium of the small intestine is not only the crypt but also the lower third of the villi. Since the intestine is constantly exposed to various biotic and abiotic adverse factors, which eventually lead to the formation of hypoxia, in addition to destructive processes, adaptive changes must occur in it. This includes a shift in the cellular ratio, which is essential for maintaining adequate functioning. One of the main achievements of cell biology in recent years has been the creation of the concept of the diffuse endocrine system (DES), which controls the mechanisms of general and local homeostasis in normal, experimental and clinical pathology. Gastrointestinal tract (GIT) endocrinocytes account for the major part (75%) of the DES, which together with pancreatic insocrine cells constitute the endocrine gastroenteropancreatic (GEP) system. Hormones produced by endocrinocytes of the GEP system have either a remote effect, entering the bloodstream, or their effect is realized at the local tissue level, when the secreted hormone acts on neighboring cells, thus showing an essential role in the regulation of digestive processes and other body functions.

According to Puzyrev A.A. evaluation of diffuse endocrinocytes of the mucous membrane of the digestive tract of female rats with chronic lesions of the hepatobiliary system of various genesis. Other authors revealed an increase in the total number of endocrine cells as well as a change in their subpopulation composition, which indicates a violation of conjugation stages of the secretory cycle in the progeny of female rats with chronic experimental liver damage. Deterioration of the ecological situation as a result of exposure to chemical toxicants is one of the factors determining changes in physiological functions and processes of physiological regeneration in the human body and causing the development of a wide range of diseases, including those of the small intestine. Already in the initial period of toxic exposure changes the composition and functions of the cells of the mucosa of the small intestine, which is most likely due to changes in the regulatory relationships in the cell cycle. Violation of control over the ratio of proliferation and cell death leads to shifts in homeostasis, changes in histoarchitectonics and development of a number of different pathological conditions. One can say that the questions of proliferative activity, cell death and reactivity in the "crypta-vortex" system under the influence of toxic exogenous factors remain open since there are no data on the influence of connective tissue framework on proliferative capabilities of intestinal epithelium against the background of pathogenic factors action. Solution of these questions is necessary for understanding of development of pathological processes in small intestine under the conditions of changed environment that will create possibility for correct approach to diagnostics, prevention and treatment of such diseases.

Epithelial barrier of large intestine consists of mucus layer, glycocalyx and epithelial lining itself. The epithelial lining of the colon is represented by a single layer of cylindrical cells, among which the main types are the absorbing camaeous colonocytes, bocalovid cells and enteroendocrine cells (EECs). Epitheliocytes are bound together by a complex of intercellular contacts that maintain the integrity of the epithelial lining and prevent paracellular transport of macromolecules and bacteria. Intestinal

epithelial cells (ESCs) are involved in the regulation of immune responses. They express a number of receptors for PAMP (Pathogen-Associated Molecular Patterns), can act as lay antigen-presenting cells, and secrete a number of cytokines, thus regulating both innate and adaptive immune system responses. The apical surface of absorbing colonocytes, the predominant cell type forming the lining of the luminal surface of the intestine, is covered with glycocalyx, a dense layer of transmembrane glycoproteins that perform protective and sensory functions. Bocalovid cells produce mucus, which forms two layers on the surface of the epithelial lining. The inner layer of mucus is not permeable to bacteria, while the outer layer serves as a substrate for attachment and nutrition of commensal microflora. The mucus also contains bactericidal substances synthesized by ESCs and secretory immunoglobulins produced by mucosal plasmocytes. This complex complex of the epithelial barrier of the colon allows to maintain tolerance to commensal microflora and food antigens, effectively protecting the body against pathogens. Disruption of the structure and function of the barrier can lead to disruption of this balance and the development of inflammation. In particular, disorders of the epithelial barrier of the colon are thought to play a leading role in the initiation of ulcerative colitis (UC), a widespread chronic recurrent inflammatory disease of the colon. The first barrier of the colon, which protects the body's internal environment from bacteria and damaging agents such as lumen proteases and bile acids, is the mucus produced by bocalytic cells. Intestinal mucus prevents adhesion and invasion of microorganisms, while it does not interfere with nutrient transport, serves as a substrate for attachment and nutrition of commensal microflora, and acts as a lubricant, facilitating the passage of the chyme through the intestine. The main structural components of mucus are mucins.

Mucins are highly glycosylated glyco-proteins consisting of a protein axis (apomucin) and multiple O-linked oligosaccharide chains. Over 20 different human genes encoding the protein part of mucins, from MiS1 to MiS22, have been found. Two types of mucins are distinguished according to the structure of the protein axis: secretory and membrane-associated. The main part of all mature mucins consists of carbohydrates. They determine the main physicochemical properties of these molecules. Mucin domain glycans bind a large amount of water, giving the mucin gel-like properties. Based on the biochemical properties of the peripheral glycan regions, mucins are divided into neutral and acidic, and acidic into sulfated (sulfomucins) and non-sulfated (sialomucins) .

The main structural component of the mucus covering the epithelial lining of the human colon is mucin MiC2. The mucus forms two layers: inner and outer. The inner layer of mucus is dense, cannot be removed by aspiration, is not permeable to bacteria and particles larger than 0.5 μm. In the distal parts of the human colon, it is about 200-300 μm thick. The outer layer of mucus is looser, easily washed away and abundantly populated with bacteria. It is formed as a result of partial degradation and loosening of the mucin network of the inner mucus layer. Mucin carbohydrates are used by commensal bacteria as a food source. Many bacteria have specialized operons for different types of carbohydrate structures, so features of mucin glycosylation may contribute to bacterial selection

Acidic mucins predominate in the colon normally and are thought to protect better than neutral mucins against bacterial translocation because the former, especially the sulfated ones, are less susceptible to degradation by bacterial glycosidases. Reduced content of sulfated mucins in GlcNAc6ST-2 (N-Acetylglucosamine 6-O-sulfotransferase-2) sulfatase-deficient mice results in a more severe experimental colitis than in wild-type mice. In addition to mucins, other products of bocalytic cells (trefoil factor 3 (TFF3), resistin-like molecule p (RELMp), and Fc-y binding protein (FCGBP)), antimicrobial peptides secreted by epithelial and immune cells, and secretory IgA produced by plasmacytes are also included in the mucin. It has been shown that disruption of the barrier function of

the inner mucus layer plays an important role in the development of UC. Muc2 (Muc2) gene knockout mice lack the mucus layer on the surface of colonic epithelial lining and develop spontaneous colitis. In UC patients, an increase in the permeability of the inner mucus layer is observed during exacerbation of the disease. In UC a significant decrease of mucus layer thickness in the left colon and rectum is shown, and the decrease of mucus thickness correlates with the activity of inflammatory process: in the areas of the colon with mild inflammation or its absence the thickness of mucus corresponds to the norm, and in the areas with more severe inflammatory changes there is little or no mucus. In UC, a decrease in the number of bocalovid cells, the amount of intracellular and extracellular mucus, and a decrease of carbohydrate components in it have been revealed. Decrease in the number of boccal cells correlates with the severity of UC in humans and varies from a slight decrease in their number with the predominance of cells with small, immature vacuoles in patients with mild UC to a pronounced decrease and sometimes absence in patients with a moderately severe course of UC. Constancy of mucus layer is determined by balance of processes of its secretion by bocalytic cells, degradation by proteases and glycosidases, as well as mechanical washing out by intestinal contents. In UC there is a significant increase in the activity of bacterial proteases. In the feces of UC patients there is also an increase in the activity of sulfa-tase and sialate 0-acetyl esterase. Fecal extracts from UC patients have been shown to degrade intestinal mucin more effectively compared with extracts from healthy individuals. Histochemical study of mucin glycoprotein composition in UC revealed increased sialylation and decreased sulfation, decreased O-glycosylation, shortening of oligosaccharide chains, and decreased O-acetylation of mucins. The increased number of sialomucins, decreased O-acetylation and decreased sulfation of mucins in UC correlate with the inflammatory index. According to B. J. VanKlinkenetal. a significant decrease in sulfation of mucin in bocalytic cells is revealed in active UC, but sulfomucin content in extracellular mucus does not change due to a compensatory mechanism providing preferential secretion of sulfated form. Mucin MUC2 biosynthesis is decreased in UC, secretion of glycoprotein MUC2 is reduced in active UC, but no changes in MUC2 mRNA levels in bocalytic cells in this disease have been detected.

According to immunohistochemical study in UC patients, the level of MUC1 expression in the colon increases. In severe UC, increased expression of MUC1 mRNA was detected in the zone of crypts-abscesses. Circulating anti-MUCl antibodies have been detected in UC patients. MUC1 is expressed in the epithelial lining of many organs; its physiological role in the colon is not fully understood. Overexpression, abnormal intracellular localization, and changes in glycosylation of this mucin have been observed in tumors. Circulating antibodies to MUC1 are one of the markers of breast cancer . It has been shown that manifestations of experimental colitis in Mys1-deficient mice are less pronounced than in wild-type animals . According to R. J. Longman et al. the expression of the MUC3 gene is not altered in UC. However, A.E. Dorofeev, I.V. Vasilenko and O.A. Rassokhina using immunohistochemical method revealed decreased MUC3 expression in UC patients, and in severe course of the disease - the absence of MUC3 in the bocalytic cells. According to R. J. Longman et al. the expression of MUC4 gene in the colon in UC does not change, and the results of C. Moehle et al. and A.E. Dorofeev I.V. Vasilenko and O.A. Rassokhina indicate its decrease. MUC12 gene expression in the colon in UC patients is statistically significantly reduced even in intact mucosal areas. Data on changes in MUC13 and MUC17 expression in the human colon in UC are scarce and contradictory, even within a single study. For example, in the work of C. Moehle et al. in the colonic mucosa of UC patients by micro-array revealed decreased levels of MUC13 and MUC17 mRNA, and by real-time polymerase chain reaction (PCR) showed their increase. Senapati et al. immunohistochemically demonstrated a significant decrease in MUC17 expression on

the surface and in the crypts of the colonic mucosa. Mucin 13 (Muc13-/-) gene knockout mice were shown to develop more severe experimental colitis than wild-type animals. The data regarding MUC20 levels in UC are also equivocal: according to micro-array studies, the expression of this gene in the colon is decreased, while according to real-time PCR, it does not change. J. Ya-mamoto-Furusho et al. identified a decrease in MUC16 and MUC20 gene expression and decreased production of the corresponding glycoproteins in patients with exacerbation of UC, and their increase during remission. No data on the expression of MUC14, MUC15, MUC21 and MUC22 mucins in UC are available in the literature.The mucosa of the colon is lined by a single-layer prismatic epithelium. All epithelial cells are derived from stem cells located at the bottom of the crypts. The number of stem cells is not exactly known; according to different versions, there are from 1 to 6 per crypt. Stem cells give rise to progenitor cells, capillary-free colonocytes, which, moving up the crypt, divide and differentiate. Seamless colonocytes contain separate secretory vacuoles with mucin; in the upper part of the crypt, they lose their secretory vacuoles and acquire a cheek border when differentiating into camaeous colonocytes. In the early stages of differentiation, the Notch signaling pathway divides the progenitor cells into two cell lines: sucking cells and secretory cells. The first line further differentiates into caemic colonocytes, the second - into bocalytic, EEC and insufficiently well studied brush cells (tuft). In addition, two more types of differentiated colon cells are distinguished: M-cells and "cup" cells, the ways of their differentiation are still unclear. The renewal time of the colon epithelium is about 6 days for capillary colonocytes and bocalytic cells and about 4 weeks for EECs. Epithelial cells that have reached the surface of the mucosa enter apoptosis and desquamate.

Caemic colonocytes are tall cylindrical cells with a basally located nucleus, on the apical surface of which many densely located microvilli are localized, increasing the absorptive surface of the intestine by 30-40 times. This is the predominant cell type of the colon. Their microvilli are covered with glycocalyx. The glycocalyx, microvilli and apical membrane together form a striated fringe. Caiminal colonocytes carry out absorption of products of hydrolysis of nutrients, water and a variety of ions. Ultrastructural study of UC patients shows disorganization of absorbing cells and damage of microvilli. In acute UC a significant decrease in absorption of sodium and water ions in the colon is shown. Bocalovid cells are glass-shaped cells, narrowed at the base where the nucleus is located, with a rounded wide apical part filled with secretory vesicles. In the colon, there are about 4 times fewer bocalytic cells than fossa colonocytes. Mucinogen granules accumulate in the apical part, which bind water and form mucus when secreted. Mucus secreted by bocalovid cells moistens the surface of the mucous membrane, promotes chyme promotion, participates in the processes of interstitial digestion, and is also the first line of defense of the body against endogenous and exogenous irritants, prevents attachment and invasion of microorganisms. Reduction in the number of bocalovid cells is characteristic of UC in humans, it correlates with the severity of UC and varies from a slight decrease in their number with the predominance of cells with small, immature vacuoles in patients with mild UC to a pronounced reduction and sometimes complete absence in patients with a moderately severe course of UC.

EECs are cells with a narrow apical part and a wide basal part in which secretory granules are localized. They constitute about 1% of the epithelial cells of the colon. In response to stimuli from the external and internal environment of the body, EECs secrete biogenic amines and peptide hormones, implementing a wide range of biological reactions. An increase in the number of EECs in the colon has been shown in human UC. The main types of colonic EECs are Her-, B- and D-cells. Enterochromaffin (EC) cells are the most common type of EECs in the gastrointestinal tract. In the proximal colon, they account for more than 70% of all EECs. In the distal direction in the colon, their number remains

approximately constant, but the proportion decreases (in the rectum they account for 40%) due to an increase in the number of EECs of other types. EC cells secrete serotonin, which in the digestive system stimulates peristalsis and accelerates the transit of intestinal contents. In addition, serotonin has been shown to be involved in the regulation of immune reactions. Receptors for this hormone have been identified on B- and T-lymphocytes, monocytes, macrophages, and dendritic cells. Administration of serotonin to mice against the background of experimental colitis aggravates its course, while suppression of serotonin production, on the contrary, reduces the severity of the course of colitis. Regarding changes in the number of EC-cells in UC, literature data are contradictory: M. D. Coates et al. revealed a decrease in the number of EC-cells and serotonin production in the rectum during a severe course of UC. However, according to M. El-Salhy et al. the number of chromogranin A- and serotonin-positive cells increases significantly in the colon of UC patients. L-cells are the second most abundant colonic EECs. Their number increases distally, and in the rectum they account for approximately 14% of EECs. Their secretory products are enteroglucagones (glucagon-like peptides 1 (GLP-1) and 2 (GLP-2), glicentin and oxytomodulin) and peptide YY. GLP-1 stimulates insulin production in response to glucose uptake and inhibits gastric juice secretion. GLP-2 and glicentin stimulate epithelial proliferation. Oxynto-modulin slows gastric emptying. Peptide YY suppresses chyme evacuation from the stomach and intestinal peristalsis, inhibits gastric juice secretion and pancreatic exocrine cell function, suppresses appetite, and stimulates mucosal epithelial proliferation. In inflammatory bowel diseases, the production of peptide YY is decreased in the L-cells of the colon, and the production of enterogluc-gon is either increased or unchanged. D-cells are found throughout the gastrointestinal tract; in the colon, they account for 3-5% of EECs. Their main secretory product is somatostatin, a hormone that suppresses exocrine function and secretion of all gastrointestinal hormones. It is also shown that somatostatin is involved in the regulation of immune reactions: it inhibits the secretion of pro-inflammatory cytokines. In human inflammatory bowel diseases a decrease in the number of D-cells and the level of somatostatin in the blood has been shown.

M cells (Membranous or Microfolded cells) are cells located in the epithelial lining areas covering the lymphoid follicles in the mucosa's own lamina. Their basolateral membrane forms deep pocket-like depressions in which dendritic cells, macrophages, T-lymphocytes are located. The apical membrane forms wide microfolds covered by a thin layer of glycocalyx. M-cells capture lumen antigens and microorganisms and transfer them to the underlying immune cells. In UC, the number of lymphoid nodules and M cells increases. In general, ultrastructural study of colonic epithelial lining during acute UC revealed significant damage of epithelial cells: emptying of bocalytic cells, decreased number or disappearance of microvilli, destruction of tight contacts, vacuolization and lysis of cytoplasm, pyknotic nuclei, damage of EPR, mitochondria, Golgi complex. In remission of UC, epithelial lining thickness is lower than normal, microvilli are deformed, intercellular spaces are enlarged and there are damages of organelles ECPs are connected by a complex of special intercellular connections: desmosomes, adhesive contacts and tight contacts. Adhesive contacts and desmosomes are part of a group of anchoring compounds. They consist of 2 types of proteins: the former are transmembrane "lin-core" proteins, the latter are intracellular proteins that anchor membrane elements to cytoskeleton components. Their main function in the epithelium is to maintain the integrity of the epithelial layer. Adhesive contacts can form point junctions, plaques or ribbons. The latter are characteristic of single-layered epithelia. An adhesion ribbon encircles the entire perimeter of the epithelial cell below the tight junction. Plasma membranes of neighboring cells in this zone are distant from each other at a distance of 25-30 nm, a dense junction zone of linker proteins represented by E-cadherins in epithelium can be seen between

them. Epithelial (E)-cadherin is a glycoprotein with 1 transmembrane domain, its extracellular domain forms homotypic Ca2+-dependent connections with the cadherins of neighboring cells, and the intracellular domain contains a catenin-binding domain. a- and p-catenins attach the cytoplasmic domain of E-cadherin to the actin cytoskeleton of the cell. p-catenin, in addition to the formation of adhesive contacts, also has an important signaling function in the cell, being the key protein of the Wnt-signaling pathway. Adhesive contacts not only mechanically connect neighboring cells, but also participate in the maintenance of cell polarity, regulation of migration and proliferation. In UC, a decrease in E-cadherin and p-catenin has been shown in the colonic epithelium, indicating damage to intercellular connections. In addition, the production of NF-kB (Nuclear Factor Kappa-light-chain-enhancer of activated Bcells), a transcription factor of Wnt-signaling pathway, which contributes to the development of the inflammatory process, is increased in UC.

Desmosomes are plaque-shaped intercellular junctions; a dense layer of linker glycoproteins, represented by desmogleins and desmocollins, is seen in the intercellular space in the area of desmosomes, which bind cells to each other. The intracellular domains of linker proteins are associated with a number of adaptor and framework proteins (plakoglobin, plakophilin, desmoplakin, etc.), which anchor desmosomes to intermediate filaments. Literature data on changes in desmosomes in the intestinal epithelial lining in UC are lacking. The most important for the barrier function of the intestine are the tight contacts - the connections that encircle the apical part of the cells. They form a zone of maximum convergence of lateral membranes of neighboring epithelial cells. Dense contacts are formed by intersecting chains of transmembrane proteins interacting with proteins of neighboring cells and forming a network of point membrane connections. Transmembrane proteins of dense contacts are represented by occludin, claudins, JAM (Junctional Adhesion Molecules) and tricellulin. On the cytoplasmic side, the transmembrane proteins are connected to signaling, adaptor and framework proteins such as ZO (Zona Occludens) -1,-2,-3 and cingulin, and through them are connected to the actin filaments of the cytoskeleton. Transmembrane and cytoplasmic proteins of dense contacts contain a number of signal sequences involved in the regulation of proliferation, polarization, and differentiation of epithelial cells. Dense contacts are not permeable to macromolecules and can selectively pass certain ions, depending on the composition of claudins.

Thus, dense contacts are the main regulators of paracellular transport in the epithelial lining of the intestine. The main structural components of dense contacts are claudins. To date, 27 claudins have been described. Expression of claudins 1, 2, 3, 4, 5, 7, 8, 12, 13, 18 has been shown in the human and mouse colon. Claudins of one cell homo- and heterophilically interact with claudins of the neighboring cell forming intercellular connections with different permeability to ions. According to this feature, claudins are divided into "locking" - preventing transport of ions through the tight contact, and "por-forming" - forming channels for anions or cations. Currently, however, few claudins are unambiguously classified as "pore-forming" (claudins 2, 10b and 15 form pores for cations, claudins 10A and 17 form pores for anions). Some claudins form pores only by heterophilic interaction, such as claudins 4 and 8. There is evidence that claudin 4 is "locking" in the colon. Significant changes in dense contacts are observed in UC. H. Schmitz et al. showed by freeze-thawing that in UC patients the thickness of dense contacts is significantly reduced compared to normal and the number of horizontally oriented "ribbons" of transmembrane proteins is reduced. The production of claudin 2 is increased and claudin 1, 4 and 7 are decreased during exacerbation of UC. The expression of occludin and tricellulin also decreases.

CONCLUSIONS

Thus, the main components of the epithelial barrier are mucus, which prevents adhesion and invasion of microorganisms, glycoc-lyx, which performs a barrier and sensory role, and the epithelial cells themselves, interconnected by a complex of intercellular contacts. Epithelial cells can recognize a wide range of pathogen-associated molecules and regulate immune responses in the colon through secretion of immunoregulatory molecules and contact interactions with lymphocytes, macrophages and dendritic cells. Normally, the epithelial barrier of the colon contributes to the body's tolerance to commensal microflora and food antigens, and when pathogens enter the intestine, it triggers an inflammatory response. An imbalance between tolerance and pro-inflammatory signals possibly leads to the development of ulcerative colitis.

Reduced amount of mucus, changes in its physical and biochemical properties observed in UC lead to increased permeability of mucus layer for bacteria and promote their adhesion and invasion. In UC, there are changes in the expression of transmembrane mucins that are part of the gly-cocalyx, the integrity of the epithelial lining is compromised, the absorption of ions and water is reduced, the number of bocalytic cells is reduced and changes are observed.

Thus, the presence of poorly investigated and debatable issues concerning the localization, structure and genesis of endocrinocytes require further detailed study.

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