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MODERN VIEWS ON THE PARTICICPATION OF THE THYMUS IN THE PROCESSES OF IMMUNOGENESIS

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ABSTRACT
The thymus is the central organ of T-lymphocytopoiesis, in it the formation of T-lymphocyte precursor cells and a number of thymic hormones occurs. Structural and functional rearrangements of the thymus under the influence of the temperature factor are characterized by cyclicity, where periods of early changes, peak and distant changes are distinguished. Each of the periods is characterized by its own characteristics, which determine the essence of the organ's adaptive rearrangements in response to temperature exposure.
Keywords: thymus, immunogenesis, stromal epithelial cells, T-lymphocytes, cortico-medullary zone, immunocytochemical methods

INTRODUCTION

The thymus is the central organ of T-lymphocytoposis, in it, from the bone marrow precursors of T-lymphocytes, antigen-independent differentiation into T-lymphocytes occurs, the effector cells of which carry out the reaction of cellular immunity and regulate humeral immunity. The thymus began to be studied more intensively from the classic experiments of Y. Miller (I961), which proved its dominant place in the formation of the immune system and in immune reactions.

The thymus as an organ was first identified in cartilaginous fish, and they also exhibit a reaction of T - lymphocytes to mitogens (Borysen fco, 1979). In shark fishes, the thymus has lobules and cortical and cerebral zones are well expressed in them. The thymus is more perfect in birds, in which it, together with the pouch of Fabricius, provides immune reactivity (Bellamy, Mohaned 1982). The greatest structural and functional development of the thymus reaches in mammals. In mammals, the thymus develops from pair III, and sometimes IV pairs of branchial pockets.

From this primordium, the epithelial stroma of the organ develops, lymphoid cells are formed later, their appearance is associated with the settlement of hematopoietic stem cells in the epithelial bud of the organ. In the embryonic thymus, foci of myeloid hematopoiesis are also found. Later, at 8-9 weeks, stromal epithelial cells differentiate into interdigitating reticular cells, which are responsible for creating a microenvironment for differentiating lymphocytes. (CauLecker, Muller-Hermelink 1980).

According to the data of O. P. Ryabchikov (1983), the number of lymphoid cells in the thymus of a human embryo increases at the 12th week of embryonic development. At this time, the cortical and medulla, Gassaglia's little bodies are clearly distinguished, the number of T-lymphocytes reaches

ISSN 2515-8260 Volume 07, Issue 09, 2020

73% and these indicators change little up to 34 weeks. In the same period, in the nuclei of thymic lymphocytes, the area occupied by heterochromatin is 52% (A. Kalinina, 1985). Therefore, the 12th week of embryogenesis is a critical period for the development of the human thymus.

By 18 weeks of development of the human embryo, the structural formation of the main components of the thymus is completed, although the increase in cell mass and hyperplasia continues. During this period, it is easy to distinguish between the cortical, cortico-medullary and cerebral zones of the lobules, the differences between the epithelial cells of these zones. Layered Gassal bodies appear in the medulla of the lobules (Golah et al, 1975).

There are different views regarding the histotopography of individual thymic zones. According to Clark (1973), each thymus lobe has 4 zones: external subcapsular, internal cortical, cerebral and perivascular. This point of view is more hypothetical. Other researchers distinguish 3 zones: external cortical, internal cortical (cortico-medular) and cerebral zones. The division of the thymus into 3 indicated zones is more suitable for light-optical and electron microscopic studies. (Hwangetal, 1974; Duijvestijn, Hamit 1981, K.A. Zufarov, K.R. Tukhtaev, 1987).

The thymus capsule and the connective tissue of the interlobular septa contain blood, lymphatic vessels, and nerve fibers. From the connective tissue, blood vessels enter the thymus lobule. In the cortical zone, the capillaries form loops, go to the cortico-medullary zones and collect in the venules. The richest in blood vessels is the cortico-medular zone. Further, the cortico-medular venules, together with the medullary venules, leave the thymus (Raviola Karnovsky, 1972).

The hemocapillaries of the cortical zone of the thymic lobules are surrounded by relatively densely spaced epithelial cells; thus, the latter are involved in the formation of the hemato-thymic barrier, which protects the differentiating thymocytes of this zone from various antigens that go through the bloodstream.

Lymphoid cells in the outer part of the cortical zone are mainly represented by densely located lymphoblasts. Their diameter is about 7-8 μm, they contain a rounded nucleus with nucleoli (Hwang et al, 1974). Cells at various stages of mitotic division are often detected. In the inner part of the cortical zone, lymphocytes are located less frequently compared to the outer part. Lymphocytes of this zone are smaller in diameter, contain a small number of intracellular organelle-free ribosomes, mitochondria, tubules of the granular endoplasmic reticulum.

The cortical zone of the thymus under normal physiological conditions has a smaller number of macrophages. Macrophages are more common in the cortico-medullary zone. Their shape is irregular, which is associated with a large number of protrusions and depressions of the plasmolemma. The cytoplasm of cells is filled with numerous lysosomes and large phagosomes. The decay products of differentiating lymphocytes are often found in phagosomes of macrophages; in individual cells, their cytoplasm is filled with lysosomes at various stages of decay (Duijvestijn and Hoetsmin, 1981).

Epithelial cells of various structural and functional zones of the thymus are heterogeneous in their morphological features. Cortical epithelial cells are mainly stellate. Their intracellular organelles are represented by numerous free ribosomes, polysomes, evenly distributed, with a moderate number of mitochondria (K.A. Zufarov, K. R. Tukhtaev 1987).

The epithelial cells of the cortical-medullary zone are somewhat different from the cells of the cortical zone. Along with the classic stellate, there are spindle-shaped epithelial cells. These cells contain many tonofibrils, single mitochondria and profiles of the granular endoplasmic reticulum. In

ISSN 2515-8260 Volume 07, Issue 09, 2020

the cortico-medullary zone, in addition to the types of epithelial cells described above, there are "hypertrophied" epithelial cells (Haelst, Van, 1967). Their characteristic feature is the content of numerous vacuoles in the cytoplasm, which have a cluster-like arrangement.

The size of vacuoles varies widely - from 0.3 to 4-5 microns in diameter, often take the form of intracellular secretory tubules with short microvilli protruding into the lumen (K.A. Zufarov, K.R. Tukhtaev, 1987). In the brain zone, epithelial cells significantly differ in shape and number. The work of Hwang et al. (1974) established that the number of epithelial cells in the brain zone significantly increases with age in rats. Thus, if in the outer cortical zone of the thymus of adult rats, lymphoblasts make up 62 %, lymphocytes-26, epithelial cells-12%, in the cerebral zone the proportion of epithelial cells is 7 times greater (86.3%). Thus, the epithelial-tissue stroma of the thymus is represented by cells of various shapes and submicroscopic organization, differing in its various structural and functional zones. The nature and biological properties of factors produced by thymic stromal cells are discussed in numerous works (Grutenko, 1972; Goldstein, 1978; Trainin et al, 1980; Goldstein and Lau, 1980; Bach 1984).

As early as 1966, extracts of the thymus were obtained, which had a substitution effect in thymectomized animals (Klein et al, 1966). Of the thymic hormones produced by epithelial cells of the thymic stroma, the following deserve the greatest attention:

-thymosin α l;
- thymopoietin;
-thymic humoral factor;
-timulin (serum thymic factor, STF);

Thymosin α l is a peptide, consists of 28 amino acid residues and has a molecular weight of 3108 (Goldstein et al, 1977). It increases the mitogenic activity of lymphocytes, increases the production of a factor inhibiting the migration of macrophages and the number of cells carrying T-lymphocyte antigens. Immunocytochemical methods have been established that thymosin α l is localized in the epithelial cells of the outer cortical and cerebral zones (Haynegetal, 1983).

Thymopoietin is a polypeptide of 49 amino acids with a molecular weight of 5562. There are 2 forms of its thymopoietin I and II, which differ in the substitution of only 2 amino acids. Thymopoietin is 8 times more active than thymopoietin II. Thymopoietins selectively affect the differentiation of T-lymphocytes (Andhya et al, 1981, Bach, 1984). Thymopoietin is localized analytically to thymosin I in the epithelial cells of the outer cortical and cerebral zones.

Thymic humoral factor is also a polypeptide. It contains 31 amino acids, its molecular weight is about 3000. The effect of thymic humarole factor on lymphocyte differentiation is evidenced by its ability to restore the immunocompetence of lymphocytes even in neonatally thymectomized mice and in people with secondary immunodeficiency conditions. the literature lacks data on the cytotopography of the thymic humoral factor.

Timulin is a nanoeptide. It is able to bind zinc, and the presence of zinc is necessary for the manifestation of the biological activity of the hormone. Thymulin consists of 9 amino acids. Its molecular weight with bound zinc is 922. Timulin acts exclusively on T-cells, induces the appearance of their specific receptors. The data of V.P. Lozovoy, S.M. Shergin (1981) established that thymulin under physiological conditions promotes the differentiation of T-suppressors. The results of studies using monoclonal antibodies show that thymulin is localized in almost 2-3% of the epithelial cells of the cortical and cerebral zones. Electron microscopic cytochemistry showed

ISSN 2515-8260 Volume 07, Issue 09, 2020

that thymulin is more actively detected in vacuolar formations of epithelial cells (Savino et al, 1982). Thus, the role of thymic epithelial cells in the differentiation of lymphocytes is beyond doubt, which has been repeatedly proven by the method of cell culture. However, non-epithelial cells of the thymic microenvironment also play an important role in this process. Among them, paramount importance is attached to the "interdigiting" reticular cells of the thymus Steinman, vitmer, 1978; Duijvestijn et al, 1983).

"Interdigitating" reticular cells (IDCs) are one of the essential components of immune responses. Cells similar in structure are also found in the T-dependent zones of the peripheral organs of the immune system (Steinman and Witmer, 1978). One of their obligatory ultrastructural features is the presence of special Birbeck granules in them. IDCs are especially more common in the cortico-medullary and cerebral thymus zones. Unlike typical macrophages, they exhibit low phagocytic activity. On the surface of IDCs there are Ja-antigens and receptors. Duijvestijn et al. (1983), isolating thymus suspension, distinguish three type IDK, differing in their ultrastructural and immunocytochemical parameters:

- type I cells are characterized by the content of acid phosphatase in small granules, plasmolemma gives a positive reaction to Ja-antigen;

Type II IDCs are large, light cytoplasm with an abundant number of Birbeck granules. Granules with acid phosphatase activity of these cells are mainly localized near the nucleus.

III type cells have activities of acid phosphatase and endogenous peroxidase, contain numerous vacuoles and phagosomes. They lack Ja antigens. Type 3 cells are similar in properties to cortical macrophages. One of the specific markers of IDC is the IOO protein; due to the presence of this protein, they differ sharply from thymic macrophages (Higley, Jsaacson, 1984).

Thanks to recent studies, the genesis of the thymus IDC has been established (Gjrdyal, Jsaacsjn, 1985). It turned out that IDCs are streams of a monocytic line of a bone marrow stem cell and belong to the system of phagocytic mononuclear cells. In addition to epithelial cells, macrophages and IDCs, the cells of the thymic microenvironment include mast cells, granulocytes, and plasma cells. Under normal physiological conditions, these cells are localized in the connective tissue of the organ capsule, in the interlobular septa and perivascular spaces of the cortical zone. Thus, the thymus, having in its composition lymphoid elements and cells of the thymic microenvironment, creates conditions for the differentiation of T-lymphocytes, which provide the functions of cellular immunity and regulation of humeral immunity.

As our studies have shown, the morphofunctional parameters of the thymus gland of intact and control rats do not differ from each other. Morphometry of sections of the thymus gland revealed that 71% is the area of the cortical, 26% is the medullary zone, and 3% falls on the share of the connective stromal tissue.

When counting cells per unit area of the cortical zone of control animals, small and medium lymphocytes are predominant, which is 248.5 ± 3.7 rel. The number of lymphoblasts in the cortical zone - 72.1 ± 1.8, REC - 13.7 ± 1.7 relative units; SMF cells make up a small specific gravity - 0.9 ± 0.05 relative units. (all elements combined). In the medullary zone of the thymus, firstly, the density of cells per unit area is approximately 2 times less than in the cortical zone (174.1 ± 2.3 versus 335.6 ± 4.9 relative units). The amount of REC in the medullary zone is slightly higher than the indicators of the cortical zone. When calculating the cytogram of the cortical zone, attention is drawn to the intermediate position of this zone in comparison with the

ISSN 2515-8260 Volume 07, Issue 09, 2020

indicated zones of the thymus. Thus, the thymus gland of white laboratory rats has the same structural and functional zones as other mammals, however, the density and content of cells in them has certain specific features. Studies of the thymus in the dynamics of the temperature factor have determined the following periods of structural and functional rearrangements:

- period of early changes - up to 3 days of experiments;
- the period of pronounced structural and functional rearrangements of the organ;
- days of research;
- period of distant changes - 14-21 days of experiments.

In the period of early changes, certain shifts in the quantitative and qualitative indicators of various structural zones of the thymus gland are revealed. As shown by morphometric studies, the number of small and medium lymphocytes in the thymus lobule decreases over time, reaching 537.9 ± 8.2 by day 3 versus 704.3 ± 10.5 in the control. A decrease in the number of small and medium lymphocytes is accompanied by an increase in the number of lymphoblasts. By day 3, the number of lymphoblasts reaches 220, 2 ± 6.5 (in control, 127.1 ± 4.9). There is also a significant increase in the number of REC and SMF cells.

Morphometry of the areas of various zones of the thymus revealed that in the period of early changes, the area of the cortical zone gradually decreases. By day 3, this figure reaches 55% against 71% in the control. On the contrary, the area occupied by the medullary zone increases (by 3 days - 37 /% compared to 26 /% in the control).

As shown by light-optical studies, the blood vessels of the thymus lobules, and especially the interlobular septa, are sharply expanded, and blood stasis is noted in them. All this leads to an increase in the area occupied by the connective tissue structures of the thymus. One of the characteristic features of early changes is a decrease in the number of small and medium lymphocytes in the cortical zone of the thymus. The number of small and medium lymphocytes on the 3rd day of the experiments decreases to 109.8 ± 3.5 relative to 248.5 ± 3.7 rel. Unit under control. The number of lymphoblasts on days 1-3 increases gradually, reaches a maximum on day 3, amounting to 82.3 ± 0.9 compared to 72.1 ± 1.8 in the control. The number of REC on the 3rd day reaches 18.3 ± 0.2 (in the control 13.7 ± 1.7 rel. Units). The number of SMF cells in the early period also actively increases.

Certain quantitative changes in cells are also detected in the corticomedular zone of the thymus. This consists in a decrease in the number of small and medium lymphocytes, an increase in the number of lymphoblasts, RECs and SMF cells. In the medullary zone, during the period of early changes, no pronounced quantitative cell shifts are detected.

Ultrastructural studies of the thymus in the period of early changes revealed certain changes in the submicroscopic organization of cells in different zones of the thymus. In the cortical area, the RECs are in contact with many medium and small lymphocytes. Moreover, among RECs, monocyte-like and dendritic cells are often detected. In the corticomedullary zone of the thymus, the hemocapillaries are dilated, in the lumen there are many lymphocytes of various types. The migration of lymphocytes through the hemocapillary wall is often different.

The perivascular spaces are also enlarged, in them lymphocytes with myogenic small and large processes are determined, indicating their migration. In the medullary zone, the RECs are submicroscopically similar to IDKs. Their numerous processes penetrate between the lymphocytes of the medullary zone and are in contact with each other.

ISSN 2515-8260 Volume 07, Issue 09, 2020

Radioautographic studies of various structural and functional zones of the thymus gland on the incorporation of H3-thymidine also showed changes in the number of labeled cells in the early stages of the experiments. The number of labeled cells of the cortical and corticomedullary zones gradually decreases in comparison with the control parameters and on the 3rd day is 18.5 ± 0.4% and 8.8 ± 0.1% / (in the control 14.4 ± 0.5% and 5.4) The cells of the medullary zone in the number of labeled cells do not show any significant differences in comparison with the control data. The most pronounced qualitative and quantitative changes in various structural and functional zones of the thymus gland are observed on the 5-7th day of the experiments. Therefore, the indicated periods were called by us the period of pronounced structural and functional rearrangements of the thymus.

On the 5-7th day of experiments in the cortical zone, the number of proliferating cells significantly increases (on the 7th day - 29.6 ± 0.5 %). At the same time, as shown by ultrastructural studies, the functional activity of macrophages and REC of the cortical zone of the thymus increases.

Macrophages contain numerous primary lysosomes and heterophogosomes are in contact with numerous thymocytes at various stages of differentiation. Monocyte-like cells are also rare among cortical macrophages. RECs have numerous invaginations of the nuclear envelope; their cytoplasm contains numerous vesicles with a finely dispersed matrix. They often come into contact with macrophages and thymocytes of the cortical zone.

CONCLUSION

We found that in the layers of interlobular connective tissue in the perivascular spaces of the cortical and cortical-medullary zones during these periods of the study, neutrophilic and eosinophilic granulocytes, mast and plasma cells are more common. As studies of the number of cells in the cortical and corticomedullary zones of the thymus have shown, on days 5-7 of the experiments, the number of small and medium lymphocytes is still low, REC and SMF cells are at a high level.

In the medullary zone of the thymus, the density of thymocytes in comparison with the indicated study periods decreases. It is dominated by reticulo-epithelial cells that contract with single thymocytes. Moreover, RECs are hypertrophied, their wide cytoplasm contains vesicles with a fibrillar continent, many mitochondria, lysosomes, and profiles of the endoplasmic reticulum.

On the 14th - 21st day of the study, the immunomorphological rearrangements of the thymus gland are still preserved. On the 21st day of experiments, the absolute weight of the thymus remains significantly high, 171.7 ± 5.5 mg versus 127.8 ± 8.67 mg in the control. Electron microscopic studies of the thymus on days 14-21 of the experiments revealed certain subcellular changes in thymocytes and stromal cells. In the cortical and corticomedullary gons, the density of thymocytes is low, around the stromal cells, in the perivascular spaces and in the interlobular connective tissue, edematous changes persist. Reticuloepithelial cells often contract with lymphocytes and fibroblast-like cells. Although the area of the medullary zone on days 14-21 of the experiments is higher than the control, the density of lymphocytes in them is low. We have also proved this by studying the submicroscopic organization of these zones. Electron microscopic medullary zones have mainly reticulo-epithelial cells in contact with single lymphocytes.

ISSN 2515-8260 Volume 07, Issue 09, 2020

Light microscopy of thymus sections during these periods shows edema, hyperemia of blood vessels in the layers of the connective tissue of the thymus. All of the above gives reason to believe that on days 14-21 of the experiments, the intensity of the processes of immunogenesis of the thymus will still persist, although there are tendencies for the stabilization of structural and functional rearrangements of the organ.

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