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MORPHOFUNCTIONAL AND CLINICAL SIGNIFICANCE OF APUD CELLS VISUALIZED IN SOME TISSUES OF HUMAN ORGANS

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Different organs and systems of the human body contain diffusely located and so-called APUD cells. There are about 40 of their varieties for today. The article provides modern information about the localization, structural features and role of this group of cells, as well as their clinical significance. Archival data of biopsies of palatine, labial, lacrimal glands, stomach, gums, and prostate gland of a person in the condition of their normal intravital functioning were studied. Some morphological and functional characteristics of APUD cells from the palatal salivary gland, interdental gingival papilla, gastric pyloric gland, and human prostate gland have been reported. The study of APUD cells retains important clinical significance because it is the basis for the treatment of apudomas.

Key words: APUD cell, low molecular weight peptide, gland, duct, apudoma.

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МОРФОФУНКЦІОНАЛЬНЕ ТА КЛІНІЧНЕ ЗНАЧЕННЯ APUD-КЛІТИН, ЩО ВІЗУАЛІЗУЮТЬСЯ У ДЕЯКИХ ТКАНИНАХ ОРГАНІВ ЛЮДИНИ

Різні органи та системи тіла людини містять дифузно-розміщені, так звані, APUD-клітини. На сьогодні виділяють близько 40 їх різновидів. У статті наведено сучасні відомості про локалізацію, особливості будови та роль даної групи клітин, а також їх клінічне значення. Було досліджено архівні дані біоптатів піднебінних, губних, слізних залоз, шлунка, ясен та передміхурової залози людини в стані їх нормального прижиттєвого функціонування. Було надано деякі морфологічні та функціональні характеристики APUD-клітин, що належать піднебінній слинній залозі, міжзубному ясенному сосочку, залозі пілоричного відділу шлунка та передміхуровій залозі людини. Дослідження APUD-клітин зберігає важливе клінічне значення, оскільки є основою для лікування апудом.

Ключові слова: APUD-клітина, низькомолекулярний пептид, залоза, протока, апудома.

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In morphology "light cells" were called cells that manifest light cytoplasm when stained with some histological dyes. As a rule, "light cells" are secretory cells of the epithelium, which are one of the elements of the secretion system. These cells are diffusely located in organs and form a diffuse endocrine system or ARUD system. Cells of this system (APUD cells) are able to absorb amino acid precursors and synthesize active amines and low-molecular peptides based on them, except for calcitriol, using the decarboxylation reaction. Organs containing APUD cells include: gastrointestinal tract, respiratory system, reproductive system, pancreatic islets, thyroid gland, adrenal medulla, carotid globe, kidney, pituitary gland, and others. The family of APUD cells currently includes about 40 representatives. All of them release their secret into the blood or have a paracrine effect on neighboring cells [9].

Currently best investigated the APUD system which is localized in the tissues of the gastrointestinal tract, where 12 main types of enteroendocrine cells are traditionally distinguished, and the same cell usually produces several hormones [11]. Confocal microscopy has shown that different hormones and neurotransmitters in the same enteroendocrine cell are stored separately in different subcellular components and can, probably, be differentially released after the action of the corresponding stimulus. Enteroendocrine cells have a wide set of unique receptors that allow them to perceive food, taste, mechanical and physicochemical stimuli, as well as microorganisms and toxic substance [14].

Another organ at the forefront of clinical and morphological research is the human prostate gland. The main reason for this attention is prostate cancer and the prospect of more effective treatment in patients at high risk of progression. It is known for today, that a significant part of recurrences of metastatic prostate cancer is associated with the development of small cell neuroendocrine carcinoma, which develops from neuroendocrine cells of the prostate [3,4]. Accordingly, studying the process of differentiation of neuroendocrine carcinoma will help to find mechanisms to prevent the development of resistance to modern hormonal drugs used in metastatic forms of prostate cancer [13].

At the time when the concept of the APUD system was being formed, the main attention of researchers was attracted by the similarity of its cells with peptidergic neurons. Ultimately, all cells of the APUD system came to be considered neuroendocrine, that is derived from the neuroectoderm. This idea explained well why some neuropeptides, namely somatostatin, bombesin, neurotensin, endorphins and others, are contained both in neurons and in basophils, secretory cardiomyocytes and cells of the diffuse endocrine system. However, recognizing them as neuroectoderm derivatives contradicted the idea of endodermal origin of pancreatic parenchyma, mesodermal origin of secretory cardiomyocytes and mast cells. Thus, it became clear that APUD cells develop from stem cells of histochemically different types [12]. In addition, investigations of the internal organs of animals during the prenatal and postnatal period of development showed a clear connection between the quantitative and qualitative changes of APUD cells and the development and growth of the corresponding organs [8,10].

The purpose of the study was to identify the cells of the diffuse endocrine system in some human organs and tissues and to analyze the latest information about their structure and functions for their in-depth study in subsequent scientific works.

Materials and methods. The isolated organs were taken from patients who died from diseases that didn`t cause changes in the organs under investigation. The materials for the study were obtained from the Pathoanatomical Department based on Agreement on scientific and practical cooperation between Poltava State Medical University and the Poltava Regional Pathoanatomical Bureau of the Poltava Regional Council. The scientific investigation complied with the moral and ethical norms in accordance with the principles of the Helsinki Declaration of Human Rights, the Ethical Code of the Physician of Ukraine, the Convention on Human Rights and Biomedicine developed by the Council of Europe, the Order of the Ministry of Health of Ukraine "Procedure for conducting clinical trials of medicinal products and examination of materials from clinical trials" and the Ethical Code of the Scientist of Ukraine. We studied histological sections of tissues of some human organs obtained on the basis of epoxy blocks (archival material was fixed in 4 % glutaraldehyde and embedded in EPON-812 epoxy resin according to the rules adopted in electron microscopy). Biopsies of palatal, labial, lacrimal glands, stomach, gums and prostate gland of a person in the condition of their normal intravital functioning were also studied. A series of semithin epoxy sections 2 μm thick were obtained, which were stained using a 0.1 % solution of toluidine blue in phosphate buffer. Part of the material was embedded in paraffin and served to obtain serial histological sections 4 μm thick, which were stained with hematoxylin and eosin according to the traditional method.

Results of the study and their discussion. On semithin epoxy sections, we detected cells of the diffuse endocrine system in the walls of excretory ducts of the palatine, labial and lacrimal glands of human, with the exception of their common (main) excretory ducts. Next to them, as a rule, myoepithelial cells are localized, the nuclei of which are intensively stained with toluidine blue (Fig. 1). Previously, some authors mistakenly considered "light cells" of salivary and lacrimal glands to be precursors of myoepithelial cells. But later it was established that the "light cells" of the exocrine glands have both a local paracrine effect on a certain population of cells of the secretory epithelium of the excretory ducts and their terminal extensions, and a remote endocrine effect on various structures of the body. As for myoepithelial cells, it is still believed, that they provide a relatively quick release of secretions and maintain the flow of fluid through the excretory ducts. In other words, myoepithelial cells are one of the components of the mechanism of laminar fluid flow through a closed, from the point of view of physics, system of biological tubes, which is a complex and branched network of excretory ducts of exocrine glands [6, 7].

It is known, that between the epithelial cells of the skin and mucous membranes "light cells" are represented by Langerhans cells and melanocytes. These cells are localized in the basal and spinosum layers and can also be in the surface layers of the flat epithelium.

In our studies, melanocytes were detected in the mucous membrane of the oral cavity, as a rule, in the attached part of the gums, especially within the gingival interdental papillae from their vestibular surface (labial and buccal). (Fig. 2). APUD cells capture antigens here, carry out their processing, transport to lymph nodes, presenting them to lymphocytes and thereby causing the development of an immune reaction. Melanin also accumulates in melanocytes, which protects the cells below from the destructive effects of ultraviolet rays. As for Langerhans cells, we did not detect them on our preparations. It is known that they contain langerin in the cytoplasm, which is a type C lectin with mannose-binding specificity.

It is assumed that antigen binding to langerin leads to the process of internalization. Some authors attribute Langerhans cells to dendritic cells along with other types (myeloid, plasmacytoid, follicular). The latter play a certain role in the development of autoimmune processes, and for some types of viruses they act as targets.

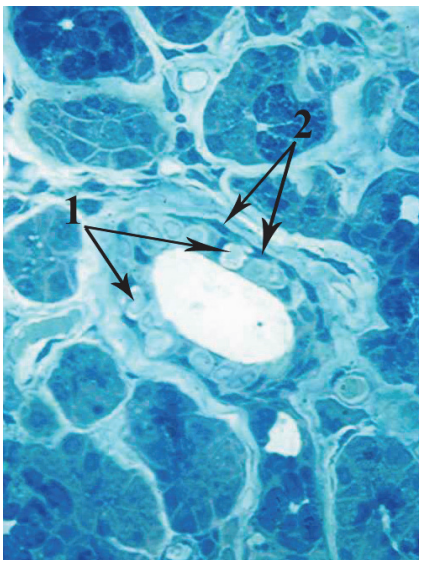

Fig. 1. Human palatine gland. Semithin epoxy section, stained with toluidine blue. 1. "Light cells" in the wall of the excretory ducts; 2. Myoepithelial cells. Magnification ×120.

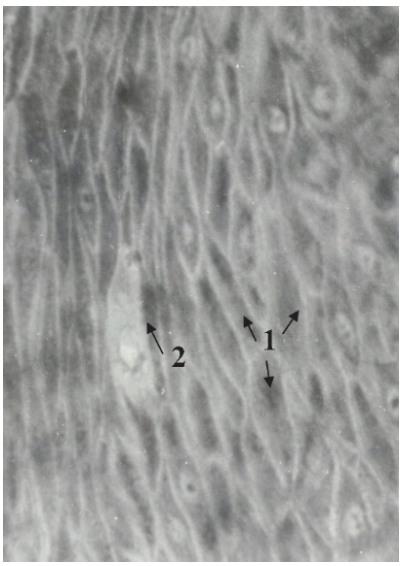

Fig. 2. Human interdental gingival papilla. Semithin epoxy section, stained with toluidine blue. 1. Cells of squamous epithelium; 2. Melanocyte. Magnification ×400.

We also have been detected APUD cells in the mucous membrane of the stomach. It is known that the main endocrine cells of the stomach are enterochromaffin-like cells (ECL cells), which make up a third of all endocrine cells in the stomach of a healthy person, a quarter are G cells, and the rest are D cells. ECL cells secrete histamine, G cells synthesize gastrin, and D cells synthesize somatostatin. In the mucous membrane of the body of the stomach, ESL cells and D cells are localized next to parietal cells, which secrete hydrogen ions, chlorine and internal anti-anemic Castle factor (Fig. 3). Parietal cells with a diameter of 20-25 μm and an oval or pyramidal shape are located in the outer part of the main (fundal) glands of the stomach (fundus and body). There is an idea, that they provide the paracrine nature of their regulation by histamine and somatostatin. There are no G-cells in this zone, they are located in the antral part of the stomach, where D-cells are located next to them. They are able to inhibit the secretion of gastrin by G-cells. In the portal tract G-cells predominate over D-cells. G-cells of the antral part of the human stomach are open type, that is, they have membrane receptors that open into the lumen of the gastrointestinal tract. D-cells of this zone are also classified as open type cells, and D-cells of the acid-producing zone are classified as closed cells that are those that do not have direct contact with the gastrointestinal tract. The secretion of closed type cells depends on the acidity of the stomach contents (pH 5-7 stimulates gastrin secretion, while at pH less than 5 it is inhibited).

In our studies of the human prostate gland in normal condition endocrine cells were also found (Fig. 4). Traditionally, the epithelium of the human prostate gland has been described as being composed of three distinct cell types: secretory luminal, basal and endocrine-paracrine. It must be said, that in comparison with the data for the stomach, there is little information about the differentiating and proliferative processes in a normally functioning human prostate. At the current stage of research of the prostate gland structure there is an idea that its three main cell types are connected by "progenitor-progeny" relations, which is confirmed by the existence of intermediate phenotypes.

In our studies "light cells" were detected in various tissues and were generally an incidental finding. The first publication about "light cells" was made by us in the journal "Morphology" in 1990 [1].

Knowledge of the structure and function of APUD cells has clear clinical significance. According to literature data APUD cells act at the level of human and animal tissues as regulators of homeostasis and control metabolic processes. Accordingly, with tumors that arise from APUD cells, symptoms of an endocrine disease can be observed, which correspond to the profile of secreted hormones. The general name of such tumors is apudomas. Depending on the type of cells from which apudomas are formed, they are divided into several types. In particular, an apudoma arising from neuroendocrine cells is called a carcinoid and is localized most often within the gastrointestinal tract and pancreas, but it can also be found in the pulmonary system [5]. At this point in time the process of discovering the latest data on the localization and functions of the APUD system cells has not stopped, which is reflected in scientific research projects of the recent years [2].

Conclusion

The discovery by E. Pearce in 1968 of a highly organized neuroendocrine cellular system, the main specific property of which is the ability of its cells to produce biogenic amines and polypeptide hormones, served as an impetus for the search for such cells in various organs and the study of their function and role in the regulation of homeostasis. Investigations in this direction continue to this day, because they have not only theoretical but also clinical significance, particularly in the diagnosis and treatment of apudomas.

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