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Modern Concepts on the Structure and Function of the Thymus

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Abstarct: The article is devoted to the study of the structural and functional features of the thymus. The main function of the formation of subpopulations of T-lymphocytes is the thymus, due to the intertissue and intercellular relationships of microenvironment cells, which have their own structural and functional features.

Key words: thymus, cortex, medulla, interdigitating cells, reticuloepitheliocytes, nurse cells.

Relevance. The thymus, or thymus gland, is the central organ of the immune system. The great importance attached to the study of ontogenesis, phylogenesis, morphology, physiology, and pathology of the thymus emphasizes the exceptional role of this organ in immune responses [2, 6, 7, 50, 54]. Currently, there are numerous reviews and monographs devoted to various aspects of the morphology, physiology and pathology of the thymus [8, 10, 11, 16, 18, 59]. A lot of questions arise when studying the relationship between mother-fetus and mother-newborn, in particular, the influence of the state of the maternal organism during pregnancy and postpartum lactation on the formation of the immune system, including the thymus, in the antenatal and early postnatal periods of development [4, 5]. In a brief review of the literature, even a simple listing of works devoted to the structural and functional features of the thymus is impossible, not to mention a detailed analysis of the vast amount of information available.

Classical ideas about the thymus over the past 15–20 years have been significantly supplemented by data obtained using modern ultrastructural, radioautographic, immunocytochemical, and biochemical studies [59].

It is now firmly established that the basis of the thymus parenchyma is epithelial tissue. In each lobule of the organ, some researchers distinguish 4 zones: external, subcapsular, internal cortical, cerebral and periveascular zones, respectively [4]. Other researchers distinguish cortical, corticomedullary and medullary parenchyma in the thymus parenchyma [2, 3].

Thymus epithelial cells are heterogeneous in structure in different zones [14, 15]. Cortical epitheliocytes have a stellate shape due to long cytoplasmic processes, which are interconnected by means of desmosomes and form a kind of network [6, 7]. In the cells of this network, lymphocytes are located, the plasmolemma of which is in close contact with the membrane of epithelial cells [7]. In the cytoplasm of cortical epitheliocytes there are rounded or oval secretory vacuoles, which, along with tonofibrils located parallel to the plasmolemma and nucleus, are a characteristic feature of cortical epithelial cells. Some authors distinguish two types of cortical epithelial cells. The first type is supportive, with a large number of tonofilaments, and the second type is represented by secretory cells that contain numerous vesicles in the zone of the Golgi complex and ultimately form in the form of secretory cytoplasmic vacuoles [10, 11, 59]. Interesting data from the study of human and animal thymus epithelial cells with the simultaneous use of scanning and transmission electron microscopy. It has been established that the thymus marginal zone is structurally represented by syncytium and thus differs significantly from other zones.

In the outer and middle parts of the cortical zone, peculiar thymic "nanny cells" or TKNs were found [7, 12, 59]. A study in isolated mouse tissue homogenates showed that TKNs are a complex of an epithelial cell with a "learning" lymphocyte, the number of which can reach up to 20 per epithelial cell. The plasma membrane of the lymphocyte is in close contact with the plasma membrane of the epithelial cell. The presence of keratin in their cytoplasm testifies to the epithelial nature of "nanny cells". Reliable data confirming the epithelial nature of SBOs were obtained by electron microscopic examination of the human thymus [7, 14, 59].

In the corticomedullary zone, epithelial cells have some ultrastructural features. Along with typical stellate cells, there are groups of specialized epithelial cells [11, 14, 15]. A number of authors isolated the so-called "myoid" or "myoepithelial" cells, which have undoubted features of epithelial cells, and at the same time resemble muscle cells in their structure [32]. These cells are often oval or irregular in shape, with slightly acidophilic cytoplasm and a large light nucleus. Myofibrils are located in their cytoplasm in the form of glomeruli. Immunofluorescence revealed proteins characteristic of skeletal muscles, myocardial cardiomyocytes and smooth muscle cells. These antigens are also found around myoid cells, which indicates their excretion into the intercellular environment. Myoid cells are localized mainly in the corticomedullary zone of the thymus lobules [7, 59].

In the medulla, epithelioid cells are represented mainly by "hypertrophic" epithelial cells [31]. These cells have a developed cytoplasm rich in organelles, contain a significant number of thick tonofibrils, as well as single electron-dense granules. The epithelial cells of the medulla have wide and short processes, which are in contact with the processes of neighboring cells for a

considerable distance with the help of desmosomes. The cells are surrounded by an unstable basement membrane [32, 33, 59].

The calculation of the ratio of epithelial cells and thymocytes in the medullary zone indicates a significant predominance of epithelial cells in this zone. According to morphometric data, in adult rats in the outer part of the cortical zone, lymphoblasts make up 62%, lymphocytes - 26%, epithelial cells - 12%. In the medullary zone, these figures are 4.2%, 9.5% and 86.3%, respectively. Consequently, the number of epithelial cells in the medullary zone is more than 7 times higher than in the cortical zone [4, 5, 7, 14].

Until now, the role of the peculiar layered epithelial structures of the medullary zone, or Hassall's bodies, remains unclear. They are found only in some species of the class of mammals, including humans. However, in most strains of mice and rats, these bodies were not detected. The structure of Hassall's bodies is covered in some detail in the literature. There are separate data on the secretory activity of these formations. It is believed that Hassall's bodies containing keratinized epithelial cells are the result of morphological rearrangements in the process of physiological regeneration of epithelial cells in the thymus [7, 52, 59].

The thymus is an organ that produces numerous biologically active substances [51, 52]. The establishment of its relationship with other organs of the endocrine system led to the formulation of ideas about the thymus as an endocrine organ. Works where millipore filters were used, impermeable to cells and passing molecules of biologically active substances, contributed to an in-depth study of the humoral function of the thymus [8, 9, 59].

A significant number of works devoted to the study of the chemical nature of thymic humoral factors, sources of their formation, and mechanisms of action have accumulated [57]. It has been established that thymic epithelial cells play the main role in the secretion of thymic hormones. In this case, the epithelial cells of the cortical zone of the thymus are assigned a local function, carried out with the help of short-range thymic factors, as well as the direct contact of epithelial cells with thymocytes, followed by the formation of lymphoepithelial complexes. In the medullary zone, epithelial cells also secrete long-range hormones, which are basically identical to local thymic factors. Fenestrated capillaries typical of endocrine glands are also found in this zone. The localization of protaglandins, thymosin, and thymulin in the epithelial cells of the cortical zone was established by immunocytochemical method, and serotonin, thymopoietin, thymulin, thymosin, etc., were established in the epithelial cells of the medulla [7, 14, 31, 58, 59]. Thymic epithelial cells are essential components of the thymic microenvironment, playing an important role in the proliferation and differentiation of T-lymphocytes. At the same time, the presence of only epithelial cells is not enough to ensure the maturation of T-lymphocytes [14, 15]. There are other groups of “auxiliary” cells that play an important role in creating the thymus

microenvironment and ensuring the differentiation of T-lymphocytes [32, 33]. This group is heterogeneous in its morphological and functional properties and is currently the object of close attention of researchers. One of the representatives of the group of "auxiliary" cells are macrophages. It has been established that thymus macrophages, like other macrophages, belong to the system of mononuclear phagocytes and originate from a hematopoietic stem cell through the monocyte stage. They are characterized by a round or irregular shape, have a wide cytoplasm containing a large number of lysosomes. The role of macrophages in the thymus is multifaceted. Along with phagocytosis of destructive thymocytes, they produce a number of factors involved in the differentiation of T-lymphocytes. The largest number of macrophages is found in the outer third of the cortical zone, although they are also detected in sufficient numbers in other zones [31].

One interesting thymic microcirculation cell is the interdigitating reticular cells (IRCs). These cells were first described in the thymus in 1969 [33, 36]. Cells with a structure identical to IRC were found in T-dependent zones of the organs of the peripheral immune system. The main site of localization of the IRC is the cortico-medullary zone of the thymus. According to their morphological characteristics, these cells are similar to other cells of the mononuclear phagocyte system. However, the extremely low ability of IRCs to phagocytosis and their peculiar morphological characteristics necessitated the development of structural and functional criteria for their identification [7, 14, 15, 59]. Comprehensive cytochemical, immunocytochemical and ultrastructural studies of the cell population of the system of phagocytic thymus mononuclear cells made it possible to identify 3 types among them. The first type of cells has acid phosphatase activity in granules distributed throughout the cytoplasm and gives a positive reaction to the I-a antigen. The second type does not contain the I-a antigen, but is distinguished by the presence in the cytoplasm of a large number of lysosomes and phagosomes with high activity of acid phosphatase. This type, according to the authors, is closest to cortical macrophages. And finally, the third cell is characterized by a high content of the I-a antigen, the absence of endogenous peroxidase, and the presence of Birbeck granules in the cytoplasm. According to the authors, this cell type is the most likely equivalent of the thymus IRC. One of the distinguishing features of IRC from typical macrophages and thymic reticuloepithelial cells is the presence of a special S-100 protein in them with a negative reaction to lysozyme [59]. This protein is absent in macrophages, but a high content of lysozyme is observed in them [34, 36]. The origin of the IRC has long been a subject of debate. Their origin was originally assumed to be from mesenchymal cells. Numerous data in recent years have shown that thymus IRC, like other macrophages, originate from the hematopoietic stem cell of the bone marrow, passing through the stages of promonocytes, monocytes. A similar genesis of IRC in T-dependent zones of peripheral immune organs and skin [33].

In addition to what has been stated in the creation of the thymic microenvironment, a certain role of tissue basophils (mast cells), granulocytes, B-lymphocytes and semi-plasmic cells is allowed. Tissue basophils (mast cells) are detected in the capsule, in the interlobular connective tissue septa, and also in the perivascular spaces of the cortical and cortico-medullary zones. It is believed that they are involved in ensuring the homeostasis of this microdistrict and have a regulatory effect on vascular permeability [12, 14, 17]. Granulocytes are more often found in the medulla, interlobular connective tissue septa, and also in Hassall's bodies. They are mainly represented by neutrophilic granulocytes, and eosinophilic leukocytes are often found at an early age. B-lymphocytes and plasma cells are usually found only in the capsule, interlobular connective tissue, and in perivascular spaces [59]. Their appearance in the thymus parenchyma is usually observed in pathological conditions [4, 5, 8, 9].

The thymocyte population of the thymus parenchyma is represented mainly by lymphocytes at various stages of differentiation. The problem of stem cell migration into the thymus, their morphological and functional features, as well as their relationship with the cells of the microenvironment, has not yet been fully developed. Thymocytes of the subcapsular zone of the thymus cortex are mainly represented by lymphoblasts, which are 14–15 μm in size and contain a large nucleus with one or two nucleoli [7, 14]. The narrow cytoplasm surrounding the nucleus is relatively light, contains numerous free ribosomes and polysomes, single mitochondria, and profiles of the granular endoplasmic reticulum. Thymocytes with such an ultrastructure are few compared to medium and small thymocytes of the inner cortex [35, 37, 38].

Thymocytes of the cortical zone have a high proliferative activity. The largest number of mitotically dividing thymocytes is found along the periphery of the lobule, around macrophages and radially arranged vessels [56]. A significant number of mitoses end with asymmetric division, when one of the daughter cells is much larger than the other. It is assumed that it plays an important role in the differentiation of T-lymphocytes. According to a number of authors, up to 90% of small lymphocytes die inside the thymus, which is considered as a process of selection of immature and inferior forms. Despite the presence of a hematothymic barrier that prevents the penetration of antigens into the organ. The formation of the barrier involves epithelial cells connected by desmosomes and lying on the basement membrane, the perivascular space containing tissue fluid and macrophages, as well as the capillary endothelium lying on the basement membrane. At the same time, the hematothymic barrier is typical only for the cortical zone of the thymus, while similar structures are absent in the medullary zone [59].

Thymocytes of the cortico-medullary zone are mainly represented by small and medium-sized dymphocytes. Lymphoblasts and thymocytes in the state of mitotic division are very rare here [4, 5, 7]. Thymocytes of the medullary zone make up only 5-15% of all thymic lymphocytes

and are a heterogeneous population. In their ultrastructure, they do not differ significantly from thymocytes of other zones. Their size is 8-15 microns, the cytoplasm contains many ribosomes and a well-developed endoplasmic reticulum. It has been established that lymphocytes of the medullary zone can influence the differentiation of pluripotent stem hematopoietic cells. The process of differentiation of lymphocytes is accompanied by the simultaneous migration of lymphocytes from the cortical to the medullary and from there into the bloodstream. Migration is ensured by the possibility of free movement of lymphocytes along the interconnected intertrabecular spaces formed by islands of epithelial cells, as well as by the features of the structure and topography of vessels in the thymus [14, 17, 59].

Currently, there are two points of view on the differentiation of T cells in the thymus [39]. According to the first, progenitor cells of T-lymphocytes proliferate and differentiate into small cortical lymphocytes, which pass into the medulla, where they turn into medullary thymocytes [48]. According to the second point of view, in the medulla itself there is a population of self-sustaining progenitor cells of T-lymphocytes, independent of the cortical substance, which differentiate into T-lymphocytes in the same place. Moreover, the authors of this point of view admit the existence of the first path, independent of the medullary differentiation of thymocytes. The validity of the second point of view is supported by a number of factors: the absence in most thymocytes of the cortical zone, a marker characteristic of mature T-lymphocytes, the functional inferiority of cortical thymocytes, and their high death [5, 6, 7, 14, 49].

Thus, complex, interrelated processes of proliferation, differentiation, destruction, selection, and migration of T-lymphocytes occur in the thymus [3, 4, 5,17]. In the implementation of these processes, the main role belongs to thymus dura mater cells, the genesis, structure, and functions of which continue to be the subject of further research. In particular, the issues of the structural and functional development of the thymus in the period of early postnatal ontogenesis, when the immune system of the newborn, as well as the whole organism, remains immature [1, 2, 5, 7, 8, 9, 13, 14, 15, 19, 35, 41, 53, 55, 60]. Also interesting for study is the influence of extragenital pathology of the mother, in particular hepatitis [3, 10, 11, 13, 14, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30], in the pathogenesis of which , one of the main mechanisms of pathological influence is the occurrence of autoimmune processes, on the structural and functional formation of the organs of the immune system of the offspring, including the thymus [40, 41, 42, 43, 44, 45, 46, 47].

Thus, complex, interrelated processes of proliferation, differentiation, destruction, selection, and migration of T-lymphocytes take place in the thymus. In the implementation of these processes, the leading role belongs to the cells of the thymus microenvironment, the genesis, structure, and function of which continue to be the subject of further research.

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