INTESTINAL EPITHELIUM'S MORPHOFUNCTIONAL IMPORTANCE IN BOTH NORMAL AND ULCERATIVE COLITIS

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Abstract: *Time in the normal functioning of the system of diffuse endocrine cells of the mucous membrane of the digestive tract is important . Endocrine cells of the gastrointestinal tract produce a number of biologically active substances with a wide range of local and systemic effects, which ultimately affect the growth and development of the organism. Morphological changes in the diffuse endocrine system of the alimentary tract of female rats with chronic liver damage have been studied by many scientists. Other authors have examined the characteristic changes in the diffuse endocrine system of the alimentary tract of the offspring of female rats with chronic intestinal inflammation. One of the most important issues of modern morphology is the genesis, differentiation, structure and cytophysiology of tissues under normal functioning conditions and pathology. The study of these problems allows further development of cytology, histology, endocrinology, embryology and a deeper understanding of the processes occurring in clinical pathology. In this regard, it is related to the formation, structure and differentiation of the endocrine apparatus of the large intestine in the process of phylo- and ontogenesis of the intestinal epithelium of humans and vertebrates under normal, experimental conditions and in certain types of gastrointestinal tract (GI) pathologies. issues are considered.*

Key words*: colon, epithelial barrier, bacteria, mucus, glycocalyx, mucins, immune system, ulcerative colitis.*

Enter. The large intestine contains a large number of commensal bacteria and food antigens, while pathogens can enter the intestine. The macroorganism must maintain protection against the first and develop an effective immune response to the second. The epithelial barrier of the large intestine plays a leading role in this task. Dysfunction of the epithelial barrier leads to the development of an inflammatory response to normal intestinal antigens , which, according to some authors, is the initial mechanism of the development of ulcerative colitis. This review is devoted to current ideas about the structure and function of the colonic epithelial barrier and its disturbances in ulcerative colitis. However, until now, there is no concept of the types of endocrine cells of some parts of the gastrointestinal tract, the methods of their generation and regeneration.

In this regard, the large intestine is the least studied part of the digestive system. Studying the condition of the intestinal endocrine system in a number of pathological processes occurring in this department is also of interest to understand the response of

endocrinocytes to the effects of endogenous and exogenous negative factors. Intestinal epithelial cells are in constant contact with various foreign antigens that accompany food and are called biological barriers, their main function is to maintain the homeostasis of the body. Intensive processes of cell regeneration, necessary for this integrity of the epithelium, are provided, the study of their regulatory mechanisms is one of the most intensively developed scientific directions. Epithelial turnover occurs rapidly in the small intestine, as evidenced by the mitotic index (MI) and apoptosis index (AI) of the small intestinal epithelium. The ratio of MI to AI is especially low in the region of the crypts in the upper and lower thirds and on the lateral surfaces. This was the basis for the conclusion that the reproductive zone of the epithelium of the small intestine is not only the crypt, but also the lower third. Since the intestine is constantly exposed to various biotic and abiotic negative factors, resulting in the formation of hypoxia, in addition to inflammatory processes, adaptive changes must occur in it. This involves a change in the cell ratio, which is necessary to ensure adequate activity. In recent years, one of the main achievements of cell biology has been the creation of the concept of the diffuse endocrine system (DES), which controls general and local homeostasis mechanisms in normal, experimental and clinical pathology. Gastrointestinal tract (GIT) endocrinocytes make up the majority (75%) of DEC, which, together with pancreatic inocrine cells, form the endocrine gastroenteropancreatic (GEP) system. Hormones produced by the endocrinocytes of the GEP system enter the blood stream and have a distant effect, or their effect is carried out at the local tissue level, when this secreted hormone affects neighboring cells, regulating digestive processes. plays an important role. other body functions.

According to Puzyrev AA, evaluation of diffuse endocrinocytes of the mucous membrane of the digestive tract of female rats with chronic damage to the hepatobiliary system of different genesis. Other authors found an increase in the total number of endocrine cells, as well as a change in their subpopulation composition, which indicates that the conjugation stages of the secretory cycle are disturbed in the offspring of female rats with chronic experimental liver damage. Deterioration of the environmental situation under the influence of chemical toxic substances is one of the factors that determine the change of physiological functions and physiological recovery processes in the human body, which causes the development of a wide range of diseases, including diseases of the small intestine. In the initial period of toxic exposure, the composition and functions of the cells of the mucous membrane of the small intestine change, which is probably associated with changes in the regulatory relationships in the cell cycle. Violation of control over the ratio of proliferation and cell death leads to changes in homeostasis, changes in hysteric tectonics, and the development of a number of different pathological conditions. It can be said that the issues of proliferative activity, cell death and reactivity in the "crypt-vortex" system under the influence of toxic exogenous factors remain open, because there is no information about the influence of the connective tissue structure on the proliferative

ability of the intestinal epithelium. the background of the effect of pathogenic factors. The solution of these questions is necessary to understand the development of pathological processes in the small intestine under the conditions of a changed environment, which creates the possibility of a correct approach to the diagnosis, prevention and treatment of such diseases.

The epithelial barrier of the large intestine consists of the mucous membrane, the glycocalyx and the epithelial lining itself. The epithelial lining of the large intestine is represented by a single layer of cylindrical cells, the main types of which are absorptive cells. colonocytes, bocaloid cells and enteroendocrine cells (EEC). Epitheliocytes are interconnected by a complex of intercellular contacts that maintain the integrity of the epithelial cover and prevent the 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 PAMPs (pathogen-associated molecular patterns), can act as deposited antigen-presenting cells and secrete a number of cytokines, thus regulating both innate and adaptive immune system responses. The apical surface of absorptive colonocytes, the predominant cell type that forms the lining of the luminal surface of the intestine, is covered with a glycocalyx, a dense layer of transmembrane glycoproteins that perform protective and sensory functions. Bocaloid cells produce mucus that forms two layers on the surface of the epithelial lining. The inner layer of mucus is impermeable to bacteria, and the outer layer serves as a substrate for the attachment and nutrition of commensal microflora. Mucus also contains bactericidal substances synthesized by ESCs and secretory immunoglobulins produced by mucous plasma cells. This complex complex of the epithelial barrier of the large intestine effectively protects the body from pathogens and allows maintaining tolerance to commensal microflora and food antigens. Violation of the structure and function of the barrier can lead to a disturbance of this balance and the development of inflammation. In particular, disruption of the colonic epithelial barrier plays a leading role in the initiation of Ulcerative Colitis (UC), a common chronic relapsing inflammatory disease of the colon. The first barrier of the large intestine protects the internal environment of the body from bacteria and harmful substances such as luminal proteases and bile acids, which is a mucous membrane produced by biliary cells. The intestinal mucosa prevents the adhesion and penetration of microorganisms, while it does not interfere with the transport of nutrients, serves as a substrate for the attachment and nutrition of commensal microflora, and acts as a lubricant that facilitates the passage of chyme through the intestine . Mucin is the main component of mucus.

Mucins are highly glycosylated glycoproteins consisting of a protein axis (apomucin) and several O-linked oligosaccharide chains. More than 20 different human genes have been found that encode the protein portion of mucins, MiS1 to MiS22. According to the structure of the protein axis, two types of mucins are distinguished: secretory and membrane-bound. The majority of all mature mucins are carbohydrates. They determine the main physicochemical properties of these molecules. Glycans in the mucin domain

bind large amounts of water, giving mucin gel-like properties. According to the biochemical properties of peripheral glycan regions, mucins are divided into neutral and acidic, and acidic into sulfated (sulfomucins) and non-sulfated (sialomucins).

Mucin MiC2 is a major component of the mucous membrane lining the epithelial lining of the human colon. Mucus forms two layers: inner and outer. The inner layer of the mucous membrane is dense, cannot be removed by aspiration, does not pass bacteria and particles larger than 0.5 μm. It is about 200-300 μm thick in the distal parts of the human colon. The outer layer of the mucous membrane is softer, easily washed off and contains a large number of bacteria. It is formed as a result of partial degradation and loosening of the mucin network of the inner mucous membrane. Mucin carbohydrates are used as a food source by commensal bacteria. Many bacteria have specialized operons for different types of carbohydrate structures, so features of mucin glycosylation may contribute to bacterial selection.

Acidic mucins usually predominate in the large intestine and provide better protection against bacterial translocation than neutral mucins because the former, especially sulfated ones, are less prone to degradation by bacterial glycosidases. Reduced sulfated mucins in GlcNAc6ST-2 (N- Acetylglucosamine 6-O-sulfotransferase-2) sulfatase-deficient mice result in more severe experimental colitis than wild-type mice. In addition to mucins, other products of inflammatory cells (trefoil factor 3 (TFF3), resistin-like molecule β (RELMp) and Fc-γ binding protein (FCGBP)), antimicrobial peptides released by epithelial and immune cells, and secretory IgA plasma cells produced by is included in mucin. It has been shown that the disruption of the barrier function of the inner mucous membrane plays an important role in the development of hyaline. Muc2 (Muc2) gene knockout mice lack the mucosal surface of the colonic epithelial lining and develop spontaneous colitis. In patients with CKD, increased permeability of the inner mucosa is observed during the exacerbation of the disease. A significant decrease in the thickness of the mucous membrane in the left colon and rectum was shown in UA, and the decrease in the thickness of the mucosa is associated with the activity of the inflammatory process: mild inflammation of the colon or its The thickness of the mucous membrane in the areas of absence is suitable. there is little or no mucus in normal and areas with stronger inflammatory changes. A decrease in the number of bocaloid cells, the amount of intracellular and extracellular mucus, and carbohydrate components in it was found in HC . A decrease in buccal cell number correlates with the severity of CA in humans, and patients with mild CA have a predominance of cells with small, immature vacuoles, from a slight decrease in their number to a significant decrease and sometimes absence. is different. Moderately severe course of YAK. The consistency of the mucous layer is determined by the balance of secretory processes by the bucolytic cells, breakdown by proteases and glycosidases, as well as mechanical washing of intestinal contents. The activity of bacterial proteases increases significantly in UA. The activity of sulfatase and sialate 0-acetyl esterase is also increased in the feces of patients with CKD. Fecal extracts

from patients with UC have been shown to break down the intestinal mucosa more effectively than extracts from healthy individuals. Histochemical study of the composition of mucin glycoproteins in YaK revealed increased sialylation and decreased sulfation, decreased O-glycosylation, shortening of oligosaccharide chains, and decreased O-acetylation of mucins. An increase in the number of sialomucins, a decrease in O- α acetylation and a decrease in sulfation of mucins in YaK are associated with an index of inflammation. According to BJ VanKlinkenetal. a significant decrease in mucin sulfation in bocalitic cells is detected in active HCV, but the amount of sulfomucin in the extracellular mucus does not change due to a compensatory mechanism that ensures the preferential secretion of the sulfated form. Biosynthesis of mucin MUC2 is reduced in CKD, MUC2 glycoprotein secretion is reduced in active CKD, but no changes in MUC2 mRNA level in bacillitic cells were detected in this disease.

According to immunohistochemical study, the expression level of MUC1 is increased in the colon. An increase in MUC1 mRNA was detected in the crypt-abscess zone in severe UC. Circulating anti-MUCl antibodies have been detected in patients with CKD. 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 hallmarks of breast cancer. It has been shown that Mys1-deficient mice exhibit less pronounced experimental colitis than wild-type animals. According to RJ Longman et al. The expression of MUC3 gene is not changed in YaK. At the same time, AE Dorofeev, IV Vasilenko, and OA Rassokina, using the immunohistochemical method, found a decrease in the expression of MUC3 in YaK patients and the absence of MUC3 in the bacillitic cells in the severe course of the disease. According to RJ Longman et al. MUC4 gene expression is not altered in the colon in UC, and the results of C. Moehle et al. and AE Dorofeev IV Vasilenko and OA Rassokina show its decrease. MUC12 gene expression is statistically significantly reduced in the colon of patients with UC, even in intact mucosal areas. Data on altered expression of MUC13 and MUC17 in human colon in UC are scarce and conflicting, even in a single study. For example, in the work of C. Moehle et al. Decreased MUC13 and MUC17 mRNA levels were detected by microarray and increased by real-time polymerase chain reaction (PCR). Senapati and others. immunohistochemically demonstrated a significant decrease in MUC17 expression on the surface and crypts of the colonic mucosa. Mucin 13 (Muc13-/-) gene knockout mice developed more severe experimental colitis than wild-type animals. Data on the level of MUC20 in UC are also questionable: according to micro-array studies, the expression of this gene in the colon decreases, but according to real-time PCR, it does not change. J. Ya-mamoto-Furusho et al. A decrease in MUC16 and MUC20 gene expression and a decrease in the production of the corresponding glycoproteins were found in patients with increased CKD, and their increase during remission. There is no information in the literature about the expression of mucins MUC14, MUC15, MUC21, and MUC22 in UC. The mucous membrane of the large intestine

is covered with a single layer of prismatic epithelium. All epithelial cells originate from stem cells located at the bottom of the crypts. The exact number of stem cells is not known; according to different versions, from 1 to 6 in each crypto. Stem cells give rise to progenitor cells, noncapillary colonocytes, which ascend the crypt, divide, and differentiate. In unstained colonocytes, there are separate secretory vacuoles with mucin; at the top of the crypt, they lose their secretory vacuoles and have a cheek border when separated by kamaye. Colonocytes. During the early stages of differentiation, the Notch signaling pathway differentiates progenitor cells into two cell lineages: absorptive cells and secretory cells. The first row is additionally distinguished by seremia colonocytes, the second - into bocalytic, EEC and poorly 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. Colonic epithelium renewal time is about 6 days for capillary colonocytes and bocalitic cells and about 4 weeks for EEC. Epithelial cells that reach the surface of the mucosa undergo apoptosis and desquamate.

Injured colonocytes are tall cylindrical cells, the nucleus is located basally, and many densely located microvilli are localized on their apical surface, which increases the absorption surface of the intestine by 30-40 times. This is the main cell type of the large intestine. Their microvilli are covered with glycocalyx. Glycocalyx, microvillus and apical membrane together form a linear border. Caiminal colonocytes absorb nutrients, water and hydrolysis products of various ions. Ultrastructural examination of patients with UC shows disorganization of absorptive cells and damage to microvilli. Colonic absorption of sodium and water ions is significantly reduced in acute UC. Bocaloid cells are vitreous cells, narrowed at the nucleus, and the round wide apical part is filled with secretory vesicles. In the large intestine, there are 4 times less bocalytic cells than colonocytes. Mucinogenic granules accumulate in the apical part, they bind water and form mucus when secreted. Bocalovid moistens the surface of the mucous membrane, promotes the development of chyme, participates in the processes of interstitial digestion, and is the first line of defense of the body against endogenous and exogenous irritants, preventing the attachment and penetration of microorganisms. A decrease in the number of goblet cells is characteristic of HAC in humans, which correlates with the severity of HAC and ranges from slightly decreased to markedly decreased with a predominance of cells with small, immature vacuoles in patients with mild HAC. will change. sometimes its complete absence in patients with moderately severe UC.

EEC are cells with a narrow apical part and a wide basal part, in which secretory granules are located. They make up about 1% of the colonic epithelial cells. In response to stimuli from the external and internal environment of the body, the EEC secretes biogenic amines and peptide hormones and carries out a wide range of biological reactions. An increase in the number of colonic EECs has been shown in human UC. The main types of colonic EEC are Her -, B- and D-cells. Enterochromaffin (EC) cells are the most common type of EEC in the gastrointestinal tract. In the proximal colon, they make up more than

70% of all EECs. In the distal direction in the large intestine, their number remains approximately unchanged, but the ratio decreases due to the increase in the number of other types of EEC (in the rectum, they make up 40%). EC cells release serotonin, which stimulates peristalsis in the digestive system and accelerates the passage of intestinal contents. In addition, serotonin has been shown to be involved in the regulation of immune responses. Receptors of this hormone have been identified in B- and T-lymphocytes, monocytes, macrophages and dendritic cells. Administration of serotonin to mice against the background of experimental colitis aggravates its course, and 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, the literature data are conflicting: MD Coates et al. A decrease in the number of EC-cells and serotonin production in the rectum was found in the severe course of CKD. However, according to M. El-Salhy et al. The number of chromogranin A- and serotonin-positive cells is significantly increased in the colon of patients with CKD. L-cells are the second most abundant colonic EEC. Their number increases distally, and in the rectum they make up about 14% of the EEC. Their secretion products are enteroglucagons (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 absorption and inhibits gastric juice secretion. GLP-2 and glicentin stimulate epithelial proliferation. Oxynto-modulin slows gastric emptying. Peptide YY suppresses the evacuation of chyme from gastric and intestinal peristalsis, inhibits the secretion of gastric juice and the activity of exocrine cells of the pancreas, suppresses appetite, and stimulates the proliferation of mucosal epithelium. In inflammatory bowel diseases, the production of YY peptide in the L-cells of the large intestine decreases, and the production of enteroglucagon increases or does not change. D-cells are found throughout the gastrointestinal tract ; in the large intestine, they make up 3-5% of the EEC. Their main secretory product is somatostatin, a hormone that suppresses exocrine function and the secretion of all gastrointestinal hormones. It has also been shown that somatostatin is involved in the regulation of immune reactions: it inhibits the secretion of anti-inflammatory cytokines. Decreased D-cell counts and blood somatostatin levels have been shown in human inflammatory bowel disease.

M cells (membranous or microfold cells) are cells located in the areas of the epithelial lining that cover the lymphoid follicles of the mucous membrane itself. Their basolateral membrane forms deep pocket-like pits where dendritic cells, macrophages, and T-lymphocytes are located. The apical membrane forms wide microfolds covered with a thin glycocalyx layer. M-cells capture luminal antigens and microorganisms and transfer them to primary immune cells. The number of lymphoid nodes and M cells increases in PC. In general, the ultrastructural study of the epithelial lining of the large intestine during acute UC revealed a significant damage to the epithelial cells: loosening of bacillitic cells, a decrease in the number or disappearance of microvilli, disruption of tight junctions, cytoplasm vacuolization and lysis, pyknotic nuclei, EPR, mitochondria, Golgi complex

damage. In UC remission, the thickness of the epithelial cover is lower than normal, the microvilli are deformed, the intercellular spaces expand, and the organelles are damaged. Adhesive contacts and desmosomes belong to the group of anchoring junctions. They consist of 2 types of proteins: the first are transmembrane "lin-core" proteins, and the second are intracellular proteins that connect membrane elements to components of the cytoskeleton. Their main function in the epithelium is to maintain the integrity of the epithelial layer. Adhesive contacts can form point joints, plaques, or tapes. The latter is characteristic of a single-layered epithelium. An adhesive tape surrounds the entire perimeter of the epithelial cell under a tight junction. The plasma membranes of neighboring cells in this zone are located at a distance of 25-30 nm from each other, and between them a dense fusion zone of connecting proteins expressed by E-cadherins in the epithelium is visible. Epithelial (E)-cadherin 1 is a glycoprotein with a transmembrane domain, whose extracellular domain forms homotypic Ca2+-dependent contacts with cadherins of neighboring cells, and the intracellular domain binds to its catenin-binding domain. includes α- and β-catenins connect the cytoplasmic domain of E-cadherin with the actin cytoskeleton of the cell. β-catenin, in addition to the formation of adhesive contacts, has an important signaling function in the cell, being the main protein of the Wnt signaling pathway. Adhesive contacts not only mechanically connect neighboring cells, but also participate in maintaining cell polarity, regulating migration and proliferation. E-cadherin and β-catenin have been shown to be reduced in the colonic epithelium in CKD, indicating damage to intercellular junctions. In addition, the production of NF-κB (Nuclear Factor Kappa-light-chain-enhancer of activated Bcells), a transcription factor of the Wnt signaling pathway, which contributes to the development of the inflammatory process, increases.

Desmosomes are plaque-shaped intercellular junctions; a dense layer of binding glycoproteins represented by desmogleins and desmocollins is seen in the intercellular space in the region of desmosomes that connect cells to each other. The intracellular domains of binding proteins are associated with a number of adapter and framework proteins (plakoglobin, plakophilin, desmoplakin, etc.) that connect desmosomes to intermediate filaments. There are no literature data on changes in desmosomes in the intestinal epithelial lining in UC. The most important for the barrier function of the intestine are tight junctions - junctions that surround the apical part of the cells. They form the maximum convergence zone of the lateral membranes of adjacent epithelial cells. Dense contacts are formed by crossing chains of transmembrane proteins that interact with proteins of neighboring cells and form a network of point membrane junctions. Transmembrane proteins of tight junctions are represented by occludin, claudins, JAM (Junctional Adhesion Molecules) and tricellulin. On the cytoplasmic side, transmembrane proteins are associated with signaling, adapter, and framework proteins such as ZO (Zona). occludens) -1, -2, -3 and singulin and through them connect to the actin filaments of the cytoskeleton. Transmembrane and cytoplasmic proteins of tight junctions contain a number of signal sequences involved in the regulation of proliferation, polarization and

differentiation of epithelial cells. Tight junctions are impermeable to macromolecules and can selectively pass certain ions depending on the composition of claudins.

They are the main regulators of paracellular transport in the intestinal epithelial lining. The main components of tight junctions are claudins. To date, 27 claudins have been described. Expression of claudins 1, 2, 3, 4, 5, 7, 8, 12, 13, 18 has been demonstrated in human and mouse colon. Claudins of one cell interact homo- and heterophilically with claudins of neighboring cells and form intercellular junctions with different ion permeability. According to this feature, claudins are divided into channels that "lock" - preventing the transport of ions through a tight junction, and "pore-forming" channels for anions or cations. However, several claudins are now 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 through heterophilic interactions, such as claudins 4 and 8. There is evidence that claudin 4 is "locked" in the colon. Significant changes in dense contacts are observed in the YaK. H. Schmitz and others. showed by freezing-thawing that in UC patients, the thickness of tight junctions is significantly reduced compared to normal, and the number of horizontally oriented "ribbons" of transmembrane proteins is reduced. As UC progresses, claudin 2 production increases and claudin 1, 4, and 7 decrease. The expression of occludin and tricellulin is also decreased.

Conclusion: Thus, the main components of the epithelial barrier are epithelial cells interconnected by a complex of glycolysis and intercellular connections, which perform a mucous, barrier and sensory role that prevents the adhesion and invasion of microorganisms. Epithelial cells can recognize a wide range of pathogen-associated molecules and regulate immune responses in the colon through secretion of immunoregulatory molecules and communication interactions with lymphocytes, macrophages, and dendritic cells. Normally, the epithelial barrier of the large intestine contributes to the compensatory microflora of the body and tolerance to food antigens, and when pathogens enter the intestine, it provokes an inflammatory reaction. An imbalance between tolerance and pro-inflammatory signals can lead to the development of ulcerative colitis.

The decrease in the amount of mucus, the changes in its physical and biochemical properties observed in HCV lead to an increase in the permeability of the mucous membrane for bacteria and help their adhesion and invasion. There are changes in the expression of transmembrane mucins, which are part of the gly-cocalyx, the integrity of the epithelial cover is disturbed, the absorption of ions and water decreases, the number of bacillitic cells decreases and changes are observed.

The presence of little-studied and controversial issues related to the localization, structure and genesis of endocrinocytes requires detailed study.

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