ENDOCRINE CELLS OF THE COLON EPITHELIA AS PART OF THE DIFFUSE ENDOCRINE SYSTEM

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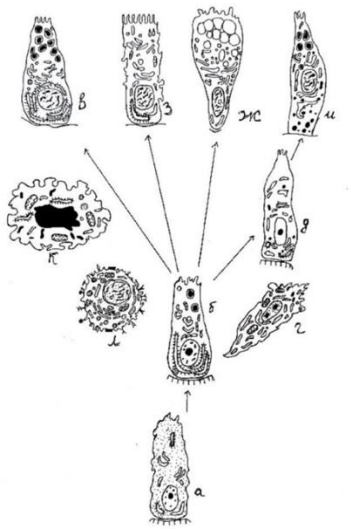
Abstract. *One of the cytogenetic options for divergent differentiation of cells of the cambial reserve of intestinal epithelial tissue is the so-called. entero- and colonoendocrinocytes. They produce biologically active substances that maintain homeostasis and regulate the functioning of the gastrointestinal tract. Being the functionally leading tissue of the entire gastrointestinal tract, all types of epithelial cells, and enteroendocrine cells, in particular, are involved in the pathomorphogenesis of intestinal diseases. Dysfunction of these cells leads to disturbances in microcirculation and regeneration, which and/or contributes to the development of inflammatory diseases, or is an important part of their pathomorphogenesis.*

The surface layer of the colon mucosa is formed by single-layer columnar epithelial cells of endodermal histogenesis lining the crypts and the spaces between them [9]. One of the cytogenetic options for divergent differentiation of cells of the cambial reserve of intestinal epithelial tissue is the so-called. entero- and colonoendocrinocytes [10] (Fig. 1).

Epithelial endocrinocytes of the colon mucosa are part of the diffuse endocrine system (DES), or more precisely, the gastroenteropancreatic endocrine system (GEPES) - the largest link of the DES. Cells of the diffuse endocrine

system are classified as the APUD series, but it is important to note that these are not identical concepts. APUD cells include not only endocrine epithelial cells, united by a common source of development, capable of metabolizing the amine precursor and decarboxylating



we can define it (Amine Precursor Uptake and Decarboxylation), but also connective tissue cells (mast nervous (aminergic and peptidergic neuronsc)eallnsd), secretory cardiomyocytes fabrics

[7]. A. Pearse (1973), who is the author of the concept of the APUD system, considered them a common source development of neuroectoderm, due to which they received the name neuroendocrine cells. This conclusion was made based on the similarity of the metabolic processes of the synthesis of biogenic amines in these cells, as well as the content of neuron-specific enolase and chromogranin A (the so-called "markers of neuroectodermal differentiation"). According to A. Pearse (1973), cells of the neural crest (ganglionic plate) migrate to different tissues and differentiate into neuroendocrine tissues [3]. However, this hypothesis has not been fully confirmed, since it takes into account data on the tissues. the development of acinar islet cells of the pancreas, combining in their morphofunctional organization the characteristics of exocrine and endocrine cells. In accordance with the hypothesis of acido- insular modification of acinar cells into endocrine cells, endodemal histogenesis of these cells has been established;

Thus, the parenchyma of the endocrine and exocrine parts of the pancreas has a single embryonic rudiment - the intestinal endoderm.

Rice. 1. Scheme of divergent differentiation of intestinal epithelial stem cells. a) stem cell; b-d) poorly differentiated

progenitor cells: b) Panetov cells; c) mucous membranes;

d) suction; e) enteroendocrine; g-i) mature cells: g) goblet;

h) border suction; i) endocrine; j) macrophage; d)

The presence of "markers of neuroectodermal differentiation" fibroblast; l) lymphocyte. in all APUD-series cells does not prove their common origin from a single germ, since neuron-specific enolase is contained in APUD cells of different tissues that have different sources of development. In addition, such substances include the acidic glycoprotein chromogranin A (CgA), which was found in the secretory granules of not only endocrine cells, but also bulbourethral glands [1], cardiomyocytes [5] and other large optical cells. dense granules of most neuroendocrine cells. Upon specific stimulation of cells, chromogranins are secreted together with biogenic amines and play a significant role in the processes of formation, maturation, intracellular transport and exocytosis of secretory granules in neuroendocrine cells and neurons. In addition, as a result of enzymatic cleavage of chromogranins, a number of smaller peptides are formed that have various biological activities. When released, chromogranin A has a vasostabilizing effect on the blood vessels of the circulatory system.

Thus, APUD-series cells are a set of derivatives of different primordia, just like DES cells, they develop from stem cells of endodermal, ectodermal and mesodermal origin, representing different cytogenetic types; but we emphasize that according to today's ideas, all intestinal epithelial cells, including those forming the gastroenteropancreatic endocrine system, are the result of differentiation of a single stem cell of endodermal origin, which in the literature has received different names - stem enterocyte, intestinal epithelial stem cell, stem cell colonocyte, etc.

A periodization of differentiation of intestinal epithelial cells has been proposed; according to it, 5 stages of this process are distinguished. I Art. – mitosis of the intestinal epithelial stem cell, resulting in the formation of a poorly differentiated cell (grade II), which retains the ability to mitosis, while at the same time, structures characteristic of epithelial cells of a certain type appear in its cytoplasm. III Art. – a transitional cell that is in the process of differentiation and acquiring signs of cellular specialization. Art. IV is a differentiated intestinal epithelial cell of a certain type, actively performing specific functions. Cell death and desquamation – stage V [2].

Stem cells are characterized by a high nuclear-cytoplasmic ratio, a large nucleolus, diffuse distribution of chromatin in the nucleus, and numerous ribosomes in the cytoplasm. Apparently, these cells divide asymmetrically; as a result of division, a similar stem cell and a daughter cell are formed, which undergo further differentiation.Poorly differentiated cells are characterized by the presence of large precursor granules in the cytoplasm. Mitosis of these endocrinocytes is sometimes observed, but in most cases poorly differentiated cells are the result of differentiation specifically stem cells.

Among differentiated endocrinocytes, binucleate cells are found. Unlike other cells, only 50% of apudocytes undergo renewal. They are characterized by a longer development cycle (up to 23 days), while other epithelial cells go through the cell cycle in 5 days. Due to slow cell migration and tight connection with the basement membrane, the formation of cytoplasmic processes characteristic of EC cells occurs.

The mechanism of differentiation of intestinal endocrinocytes is the subject of debate. One of the participants in differentiation is the Notch signaling pathway. Notch proteins constitute a family of four transmembrane receptors in mammals that interact with cell surface ligands of neighboring cells. Ligand binding activates a series of proteolytic cleavages and post- translational modifications, releasing the intracellular Notch-NICD domain. NICD translocates to the nucleus and binds to DNA-binding protein to form a complex that activates

the promoters of cleavage enhancers (HES). The latter suppresses the expression of several transcription factors important for terminal differentiation. One of the functions of Notch signaling is to provide lateral inhibition between neighboring cells in a population of initially equivalent cells; thus, the first cell to begin differentiation prevents its neighbors from differentiating along the same path. It is believed that this mechanism of inhibition allows the reproduction of specialized types of cells, including endocrine ones.

Gene inactivation in mice has identified three associated bHLH factors that are important for endocrine differentiation of intestinal epithelial cells—

Math1, neurogenin3 (NGN3) and BETA2/NeuroD (BETA2). This family of transcription regulators functions in a cascade, where one factor activates a subsequent factor [6].

Rapid progress in the study of GEPES is reflected in the number of cell types identified and included in it. The earliest classification included 7 types of endocrinocytes (Wiesbaden, 1969), the second - 10 (Bologna, 1973), the third -

15 (Lausanne, 1977), fourth – 19 (Santa-Monica, 1980). According to modern concepts, the GEPES, depending on the substance produced, is represented by the following variety of cells: A (glucagon), B (insulin), D (somatostatin), D1 (vasoactive intestinal polypeptide -VIP), EC1 (serotonin), EC2 (melatonin), Ecl (histamine), G (gastrin), I (cholecystokinin-pancreozymin), K (gastric inhibitory factor GIP), L (enteroglucagon), M (motilin), N (neurotensin), P (bombesin-like peptide - gastrinreleasing peptide), PP (pancreatic polypeptide), S (secretin). Moreover, from this variety, the following have been identified in the epithelium of the colon:

1). EC1 cells that produce serotonin; 2). EC2 cells producing melatonin; 3). D-cells producing somatostatin 4). L-cells producing enteroglucagon [2].

There are open and closed endocrine cells. Open cells with their apical part border the lumen of the hollow organ, which allows them to secrete, and their lower pole is fixed to the basement membrane. Also on the surface of the cells there is a receptor apparatus, which allows it to realize its endocrine function

under the influence of external regulatory signals. Some of these high-value signals are produced by cells of the epithelial microenvironment, including fibroblastic differential cells localized in the connective tissue of the mucous membrane located under the basement membrane, as well as intra- and subepithelial lymphocytes, and histiocytes-macrophages . Changes in the ratio of these cells or their functional activity in a number of diseases, including inflammatory ones, naturally involve endocrine cells of the small and large intestines in pathomorphogenesis [8].

Under the influence of regulatory factors, open cells thus function as transepithelial channels for transmitting signals from the apical compartment and leading to basolateral exocytosis of biological mediators. They act either in a classical endocrine manner or through paracrine effects on neighboring cells, especially the afferent fibers of the vagus nerve.

Closed cells secrete secretory granules in response to changes in the chemical composition of the intercellular substance, osmotic pressure, internal temperature and mechanical stretching of tissues. Elements of the GEPES are characterized by a different structure throughout the crypts: the largest number of cells is recorded at the base; they have a round, triangular or trapezoidal shape, while in the middle sections of the crypts a single arrangement, fusiform or teardrop shape is described. Each type of endocrine cell has ultrastructural characteristics. EC cells contain polymorphic electron-dense granules in the perinuclear zone and basal part of the cytoplasm, surrounded by a continuous smooth membrane. The diameter of the granules is 241±51 nm. These cells are predominantly of an open type; the largest number of granules in them are located at the lower pole of the cell. Along the basement membrane, EC cells form long cytoplasmic processes filled with secretion granules, which significantly increases the secretion area. A feature of the constitution of these cells, in comparison with other types, is the possibility of intracellular destruction of secretory vesicles. Sometimes mucous granules, granules similar to those in Paneth cells, granules containing peptide YY or substance P are found in EC cells.

In some studies, such endocrinocytes are isolated into a separate subpopulation of EC cells. The phenomenon of granules containing different hormones being found in the same type of cells indicates a common origin and confirms the unitary theory of their development.

In the depths of the crypts, poorly differentiated endocrinocytes are detected; sometimes they are called half-stem, cambial, or intermediate, but it is believed that they have already embarked on their differentiation path. They are characterized by a light cytoplasm, in which there are numerous polysomes, a few tubules of the granular endoplasmic reticulum, the Golgi complex, mitochondria and single secretory granules.

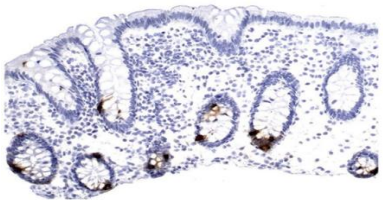
L cells are the second most numerous endocrinocytes of the colon epithelium. The largest number of them was found in the sigmoid and rectum. They contain the largest (up to 400 nm), but few secretory granules with contents of high electron density, sometimes of irregular shape. Their membrane is thin, and there are narrow gaps between it and the contents. Cells are predominantly open type. Chromogranin A is found in granules.

D-cells are characterized by: round, large secretory granules containing low electron density contents with a fuzzy membrane surrounding them; granules size (283±70 nm). The cells have a small number of organelles, sometimes including myelin-like bodies, cytoplasm with rarefaction zones. Granules are formed in the Golji and gather in the basal part of the cell. The largest number of such endocrinocytes was recorded in the duodenum and rectum. In the epithelium of the rectal mucosa, “mixed” cells were also identified, which simultaneously contain several types of endocrine granules - granules of L- and D-cells. Unlike other endocrinocytes, D-cells contain secretoneurin, a protein of the chromogranin family, which is also localized in nerve endings.

D1 apudocytes are a heterogeneous population of cells, including PP, GIP, and VIP cells that secrete pancreatic polypeptide, gastrin inhibitory polypeptide, and vasointestinal-like polypeptide. The cytoplasm contains round granules with

varying electron density and size (from 150 to 216 nm); cells can form cytoplasmic processes; belong to the open type.

Common features of the ultrastructure for normal colon apudocytes are: an average ratio of hetero and euchromatin of the nucleus, a moderate amount of general -purpose organelles, mature secretory granules without signs of secretion, as well as developed intercellular contacts arranged like a lock, finger-like processes or degenerative processes. SMS. These characteristics indicate a high level of differentiation of GEPES cells.

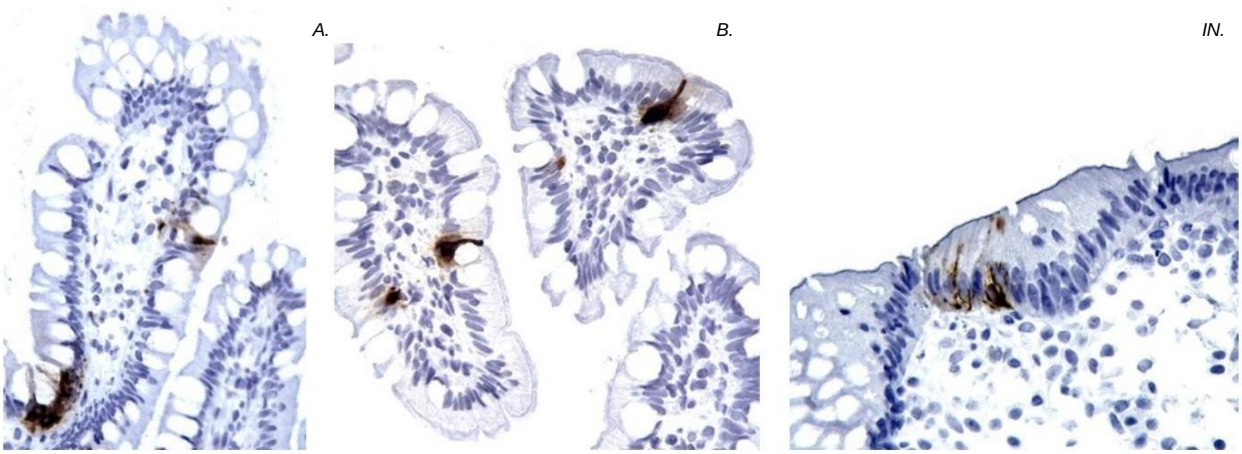


Rice. 2. Biopsy of the mucous membrane of the human

It has been shown that in humans, endocrinocytes are unevenly distributed among the sections of the large intestine: the largest number of them is in the sigmoid and rectum (111±15 cells/mm2), the smallest number is in the appendix (13±3 cells. /mm2), which suggests a cranial-caudal gradient of development. This pattern, in general, is preserved in vertebrates with the exception of some representatives. For example, in a rabbit, the number of endocrinocytes in the rectum is the largest, but it is comparable to the number of cells in the appendix ; the quantitative differences are minimal. In the rat, the histotopography of these cells is different - a decrease in the number of endocrine cells in the distal direction was recorded. In the pig, there is practically no gradient in cell distribution; only a slight increase in the number of cells in the distal direction was detected. A comparison of the ascending colon. Endocrine cells are brown. Immunohistochemicatol pography of endocrine cells in the epithelium reaction to

chromogranin A. Counter-staining with Mayer's hematoxylin. Uv. ×200. of the human colon throughout ontogenesis with that in vertebrates showed that during embryonic development there is a recapitulation of the pattern of distribution of endocrinocytes in the epithelium of vertebrates [2]. A comparison of the number and structure of such cells in the large intestine and in the small intestine shows (Fig. 3).

Typically, cells differentiate as they migrate from the crypt to the tip of the villus. Upon reaching the apex, endocrinocytes undergo death and enter the intestinal lumen [1].The death of endocrinocytes is an integral stage of histo(cyto)genesis and is important for maintaining the structural homeostasis of the epithelium. A number of ways to implement this are described -



Rice. 3. Endocrine cells among the epithelial cells of the villi of the mucous membrane of the ileum

(A, B) and in the surface epithelium of the ascending colon (C). Immunohistochemical reaction to chromogranin A. Counter-staining with Mayer's hematoxylin. UV: ×200th process: apoptosis – programmed cell death, accompanied by shrinkage and shrinkage of the cell; necrosis-like cell death (autophagic); fragmentation of nuclei without karyopyknosis. However, as new modes of cell death are described, some of the previously undescribed variants may also be discovered as part of the histophysiology of this tissue.Despite the satisfactory level of knowledge of the cytophysiology of normal intestinal endocrine cells, their transformations, incl. from the standpoint of the cellular-

differential organization of tissues in a number of reactive conditions and diseases remains unexplored . In particular, the cellular dynamics of entero- and colonoendocrinocytes in irritable bowel syndrome and its inflammatory diseases (Crohn's disease and ulcerative colitis) have not been sufficiently studied and should attract the attention of histologists.

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