МЕДИЦИНА, ПЕДАГОГИКА И ТЕХНОЛОГИЯ: ТЕОРИЯ И ПРАКТИКА
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CELL SPECIALIZATION AND STRUCTURE IN THE INTESTINAL APUD SYSTEM

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КЛЕТОЧНАЯ ДИФФЕРЕНЦИРОВКА И МОРФОЛОГИЧЕСКИЕ ОСОБЕННОСТИ АПУД-СИСТЕМЫ КИШЕЧНОГО ЭПИТЕЛИЯ

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Abstract: This article provides a detailed review of the morphological aspects of the APUD system in the intestinal epithelium, as well as the mechanisms underlying cellular specialization. The APUD system, a component of the gastroenteropancreatic endocrine system, comprises endocrine and neuroendocrine cells involved in regulating various physiological processes. The main types of endocrine cells, their localization, and characteristic ultrastructural features are discussed, along with the stages of their differentiation from intestinal epithelial stem cells. Special attention is given to the role of the Notch signaling pathway and the cascade of bHLH family transcription factors (Math1, neurogenin3, BETA2/NeuroD), which ensure the sequential activation of cellular specialization programs. The article also analyzes the influence of the intestinal mucosal microenvironment on endocrine cell function through interactions with fibroblasts, immune cells, and other components. A cranio-caudal gradient of endocrine cell distribution in the human colon is highlighted, along with comparative analyses in other vertebrates. The importance of endocrine cell death processes for maintaining epithelial homeostasis is emphasized, including mechanisms such as apoptosis and autophagy.

Keywords: APUD system, intestinal epithelium, endocrine cells, gastroenteropancreatic endocrine system, differentiation, Notch, transcription factors, morphology, cell death, histophysiology.

Аннотация:

В данной статье подробно рассматриваются морфологические аспекты APUD-системы кишечного эпителия, а также механизмы специализации её клеток. APUD-система, входящая в состав гастроэнтеропанкреатической эндокринной системы, представляет собой совокупность эндокринных и нейроэндокринных клеток, участвующих в регуляции различных физиологических процессов. Обсуждаются основные типы эндокриноцитов, их локализация и характерные ультраструктурные особенности, а также этапы их дифференцировки от стволовых клеток кишечного эпителия. Особое внимание уделяется роли сигнального пути Notch и каскада транскрипционных факторов семейства bHLH (Math1, neurogenin3, BETA2/NeuroD), которые обеспечивают последовательную активацию программ клеточной специализации. В статье также анализируется влияние микросреды слизистой оболочки кишечника на функционирование эндокринных клеток через взаимодействие с фибробластами, иммунными клетками и другими элементами. Подчеркивается краниокаудальный градиент распределения эндокриноцитов в толстой кишке человека и сравнительный анализ с другими позвоночными. Отмечается важность процессов клеточной гибели эндокриноцитов для поддержания гомеостаза эпителия и рассматриваются различные механизмы этой гибели, включая апоптоз и аутофагию.

Ключевые слова: APUD-система, кишечный эпителий, эндокринные клетки, гастроэнтеропанкреатическая эндокринная система, дифференцировка, Notch, транскрипционные факторы, морфология, клеточная гибель, гистофизиология.

Introduction. The surface layer of the large intestinal mucosa is formed by a single layer of columnar epithelial cells of endodermal origin, which line the crypts and intercryptal spaces. These epithelial cells play a crucial role in maintaining the structural and functional integrity of the intestinal lining. One of the cytogenetic manifestations of the divergent differentiation of cells from the intestinal epithelial stem cell pool is the formation of specialized enteroendocrine and colon-endocrine cells. These cells are responsible for synthesizing and secreting a variety of biologically active substances that regulate digestive, absorptive, and motility processes, as well as coordinate immune and neuroendocrine responses [9,20].

Epithelial endocrinocytes of the large intestinal mucosa are part of the diffuse endocrine system (DES), more specifically of its largest component—the gastroenteropancreatic endocrine system (GEPES). The cells of the diffuse endocrine system are commonly classified as belonging to the APUD series; however, it is important to note that these concepts are not identical. APUD cells (Amine Precursor Uptake and Decarboxylation) include not only endocrine epithelial cells that share a common developmental origin and the ability to metabolize and decarboxylate amine precursors, but also cells from other tissues, such as mast cells in connective tissue, aminergic and peptidergic neurons in the nervous system, and secretory cardiomyocytes [7,16].

The concept of the APUD system was introduced by A. Pearse in 1973. He proposed that all these cells share a neuroectodermal origin and thus referred to them as neuroendocrine cells. This conclusion was based on similarities in metabolic processes involving the synthesis of biogenic amines, as well as the presence of specific molecular markers such as neuron-specific enolase (NSE) and chromogranin A, which are considered indicators of neuroectodermal differentiation [4].

Results. Epithelial endocrine cells of the colon, therefore, not only participate in local regulatory processes by secreting a wide range of hormones and peptides but also reflect a complex developmental and functional connection to other neuroendocrine elements throughout the body. Their presence in the intestinal lining underscores the integration of endocrine, nervous, and immune systems in gastrointestinal physiology [15].

According to A. Pearse (1973), neural crest cells (ganglionic plate cells) migrate into various tissues and differentiate into neuroendocrine cells. However, this hypothesis has not been fully confirmed. It mainly draws upon data concerning the development of acinar-islet cells of the pancreas, which combine both exocrine and endocrine features within a unified morphofunctional organization. These pancreatic cells originate from a common embryonic primordium—namely, the intestinal endoderm—and therefore challenge the idea that all APUD cells share a neuroectodermal origin.

APUD cells are found in various tissues and may have different embryological sources. An important biochemical marker related to these cells is chromogranin A (CgA), an acidic glycoprotein. CgA has been identified in the secretory granules of endocrine cells, but also in tissues not typically considered endocrine, such as

bulbourethral glands and cardiomyocytes. It is also present in the large, optically dense granules of most neuroendocrine cells [1,3].

Upon specific stimulation, chromogranins are secreted along with biogenic amines and play a crucial role in the formation, maturation, intracellular transport, and exocytosis of secretory granules in both neuroendocrine cells and neurons. In addition, enzymatic cleavage of chromogranins produces several smaller peptides with distinct biological activities. One of the known effects of chromogranin A upon release is its vasostabilizing action, which helps regulate vascular tone and permeability within the circulatory system. These findings illustrate the complexity and multifunctionality of neuroendocrine markers beyond a single developmental origin [5].

Thus, APUD-series cells represent a heterogeneous population derived from multiple embryonic origins. Like the cells of the diffuse endocrine system, they develop from stem cells of endodermal, ectodermal, and mesodermal lineage, and therefore represent different cytogenetic types. However, it is important to emphasize that, according to current understanding, all epithelial cells of the intestinal type-including those forming the gastroenteropancreatic endocrine system-originate from a single stem cell of endodermal origin. In the scientific literature, this progenitor cell is referred to by various terms, such as intestinal epithelial stem cell, stem enterocyte, or colonic stem cell.

This unified origin highlights the high degree of plasticity and differentiation potential of the intestinal epithelial stem cell. It can give rise not only to absorptive and secretory epithelial lineages but also to multiple endocrine cell types that participate in complex regulatory networks within the gut. These include enteroendocrine cells involved in local and systemic hormonal signaling, integrating the digestive, immune, and nervous systems.

The recognition of this common developmental pathway reflects a shift in modern histological and embryological perspectives, moving away from older theories that presumed distinct origins for various endocrine cell types. It also has important implications for regenerative medicine and oncology, where identifying the source and behavior of intestinal stem cells is critical for understanding tissue renewal, inflammation, and tumorigenesis.

A periodization of intestinal epithelial cell differentiation has been proposed, dividing the process into five distinct stages. Stage I involves the mitosis of the intestinal epithelial stem cell, resulting in the formation of a poorly differentiated cell

(Stage II). This cell retains the ability to undergo mitosis while beginning to develop cytoplasmic structures characteristic of a specific epithelial cell type. Stage III is the transitional phase, where the cell is actively differentiating and acquiring specialized cellular features. By Stage IV, the cell becomes a fully differentiated intestinal epithelial cell of a particular type, actively performing its specialized functions essential for intestinal physiology. Finally, Stage V represents the stage of cell death and desquamation, whereby mature epithelial cells are shed from the mucosal surface as part of the normal renewal process [8,14].

This staged model reflects the dynamic nature of the intestinal epithelium, which undergoes continuous turnover to maintain tissue integrity and function. The balance between cell proliferation, differentiation, and apoptosis ensures proper renewal of the mucosal barrier, absorption, and secretion. Understanding these stages is critical for studying intestinal development, pathology, and regeneration. Aberrations at any stage may contribute to diseases such as inflammatory bowel disease or colorectal cancer. Moreover, these stages provide a framework for research into stem cell biology, cellular signaling pathways, and the effects of various factors influencing intestinal epithelial homeostasis [11].

Stem cells are characterized by a high nucleus-to-cytoplasm ratio, a large nucleolus, diffusely distributed chromatin within the nucleus, and numerous ribosomes in the cytoplasm. These cells apparently undergo asymmetric division, producing one daughter cell that retains stem cell properties and another that proceeds to differentiate further.

Poorly differentiated cells contain large precursor granules within their cytoplasm. Although mitosis of these endocrine precursors can occasionally be observed, most poorly differentiated cells arise as a direct result of stem cell differentiation.

Among differentiated endocrine cells, binucleated cells can be found. Unlike other epithelial cells, only about 50% of APUD cells undergo renewal. These cells have a longer developmental cycle, lasting up to 23 days, whereas other epithelial cells complete their cell cycle in approximately 5 days.

Due to their slower migration along the crypt-villus axis and their tight association with the basal membrane, APUD cells, particularly EC cells, develop distinctive cytoplasmic processes. These extensions are characteristic morphological

features that likely facilitate their specialized secretory functions and interactions within the mucosal microenvironment.

The prolonged lifespan and unique morphology of these endocrine cells highlight their specialized roles in gut physiology. Their relatively slow turnover compared to other epithelial cells suggests a more stable population involved in hormone secretion and local regulatory mechanisms, which is crucial for maintaining intestinal homeostasis and coordinating digestive and immune responses.

The mechanism of differentiation of intestinal endocrine cells remains a subject of ongoing debate. One key participant in this process is the Notch signaling pathway. Notch proteins form a family of four transmembrane receptors in mammals that interact with ligands located on the surface of neighboring cells. Ligand binding triggers a series of proteolytic cleavages and post-translational modifications, resulting in the release of the Notch intracellular domain (NICD). The NICD then translocates to the nucleus, where it binds to a DNA-binding protein to form a complex that activates the promoters of enhancer of split (HES) genes. HES proteins suppress the expression of several transcription factors essential for terminal differentiation [2,12].

One of the primary functions of Notch signaling is to mediate lateral inhibition among initially equivalent neighboring cells. This means that the first cell to initiate differentiation prevents adjacent cells from following the same differentiation pathway. Such lateral inhibition is believed to be a critical mechanism for generating specialized cell types, including endocrine cells.

By enabling only select cells to differentiate along a particular lineage while inhibiting others nearby, the Notch pathway helps ensure the proper balance and distribution of various cell types within the intestinal epithelium. This finely tuned regulation allows the maintenance of tissue homeostasis and the generation of functionally diverse cell populations necessary for the complex roles of the gastrointestinal tract. Understanding this pathway provides valuable insight into intestinal development and may offer targets for treating diseases involving abnormal cell differentiation.

Gene inactivation studies in mice have identified three related basic helix-loop-helix (bHLH) transcription factors that are crucial for the endocrine differentiation of intestinal epithelial cells—Math1, neurogenin3 (NGN3), and BETA2/NeuroD (BETA2). These transcriptional regulators operate in a hierarchical cascade, where the activation of one factor induces the expression of the next [18,19].

Math1 functions as an early determinant, essential for the initial commitment of progenitor cells to the secretory lineage, including endocrine cells. Following Math1 activation, NGN3 plays a pivotal role in specifying endocrine progenitors, initiating their differentiation into various hormone-producing cell types. Finally, BETA2/NeuroD acts downstream to promote terminal differentiation and maturation of these endocrine cells.

This sequential activation ensures the precise temporal and spatial regulation of gene expression required for the development of a fully functional endocrine compartment within the intestinal epithelium. Disruption of any factor in this cascade impairs endocrine cell formation, demonstrating their indispensable roles in gut development.

Understanding the function and interplay of these bHLH factors not only advances knowledge of intestinal biology but also has implications for regenerative medicine and the treatment of diseases involving endocrine cell dysfunction, such as diabetes and gastrointestinal disorders [13].

Among the wide spectrum of gastroenteropancreatic endocrine system cells, several specific types of endocrine cells have been identified within the epithelial layer of the large intestine, each characterized by the secretion of distinct biologically active substances [6]. First and foremost, EC1 cells are present, which secrete serotonin—a biogenic amine that plays a crucial role in regulating intestinal motility and vascular tone. Alongside them, EC2 cells produce melatonin, a hormone not only involved in circadian rhythm regulation but also known for its modulatory effects on local inflammatory responses in the gut.

In addition, D cells have been identified in this region; they are responsible for the production of somatostatin, a universal inhibitor that suppresses the secretion of various gastrointestinal hormones and enzymes. A related subtype, D1 cells, synthesizes vasoactive intestinal peptide (VIP), which exhibits vasodilatory, anti-secretory, and smooth muscle-relaxing properties.

Lastly, L cells are present in the epithelial layer, primarily involved in the secretion of enteroglucagon—a hormone that modulates carbohydrate metabolism and inhibits gastric motility. Taken together, these endocrine cell types contribute to the functional diversity of the large intestinal epithelium and play essential roles in maintaining local homeostasis and systemic physiological regulation [10].

Endocrine cells of the intestinal epithelium are typically categorized into open and closed types based on their structural and functional characteristics. Open-type endocrine cells are characterized by their apical surface contacting the lumen of the hollow organ, allowing direct sampling of luminal contents and regulated secretion in response to these stimuli. The basal pole of these cells is anchored to the basement membrane, and their apical region is equipped with a specialized receptor apparatus. This receptor system enables the cells to respond to external regulatory signals, thereby fulfilling their endocrine function.

A significant portion of these regulatory signals is produced by neighboring epithelial and stromal cells, forming the cellular microenvironment. These include fibroblastic cells of the stromal compartment located in the connective tissue beneath the basement membrane, as well as intraepithelial and subepithelial lymphocytes and histiocyte-macrophages. These surrounding cells participate in complex paracrine and immunomodulatory interactions, which influence the activity and differentiation of endocrine cells.

Importantly, alterations in the composition or functional state of these microenvironmental cells, particularly under pathological conditions such as inflammation, can significantly affect the endocrine component of the intestinal mucosa. Such disturbances may result in either hyperfunction or hypofunction of enteroendocrine cells, contributing to the pathomorphogenesis of various gastrointestinal disorders. The involvement of endocrine cells in these pathological processes underscores their dynamic role in maintaining mucosal homeostasis and their sensitivity to changes in the local immune and stromal environment [17].

Under the influence of regulatory factors, open-type endocrine cells function as transepithelial channels for transmitting signals from the apical compartment, resulting in basolateral exocytosis of biological mediators. These cells act either in a classical endocrine manner or via paracrine signaling, particularly affecting adjacent cells such as afferent fibers of the vagus nerve.

In contrast, closed-type cells release their secretory granules in response to changes in the chemical composition of the intercellular matrix, osmotic pressure, internal temperature, or mechanical tissue stretching. The elements of the gastroenteropancreatic endocrine system demonstrate structural diversity throughout the crypts: the highest number of cells is found at the crypt base, where they exhibit

round, triangular, or trapezoidal shapes, while in the mid-crypt regions, they appear singly with spindle-shaped or droplet-like forms.

Each type of endocrine cell possesses distinct ultrastructural features. EC cells, for instance, contain polymorphic electron-dense granules in the perinuclear zone and basal cytoplasm, enclosed by a continuous smooth membrane. These cells are predominantly of the open type, with most granules located near the basal pole. EC cells form long cytoplasmic processes along the basement membrane filled with secretory granules, significantly increasing their secretory surface. A distinguishing feature of these cells is the potential for intracellular degradation of secretory vesicles. Occasionally, EC cells contain mucous granules, Paneth cell-like granules, or granules with peptide YY or substance P. Some studies describe such cells as a separate EC subpopulation. The coexistence of granules with different hormones within the same cell type supports the idea of a common origin and confirms the unitary theory of their development.

At the base of the crypts, poorly differentiated endocrine cells can be found. Sometimes referred to as semi-stem, cambial, or intermediate cells, they are believed to have already committed to a differentiation pathway. These cells are characterized by a light cytoplasm containing numerous polysomes, a few canaliculi of rough endoplasmic reticulum, a Golgi complex, mitochondria, and single secretory granules.

It has been demonstrated that in humans, enteroendocrine cells are unevenly distributed along different segments of the large intestine: the highest concentration is found in the sigmoid and rectal regions, while the lowest is in the vermiform appendix, indicating the presence of a craniocaudal gradient of development. This distribution pattern is generally conserved among vertebrates, with the exception of certain species. In pigs, this gradient is virtually absent, with only a slight increase in cell numbers observed toward the distal regions.

A comparison of the topography of endocrine cells in the colonic epithelium of humans during ontogenesis with that of vertebrates reveals a recapitulation of the general distribution pattern of enteroendocrine cells during embryonic development. Additionally, differences in the number and structural characteristics of these cells in the large versus small intestine have been observed.

Typically, endocrine cells differentiate as they migrate from the base of the crypts toward the villus tip. Upon reaching the apex, these cells undergo cell death and are shed into the intestinal lumen. This process of cell death is an essential part of

histo(cyto)genesis and plays a critical role in maintaining epithelial structural homeostasis. Several pathways of cell death have been described, including apoptosis (characterized by cell shrinkage and nuclear condensation), necrosis-like (autophagic) cell death, and nuclear fragmentation without karyopyknosis. As new forms of cell death are described, some of these uncharacterized mechanisms may also emerge as part of the histophysiology of this tissue.

Conclusion. Despite significant progress in understanding the cytophysiology of intestinal endocrine cells under normal conditions, their transformation—particularly from the standpoint of cellular differentiation in reactive states and diseases—remains poorly explored. In particular, the cellular dynamics of enteroendocrine and colonoendocrine cells in conditions such as irritable bowel syndrome, Crohn's disease, and ulcerative colitis are not yet sufficiently studied and warrant increased attention from histological researchers.

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