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Mini Review

Anatomy of the Thymus

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Abstract

First description of the thymus probably belongs to Rufus Ephesus. The use of monoclonal antibodies since the 70s of the last century has allowed the division of bone marrow and thymus functions, as well as the determination of subpopulations of T cells in the fetal gland. Achievements in the field of research methods, especially on a molecular basis, contribute to a better understanding of the role of fetal gland and its physiology.

Thymus has a central role in the immune system. The thymic epitelial cells select the bone marrow originated lymphocytes and destroy the autoreactive ones. The involution of the organ starts after birth, however, this truly happens in the end of puberty only, as before this it is overcompensated by developmental processes. The stromal component, which is represented by epithelioreticulocytes, develops with the endoderm. The primary thymus is infiltrated by the lymphocytes that came from the bone marrow here. Lymphocytes after multiple mitoses become the largest population in the gland. The structural and functional unit of the thymus is the follicle of Clarke. This is a dense cluster of thymocytes that are surrounded by elongated epithelial reticular cells. Some chemokines such as CXCR4, CCR7 and CCR9 can affect the movement of immature thymocytes Positive selection provides the survival of thymocytes and the formation of single-positive cells (CD4 + CD8- or CD4-CD8 +). Hassal's bodies represent a cluster of flattened cells in the form of a layer in diameter from 30 to 100 microns. Thymus produces thymulin, thymosin, thymopentin, and thymus humoral factor, which are participating in the regulation of immune cell transformation and selection, and also synthesizes hormones similar to that of the other endocrine glands such as melatonin, neuropeptides, and insulin, which are transported by the immune cells to the sites of requests.

Keywords: *Thymus; Development; Thymocyte; Selection; Chemokine; Hormone*

Thymus is an organ, anatomy of some kind in the last two centuries was quite well studied. In addition, during this time, the understanding of its physiological role in the body has increased significantly in normal conditions of existence and in many pathological conditions. According to one version its name is derived from the Greek word θνμος, which is translated as smoke, spirit and, consequently, - soul, valor, courage. Ancient Greek physicians believed that the thymus was the location of the soul [1,2]. In addition, prior to the thorough study of anatomy and physiology of thymus in the 18th century, it was believed that it also performed other unusual and interesting functions, such as (1) purifying the nervous system, (2) the function of a protective pillow for the vessels of the upper mediastinum, (3) nutrition of the fetus and others. The title and first description of the thymus probably belongs to Rufus Ephesus (98-117 AD), a Greek physician who lived in Alexandria and for some time in Rome during the reign of Emperor Trajan [3]. In turn, Galen from Pergamum (130-200 AD) also studied the structure of this organ. In his work "De usu partium corporis humani" he wrote "La vena cava si appoggia nella parete inferior su una ghiandola assai voluminosa e molle chiamata timo" [4] that translates into "a cava vein in its lower part of the wall based on a very bulky and soft gland called thymus".

Among the anatomists who actually revived the anatomy in general and renewed the thymus doctrine, in particular in the Middle Ages after the epoch of decline, was Jacopo Barigazzi (1466 - 1530) and the founder of modern anatomy, André Vésale, known to us as Andrei Vesalius (1514 - 1564). After publishing his latest foundation work "De humani corporis fabrica librorum epitome" until the discovery of the microscope, Antonius van Leeuwenhoek, there were no significant changes in the knowledge of the structure of the thymus by the great anatomy of that time. The first to study the thymus at the histological level was the English anathetist, surgeon and physiologist Hewson W. In 1774, he published the first scientific treatise on the thymus, describing the change in its size with aging. He first determined the lymphatic nature of this organ [5]. Sir Astley Paston Cooper published his work "The Anatomy of the Thymus Gland" (Anatomy of the Thymus) in 1832, which was the result of his extensive animal breeding experience. He confirmed the significant variation in the size of this organ during his lifetime and denied the notion that thymus is an organ that does not perform any important function in the body. 12 years later, the London surgeon Sir Simon J. published a treatise on the thymus "An essay on the physiology of the thymus gland" [6]. For many years, this work was the guide for the anatomists and physiologists of that time, although the author adhered to the outdated thought of the function of the body as a subsidiary in the process of breathing [1]. In 1846, Hassal A.H. publishes the first English text on microscopic anatomy "The Microscopic anatomy of the human body in health and disease". A.H. Hassal, using the best optic microscope at that time, together with H. Vanarsdale described the histological differences between the thymus and other lymphoid organs [1,7]. In 1849, in the medulla of thymus, they first discovered spherical formations constructed of keratinized epithelial cells. These timings of the body were named after his name. The great German pathologist Wirchov R. restored the term "thymic asthma", which was first proposed by Klopp J.H. in 1830. For decades, the notion of "thimic asthma" and "thimic death" were identified. It was believed that the cause of sudden death among children may be mechanical compression of the respiratory tract and large vessels, hypertrophied thymus [8]. The Austrian researcher, Paltauf A., in 1889 introduced the term "status thymolimphaticus", a constitutional disorder characterized by significant hypertrophy of the entire lymphoid tissue, including increased thymus and may lead to sudden childhood death [9]. The discovery of some forms of congenital immunodeficiency states (DiGeorge and Nezelof syndromes) gave start [10] to study the organ endocrine function. During the 19th century, important studies were carried out, which revealed the role of the fetal gland in pathological conditions.

In 1961, Jaques Miller showed that thymectomy in newborn mice causes the latest immunodeficiency state. Miller's works were the first to reveal the functions of the thymus in our modern sense [2]. The use of monoclonal antibodies since the 70s of the last century has allowed the division of bone marrow and thymus functions, as well as the determination of subpopulations of T cells in the fetal gland. Achievements in the field of research methods, especially on a molecular basis, contribute to a better understanding of the role of fetal gland and its physiology. Thymus established itself as an organ of the immune system, which plays an important role in the body.

In rodents and humans, the thymus is contained in the mediastinum behind the breast bone [11,12]. It is located between the thyroid cartilage and the level of the cartilaginous part of the IV rib. Thymus lies behind fascia pretrachealis, m. sternohyoideus and m. sternothyroideus, manubrium sterni and upper body of the latter. It is located in front of the left ventricular vein between the leaves of the parietal pleura and extrapleural accumulation of adipose tissue. Lateral to the organ pass nn. rhrenici, which are as close as possible to each other in the middle segment of the gland, which is a very important circumstance when conducting thymectomy. In the thoracic cavity behind the thymus are pericard, the ascending part and the arch of the aorta, and in the neck - the trachea.

Typically, the thymus consists of two particles, although sometimes there may be additional particles. Thyroid-thymic bundle connects the upper part of the gland with thyroid gland. There are various types of the distribution of the upper parts of the particle to the left ventricular vein. By taking its classical position, one or two of its lobes may lie in the direction of a given vessel. In addition, there are cases of ectopic organ.

At the 6th week of pregnancy in the endoderma of the third pharyngeal pocket and the corresponding bronchial cleft, a thymus is formed on each side. The fourth pharyngeal pocket makes a significant contribution to its development. The rudiments of the thymus

move towards each other and come into direct contact with the midline, but they do not grow up, remaining two particles of the gland. During 8 weeks, the particle of the gland goes down to the mediastinum and occupies its final position there.

The hyperbilirubin has a common origin with the lower thyroid glands and large thoracic vessels. Thus, the structural elements of the parotid gland can be found in the study of the histological structure of the thymus, and a defect in the correct development of the thymus can lead to anomalies from the side-gland (DiGeorgi syndrome), vessels, or both.

The stromal component, which is represented by epitheliореticulocytes, develops with the endoderm. The connective tissue component of the gland is an anti-mesiodermal mediator that surrounds the corresponding pharyngeal pockets. And the bone marrow is the source of lymphocytic thymus. At the end of 9 weeks, fetal development of the embryonic thymus acquires the potential for attracting these lymphoid cells from the bloodstream, as well as providing a microenvironment in which thymocytes can become mature T cells.

At this time, the primary thymus is infiltrated by the lymphocytes that came from the bone marrow here. Lymphocytes after multiple mitoses become the largest population in the gland. The development of thymus in this period is very dependent on the development of the nerve crest. Damage of the last drive to the weakening of the attraction of thymus lymphoid cells. During embryogenesis, it is possible to delay or disturb the lowering of one or two parts of the gland in the chest, therefore, it is quite common (in almost a third of cases) that it can be observed in the ectopic region of the neck. In the case of ectopia of the gland in the thoracic cavity, the most disturbed are the areas of the pulmonary ligament, the gates of the lungs and, even in the tissue of the legions.

Throughout the life, the size and weight of the thymus undergo significant changes [13]. The adult thymus mass is 25g and the volume is 25 cm^3. The gland in childhood has a pyramidal form, and adolescents are reminiscent of the letter "N". The thymus consists of two asymmetric particles. The color of the organ is pinkish-yellow, changing from pink (due to good blood supply) from adolescence to yellow (replacement of lymphoid tissue with fat).

The thymus is covered with a fibrous capsule. Trabeculae that are separated from the capsule divide the organ into numerical lobes. Each lobe is composed of the outer part - the crust, the stroma of which consists of epithelial cells of endodermal origin, and the inner one - the medulla whose epithelial cells come from an ectoderm. The bulk of thymus cells are given thymocytes. The structural and functional unit of the thymus is the follicle of Clarke [14]. This is a dense cluster of thymocytes that are surrounded by elongated epithelial reticular cells (ERCs). Their total mass is about 90% of the mass of the body. Timocytes are present both in the cortex and in the brain substance of the gland.

In the embryonic development period, they fall into the thymus from the yolk sac and liver when the latter are in the hemopoietic phase of their development. After birth, precursors of thymocytes (Tcs) come to the thymus from the bone marrow. Precursors of Tcs, which circulate in the blood, fall into the thymus due to the attraction of toxic chemotactic substances and enter the thymus parenchyma. In the cortex thymocytes occupy both the external and internal parts of it, where they actively divide. In the process of maturation, the cells that are fasting are differentiated, are shifted to the side of the medulla. It is noted that the differentiation and maturation of thymocytes is better when the latter are located directly near the ERCs [15]. Therefore, 2 and 3 types of ERCs are called timitic nurse cells. Despite the considerable progress in the study of this issue, the issues of thymocyte and Erts interaction remain unsolved. It is known that the latter isolate factors that stimulate Tc to proliferation and differentiation. In the process of their up-dating, Tc is capable of expressing the CD3 + marker and various receptors. Thus, forming different subclasses of thymocytes. Tc in the cortex are not immune-competent cells. Only in the medulla when the thymic cells finally end up, they become T-lymphocytes.

It is believed that T-lymphocytes ultimately ripen in the secondary lymph nodes bodies. In the process of ripening, four types of thymocytes are distinguished, each of which may, in various proportions, be small, medium and large thymocytes. The first type - double-negative cells (CD4- and CD8-, except for CD3-) are over-located in the subcapsular zone and represent large blast cells that become smaller after mitosis. They express com-plex receptors of thymic cells and become CD3 +. The second type is double positive cells (CD4 +

and CD8 +, except for CD3 +), which are localized mainly in the deep cortex and make up about 90% of the entire population of thymocytes in the body. In the process of ripening, there are "errors" in their differentiation, so a large number of cells die. Cells killed in the process of apoptosis, are attracted by macrophages. The third type - one-positive brain cells (one of the markers, CD4 or CD8, is positive). These TCs, after their entry into the secondary lymphoid organs, become completely immunocompetent cells. The fourth type is activated T-lymphocytes that fall into the thymus muscle a second time [16]. In addition to the listed cells in the parenchyma of thymus, there is also a line of cells - natural killers. Immature B-lymphocytes are also present in the thymus, but they fall into the last of the bloodstream. Maturation of these cells is stimulated by one of the products of bone marrow stromal cells - IL-7. Like plasmocytes, they are basically located in the brain, or around the blood vessels in the cortico-medullar area.

In this regard, it is interesting to note that the simultaneous presence of mature B-lymphocytes and activated T-cells in the medulla confirms the hypothesis that at least part of the brain substance of the thymus is likely to be secondary, rather than the primary lymphoid organ.

In humans, progenitors of lymphoid cells enter the thymus at 8 weeks of gestation [17]. This process takes place in at least two ways. The first of these is a path that does not depend on thymus vessels. It takes place in the early stages of the embryonic development of thymus until the vascularization of the latter. The dull path is associated with thymus vessels and occurs at later stages of fetal development and after birth. It is known that fetal thymic colonization is regulated by the chemotactic attraction of progenitor lymphoid cells to the organs' germ. Different chemokines take part in this process, but today all its mechanisms remain undisclosed. After birth, the bulk of progenitors was found in the area of the cortico-medullary compound, where the body's vascularization is very developed. The latter fact confirms the opinion that the main place of receipt of progenio-thyme to the gland is precisely this site [18]. In adults, the admission of thymocyte progenitors to the gland is regulated by the adhesive interaction between P-selectin glycoprotein ligand 1, which is expressed by lymphoid progenitors and P-selectin thymic ERCs [19]. Interestingly, the arrival of progenitors to the thymus is not a continuous process. It occurs in the wake-up bone during embryonic development and in adulthood [20].

During the development of thymus, progenitors of thymocytes enter the gland, where processes of maturation and differentiation of thymocytes pass before the latter enter the secondary lymphoid. Each maturation stage of Tcs is characterized by the expression of some molecules on their surface. These processes take place in special areas of the thymus and depend on many factors. Positive selection is the result of the formation of special receptors on thymocytes consisting of α and β-links (the so-called αβ-thymocytes). This process aims to recognize the thymocytes (later T-lymphocytes) molecules of the major histocompatibility complex (MHC), which are expressed on cortical ERCs.

Thymus muscle is a place where, in most cases, negative selection of thymocytes occurs due to the recognition of the molecules of the MHC expressed on ERCs and dendritic cells of the medulla.

Thymocytes, whose receptors "recognize" MHC as an outsider, are killed by apoptosis [20]. Progenitors of thymocytes entering the thymus first enter the cortico-medullary compound, from which they then pass into the subcapsular zone of the cortex [18]. In the early stages of ripening, the latter are characterized by the absence of CD4 and CD8 receptors, α-links of the IL-2 receptor and the expression of CD44 (a glycoprotein that is involved in interaction between cells, cell adhesion and migration). These thymocytes are called CD4-CD8-CD44 + CD25-double-negative thymocytes (DN-1).

These cells are predominantly in the area of the cortico-medullary junction. Somewhat more mature thymocytes are CD4-CD8-CD44 + CD25 + double-nose-negative thymocytes (DN-2) that are located elsewhere in the cortex, while thymocytes that have lost CD44 are CD4-CD8-CD44-CD25 + DN- 3 subpopulation is found predominantly in the subcapsular zone [18].

Some chemokines such as CXCR4, CCR7 and CCR9 can affect the movement of immature Tcs [21]. In the course of the movement to the sub-capsular site on the t-molecules, an area for attachment of the β-chain of the receptor is organized. Expression of the receptor

complex of thymocytes on their surface during the so-called δ-Notch interaction between the cells gives impetus to initiate the selection of double-positive thymocytes CD4 + CD8 + expressing the αβ receptor.

The sub-tubular patch of the cortex is enriched with the transforming β-factor of rost (TFG-β), which controls the generation of double-positive Tcs [22]. The transition from DN1 to DN3 stage is also regulated by the interaction between Notch1 and inter-leukin-7 (IL-7) receptors. During this phase there is a reorganization of different loci of the tymic receptor (γ, δ, and β). During the specified period of development of thymocytes, an important role belongs to the cortical Erts, which provide a microenvironment for Tcs [23].

Double positive thymocytes of the thymus bark express αβ-TCR complex [24]. These cells interact with the peptide complex of the molecules of histological compatibility of stromal cells (epithelioreticulocytes and dendritic cells) of the cortex. This process (positive selection) provides the survival of thymocytes and the formation of single-positive cells (CD4 + CD8- or CD4-CD8 +). The latter are potentially reactive to antigens that enter the body from the outside, and to neo-antigens, but they are tolerant of autoantigens. By the way, this one-positive thymocytes move relatively rapidly to the brain-substance through signals from the interaction of cells with chemokines [25].

Thymic medulla introduces a highly specialized environment for the removal of thymocytes reactive to its own cells. It is presented by thymocytes of the medulla, dendritic cells, and the ERCs of the medulla. Single-positive Tcs are present in the thymus medulla for about 12 days before they leave the thymus [26]. During this period, single-positive thymocytes undergo maturation, which can be analyzed by the expression of CD62L ligand, also known as lymphocyte (L) -leucine and lectin-receptor C-type CD69 [27]. The newly formed OP-thymocytes are CD62Llow CD69hi cells that are not yet immunocompetent, which need to be ripened in order to acquire CD62Lhi CD69low. In the process of negative selection, a significant place belongs to the "transcription factor of autoimmune regulation" [28,29]. With deficiency of this factor in humans [30,31] and animals [32] there are autoimmune diseases.

The period of maturation of thymocytes in the brain is necessary for the establishment of the central tolerance of the single-positive cells, ensuring the removal of autoreactive T cells [33,34], as well as the production of regulatory T-cells (Treg) [35-37]. It has been shown that most of the regulatory thymocytes that carry FoxP3 are in the brain [35]. The interaction between Tc and Mertz has a feedback. These may affect the maturation of mercury. In the end, positively and negatively selected thymocytes may leave the thymus and create a peripheral pool of T-lymphocytes.

The release of mature thymocytes to the bloodstream occurs through the peri-vascular spaces surrounding arterioles, venules and lymphatic capillaries [38,39]. However, the way that T-lymphocytes leave the gland is still unsolved. These are blood or lymph capillaries, or both of these paths?

Although the signals inducing mature TCs to move are still unknown, this is partly due to the presence of the S1P1 receptor on thymocytes [40] and the S1P receptor on ERCs [41,42]. The latter also contains blood and lymph, which can also play an important role in the migration of T-lymphocytes to secondary lymphoid organs. In addition to the named cells, thymus is the site of the formation of other lines of thymocytes. These are regulatory T cells, natural killers and γδ-T cells.

Regulatory T cells: The specialized microenvironment formed by mercer and medullar dendritic cells is necessary for the formation of regulatory T-cells. These cells help to support auto-tolerance by way of suppressing the immune response [43,44]. Most regulatory T-cells coverage conventional CD4 + T cells, but differ from the latest expression of FoxP3 [35,45] and expression of high levels of CD25 and low CD127 [46].

Natural Killers: Cortical double-positive thymocytes are holistic cells that provide the development of natural killers. The latter are large grainy lymphocytes with characteristic morphology: a large part of the cytoplasm contains several mitochondria, free ribosomes with individual elements of granular endoplasmic reticulum, Golgi apparatus and characteristic electron-bearing granules bound to the

membrane. Natural killers carry cytotoxic functions, as well as cytotoxic T-lymphocytes [27,47]. Conventional αβ-T cells are mainly within the lymphoid organs and play a central role in the adapted immune response. On the contrary, most T cells expressing the γδ receptor are contained in epithelial layers that form the basis of internal and external body surfaces such as skin, epithelium of the intestines, lungs, tongue, where they act as the first line of defense [48-51]. Early stages of development of Tc are characterized by differentiation processes of various γδ-subpopulations of cells by expression of the Vγ and Vδ genes [52].

Thymus macrophages, which originate from bone marrow, form a very vivid population of organ cells. They are predominantly located in the cortico-medullary joint. By phagocytosis, they destroy the remains of cells that died in the process of apoptosis.

ERCs form a three-dimensional mesh. Unlike thymus, the stroma of other lymphoid organs has a mesenchymal origin. In the gland, 6 types of epithelio-reticulocytes are singled out. Type 1 ERCs is located predominantly in the subcapsular zone and in the perivascular space. They are presented with flattened cells with a beautifully pronounced basement membrane. Other features of these cells are the small, short tanks of the granular endoplasmic reticulum and the tubular complex whose function has not yet been disclosed. The function of these cells is secretion of hormones [53,54]. Type 2 of ERCs is located throughout the thickness of the cortex to the medullary vein. Their size is larger than the size of the first type of cell. In them, the Golgi apparatus is beautifully different, and the processes reach a length of 100 microns. Type 2 of ERCs are large light cells, while the ERCs type 4 is darker and smaller than the previous ones. ERCs of the medulla are represented by 5 and 6 types of cells. Type 5 is very small cells without a special function. The sixth type of ERCs is the most common type of epithelial cells in the medulla. Their shape will undergo significant variations. If the function of the spindle-like cells lies in the secretion of hormones, then flattened cells participate in the formation of thymic bodies.

Hassal's bodies are formed by ERCs 4 and 6 types. They represent a cluster of flattened cells in the form of a layer in diameter from 30 to 100 microns. Signs of cell forming cells are also the sealing, fragmentation and vacuolization of nuclei, as well as the presence in the cytoplasm of destroyed organelles, devastated vacuoles or vacuoles with dense content and tone fibril packets, which is regarded by most authors as signs of destruction of epithelial cells.

A special place among the structures of thymus is occupied by epithelial tubules. In the works of Voloshin N.A. proved that the presence of such tubules is observed in newborn babies in the early days. The use of serial sections in the study of the structure of the thymus suggests that most canal cells are contained in the apical part of the thymus, less in the middle sections, and practically do not occur in the basal divisions. Within the lobe of the thymus, canalicles are localized predominantly at the level of the cortico-medullary connection with the transition to the cortex, medulla or into the septum.

In the spaces between the ERCs and their appendages, thymocytes are contained. The bark is given from fast-moving thymocytes and a small number of macrophages between them. In the medulla, the overwhelming majority of thymocytes are small clindins, with the density of their location in comparison with the bark is much smaller. The brain also contains keratinized epithelial cells, which form specific thyme germs (Hassal's bodies). Their functional significance still remains undiscovered. Although recent research shows a link between increasing their number and increasing functional activity of the gland.

The arteries that blood supply to the thymus are branched branches from the lower thyroid artery or from the upper thyroid and from the mediastinodiaphragmatic artery. Rarely, the posterior thymic arteries depart from the arch of the aorta, the shoulder-head barrel or from the left common carotid artery. Thymus has no hilum. Therefore, the arteries enter the body through the capsule, then by trabeculae, parenchyma reaches the level of the cortico-medullary junction.

The microcirculation in the thymus cortex differs from that in the medulla. In each lumen the arteries give small capillaries in the direction of the cortex and relatively large vessels into the thymus medulla. Capillaries of the gland crust pass along the crust at different depths.

Post-capillaries fall into the veins at the level of the cortico-medullary compound. Some capillaries reach the body's capsules, where post-capillaries and veins are tributaries of veins that carry out blood outflow from the gland. The main feature of the capillaries of the thymus cortex is that they surround the Erts, forming a hemo-thymic barrier [55]. Capillaries of the medulla are different in size. They are not surrounded by epitheliореticulocytes. At the level of the cortico-medullary compound, some post-capillaries are broad with a high epithelium similar to the epithelium that is observed in other lymphoid organs.

The veins that accompany the lower thyroid and axial-diaphragmatic arteries carry out blood outflow from the gland. Significantly, the venous outflow occurs through the veins that go from the posterior surface of the gland directly to the left lobe of the vein. As an option, these tributaries can form venous trunk that enters the brachiocephalic vein.

Thymus has no afferent lymphatic vessels. Efferent lymphatic vessels are accompanied by blood vessels located in the perivascular space and carry out lymph outflow from the cerebrospinal fluid and the cortico-medullary junction in the mediastinal, nonspecific, tracheobronchial and internal parasternal lymph nodes.

After weight sympathetic fibers originate from the cervical-thoracic nodes of the sympathetic trunk and accompany blood vessels in the form of periarterial nerve plexuses, and parasympathetic fibers are sent to the thymus in the composition of the vagus nerve. The diaphragmatic nerve directs to the thymus capsule, and then forms a nerve plexus at the level of the cortico-medullary connection. Both parts of the thymus are inverted separately. The formation of sympathetic and parasympathetic organ inactivation occurs at different times. The nodes of the vagus nerve reach the thymus even before it is lowered into the chest, while the sympathetic fibers enter the gland after the latter takes its final position. The presence of sympathetic organ inactivation is explained mainly by the vasomotor function of the latter, while the function of cholinergic fibers in the thymus is still debated.

After birth, the size and weight of the thymus during the first year of life increases, reaching a maximum weight of 25g. This weight remains a constant value up to 6 decades of life. After that, the thymus decreases in size, which is accompanied by appropriate changes in the microscopic structure of the gland. This phenomenon is known as the "involution" of the thymus, although the differentiation of thymocytes and their transmission to the secondary lymphoid thymus arthritis occurs throughout their lives. The process of thymus atrophy is closely linked to increased production and high levels of sex hormones in the blood. Some authors in their studies prove an increase in organ size after an androgenic blockade [56].

As a result of involutive changes in the gland, the lymphoid tissue of the body is replaced by fat, which leads to the formation of "fatty loose fat". It is accepted to allocate four phases of the thymus involution. The first phase (up to 10 years of life) is characterized by loss of thymus about 5% of lymphoid tissue each year; In the second phase (from 10 to 25 years), infiltration of the neurvacial spaces predominantly occurs in the thymus medulla. From 25 to 40 years, fatty tissue replaces lymphoid in the bark as well (third phase). The "loss" of lymphoid tissue by thymus is about 5% annually; after 40 years (the fourth phase of the involution of the gland), the reduction of the lymphoid population of the cells in the vein slows down to 0.1% annually. However, despite the significant invasion of thymus in the specified period of life, the cells of the lymphoid tissue in the thymus still remain in the elderly.

Epithelio-reliculocytes play an important role in the development of thymocytes. And not only do these cells secrete numerous cytokines, including IL-1 and IL-6, stimulating factor of the colony of granulocytes, macrophages. In addition, they produce some hormones. The proof was that some extracts made from thymus contributed to maturation and differentiation of thymocytes [57-59]. Well-studied peptides that have a sequence of amino acids and biological properties. These are thymosin, thymopoietin, timulin [60] and the humoral factor of the thymus gland [61].

Isolation of thymosin (a family of biologically active molecules with properties similar to hormones) from thymus occurred more than 40 years ago [62]. In the 70s of the last century, studies have shown the immunotropic effect of partially purified thymosin, which was

called "thymosin fraction 5". This fraction consists of polypeptides, each of which was carefully studied. Although thymosin was isolated from thymus, this hormone is quite widely distributed in other tissues [63,64]. There are three main groups of this hormone - α-, β- and γ-thymosin. α-thymosin participates in the following processes: (1) induction T-helper; (2) expression of phenotypic markers of T cells; (3) motilization of lymphoproliferative processes; (4) production of antibodies; (5) the cytotoxicity of T cells and (6) the activity of natural killers [65-70].

Thymopoietin and thymopentin. Thymopoietin is a polypeptide that consists of 49 amino acids. The pentapeptide thymopoietin corresponds to 32-36 amino acids-there is thymopentin (Arg-Lys-Asp-Val-Tyr). Thymopoietin plays an important role in early T-cell differentiation. Thymopentin is associated with class II histocompatibility molecules expressing on antigen-presenting cells. Therefore, currently, research is being carried out to establish mechanisms of immunomodulating action of thymopentin [71].

Thymulin (the original name is "facteur thymique sérique") is made exclusively by the Eucalyptus thymus. It consists of a non-peptide component associated with zinc ions, which provide this molecule of high biological activity [60,72]. After its discovery in the early 70's of the last century, thymulin was characterized as a hormone involved in some aspects of intra-and extra-matrix T-cell differentiation [73]. Subsequently, it was reported that the production of thymulin is highly dependent on neuroendocrine effects. Thus, the role of the growth hormone in stimulating the secretion of thymulin is shown [74].

The temporal humoral factor γ2 is the immunoregulatory peptide present in the thymus extract [75]. Selected and purified from calf thymus, it was identified as an octapeptide [76]. It is characterized as a stimulatory function of T-lymphocytes and IL-2 products [77].

In the twentieth century Canadian scientist Hans Selye conducted many animal studies, exposing them to emotional stress. As a result, he monitored the enlargement of the adrenal glands and reduced bowel movements. It was found that during stress, increased concentration of steroid hormones suppresses the activity of the immune system. As a result of such studies, a new medical-biological discipline-neuro-immuno-endocrinology is being developed.

The interaction between the neuroendocrine and the immune system has recently been the subject of careful research by many scientists. Hormones and neuropeptides have an effect on the gland and its cells through the endocrine or autocrine/paracrine pathways. The fact is that both the immune and neuroendocrine systems use the same ligands and receptors to establish interconnections between cells within the system and inter-system bonds, which is of great importance in maintaining homeostasis. It is known that growth hormone regulates proliferation of thymocytes and ERCs [78]. Growth hormone stimulates production of thymus hormones, cytokines and chemokines by micronutrition, as well as extracellular protein matrix products that facilitate the migration of thymocytes.

JA Hammar [79] distinguishes three types of thymus in mammals, depending on the location of the latter. 1 type is cervical; 2 - thoracic; 3 - cervical and thoracic. In pigs, for example, most of the thymus is located in the neck area, and only a small part is in the chest cavity.

This is also typical for insectivorous. Breast type is observed in humans, horses, elephants, monkeys, and others. In predators, the thymus - it is mainly the organ of the thoracic cavity. According to KD Budras [80] in dogs only 1/5 or 1/6 of the organ is motivated in the neck area. The cervico-thoracic type is beautifully illustrated by the example of sheep.

Conclusion

The thymus gland is an essential organ for the development of the immune system. The presented review shows large number of studies devoted to the study of the anatomy and physiology of the thymus. Demonstrated modern ideas about the structure of this organ and its central role in protecting the body from damaging factors.

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