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Modern data on embryogenesis and functional morphology of thymus (Literature review, part I)

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Abstract

In the following article we have provided modern data on main stages of implementation, formation as well as stabilization of functional activity of thymus of the fetus on different stages of fetal development. Thus, we have analyzed specific features of gland's location in case of children, adolescents and adults. We have described two main stages of the organ's ontogenesis. In addition, histological features of the fetal thymus implementation, starting with the 8th week of embryonic development were studied and provided below. The criteria of completion of the gland's formation on the gestational term of 24 weeks were clearly emphasized. The stages of maturing of lymphocytes as well as appearance of the surface markers of the lymphocytes on them as well as division of the T-cells into subpopulations were described. The role of thymus in the sphere of formation of all types of the organism's immune defence was explained. We have analyzed an endocrine function of the gland with providing the hormones, hormone-like substances, as well as extracts of the organ, which have their influence onto lymphoid tissue development as well as play their leading role in the hormonal homeostasis of the child's organism. The morphological features of the main structural components of the gland, as well as their functions in the thymus

stabilization were disclosed. The nature of relations between structural components was clearly described. It has been proved also, that in case of full-term fetus, the thymus is a main lymphoid organ, which is structurally and functionally formed for the moment of birth. Moreover, under the conditions of the physiological pregnancy the lymphoid and epithelial components are sufficiently and harmoniously developed, and the thymocytes are differentiated and immunologically mature. Finally, we came up with the conclusion, that the pathology of pregnancy and childbirth can lead to the impaired embryogenesis and fetogenesis of the fetal thymus.

Key words: fetus; thymus; embryogenesis; lymphocyte; immunity; hormonal activity.

Сучасні дані стосовно ембріогенезу та функціональної морфології тимусу (огляд літератури, частина I)

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В статті наведено сучасні дані стосовно основних етапів закладки, формування та становлення функціональної активності тимусу плода у різні етапи внутрішньоутробного розвитку. Так, розглянуто особливості розташування залози у дітей, юнаків та дорослих. Описано два основні етапи онтогенезу органу. Вивчено та наведено гістологічні особливості закладки тимусу плода, починаючи з 8 тижня ембріонального розвитку. Чітко виявлені критерії завершення формування залози на терміні гестації 24 тижні. Описані стадії дозрівання лімфоцитів в тимусі та поява на них поверхневих маркерів лімфоцитів та розподілу T – клітин на субпопуляції. Пояснено роль тимусу у формуванні всіх видів імунологічного захисту організму. Розглянуто ендокринну функцію залози з наведенням гормонів, гормоноподібних субстанцій, а також екстрактів органу, що мають вплив на розвиток лімфоїдної тканини та відіграють ведучу роль у гормональному гомеостазі організму дитини. Виявлено морфологічні особливості будови основних структурних компонентів залози, їх функції у становленні тимусу. Чітко описаний характер взаємозв'язку структурних компонентів між собою. Доведено, що у доношеного плода на момент народження тимус є ведучим

лімфоїдним органом, що структурно та функціонально сформований повністю. При цьому в умовах фізіологічної вагітності лімфоїдний та епітеліальний компоненти достатньо та гармонійно розвинуті, а тимоцити диференційовані та імунологічно зрілі. Зроблено висновок, що патологія вагітності та пологів можуть призвести до порушення ембріогенезу та фетогенезу тимусу плода.

Ключові слова: плід; тимус; ембріогенез; лімфоцит; імунітет; гормональна активність.

Thymus plays an important role in the human organism, as a central organ of lymphocytopoiesis and immunogenesis on the one side, and as a source of hormones and hormones-like substances on the other [1, 2, 4].

The thymus is located in the upper-front part of the chest, just behind the breastbone. The mass of the thymus in organism of newborn is 12-28 g. [3, 6, 7]. It consists of two triangular particles flattened in the anteroposterior direction, and the left particle is bigger than right one. The upper sections of the particles are beyond the chest cavity, ending at the jugular fossa, or they also reach the lower pole of the thyroid gland, and rarely they can extend lower [8, 9, 10]. The lower limit of the organ is situated on the one line with heart basis. Thymus has a polygonal shape, which is characteristically changeable depends on age. For ancient anatomists this gland reminded a leaf of the thyme, so, because of it, the name of this gland is thymus [11, 12, 13]. Thymus has something in common with the group of brahiogenesis organs, which are developing from gill pockets, so, because of this fact, it is often enough when outside the capsule of the main particles around or in the tissue deep of the thyroid gland or in the koloshyto-similar glands, in the region of the tonsils, in the soft tissues of the neck, mediastinal adipose tissue may occur an ectopical areas (as added particles or aberrant ones) additional gland. In additional particles of the gland may be developed the same pathological changes as in the main gland [14, 15, 16].

The thymus' ontogenesis can be divided into two periods: from 6th week - to the end of the 2-nd month of fetal development, and the second: from the beginning of the 3-rd month till birth. This distribution is mainly based on data, which tell that during the first period thymus is similar to epithelial cord, and during the second ones - it is similar to lymphoepithelial organ [17].

Formation of the thymus begins from pharyngeal epithelium, in section there are 3 or 4 pairs of gill pockets in form of bands of stratified squamous epithelium. Embryos with length of 8mm formation of the thymus looks like protrusion, which is maintain the

communication with gill pocket by using ductus thymico-pharyngeus. The distal part of the rudiments of the 3-rd section of the gill pockets, by becoming thicker, forms the body of thymus and its extracted proximally, like clamps strait of the exocrine gland [18, 19]. Tends gradually lose their cavities as well as increase their size, their distal ends converge and form together with thyroid and parathyroid glands and telebrahial corpuscles something, what will be called brahial complex, which is on the 8-week period falls down into the neck. The thymus separates from gill pocket and it takes its place on the front surface of the pericardium. During all this time gland consists of compact epithelial strands. Mesenchyme, that is grows into epithelial formation, together with blood vessels divides it into segments [20, 21]. On the 7-8th week of the fetal development hematopoietic colonies formed cells come from liver to thymus and, further, this cells under the influence of the thymus hormones, differentiate into lymphocytes. Lymphocytes of thymus are also can be called thymocytes (lymphocyti thymi). Since the 9-th week epithelial strands transform into a loose network structure, in which loops are situated lymph cells. The density of structures of the central and peripheral areas is not the same, so, in the formation we can differ brain and cortical parts. Cortical part of thymus is more abundant infiltrated by lymphocytes than brain one. As a result epithelial structure of the germ is difficult to discern. In the stroma medulla appear layered epithelial cells (concentrical clusters of the cambial epithelial cells, which can be transformed) - that are Hasal's cells [22, 23]. the biggest number of Hasal's cells per unit we can count on the 27-32 weeks of prenatal development, when they occupy large areas as well as they can connect with each other by epithelial strands and, as a result, to form whole complexes. Each complex has a form of the complicated body with large mass of cornified cells, as well as cells that are continuing to cornify [24].

Formation of the thymus completed till the 6th month of the intrauterine development of fetus, when organ's lymphocytes begin to secret hormones and outside of thymus there are differentiated forms [25, 26]. on the 11-12th weeks of embryo's development take place a differentiation of the lymphocytes, and on the surface of the cells appear specific receptors and antigens [27]. As you know, there are three stages of lymphocytes' maturation in thymus: 1 and 2 occur in paracortical and cortical layers, 3- in the medullary layer [28, 29]. As characteristic features of this stages we can name the change of the surface of lymphocytes' markers [30]. On the first stage the most early immature T-cells are shown, which react with anti CD-1, anti CD-38, monoclonal antibodies (MAbs), and they are counted as 10 % among all lymphocytes of population. On the 2nd stage tymocytes acquire markers of cortical tymocytes (CD1) and they express antigens of the T-helper-inducers (CD4), suppressors of

the cytotoxic cells (CD8) and E-ROK cells (CD2). They are expressed on the membrane at the same time, by not dividing cells into populations that are different functionally [31]. For medulla substances as more characteristic are cells of the later stages of differentiation, which do not express markers CD1. On the 3rd stage of the development T-cells are divided into different subpopulations with CD4 or CD8 antigens, but, regardless of this difference, all of them are expressing CD38 antigens [30]. The loss by cells of the CD38 antigen can be shown on the fact of complete differentiation of T-cells. By using the method of double or triple label M. M. Dubrovina; E. S. Dubrovina; A. G. Rumiyansev [32] showed, that the most thymocytes have a phenotype CD4/CD8/CD38, and from 14% to 41 % of cells are expressing CD1 and CD3, which means, that on the membrane of the cells can be found as both: young and mature T-lymphocytes. T-cells also express CD4 ligand which is necessary for activation of B-cells and switching them into the production of another class of IG. A. M. Partenadze and V. M. Studenkin [33] during their study in the sphere of thymus of fetuses and newborns concluded, that on the thymocytes of the human fetuses till the 1st year of life is expressed at the same time a great number of receptors, what allows to characterize cells of the thymus as immature T-lymphocytes, which are able to differ themselves as well as they can be characterized by their high proliferative activity [34].

As we told earlier, on the 3rd stage of the development T-lymphocytes are divided into different subpopulations. Among them we can differ T-helpers, T-suppressors, T-killers. In the population of T-helpers we can tell about T-helpers for B-cells, which are used for recognition of “his” and “alien” and, those, which together with macrophages include B-cells into proliferation, and, thereby, ensuring the production of antibodies [25, 35]. T-helpers of T-cells (amplifiers) increase the activity of other subpopulations of cells. T-suppressors belong to their role in the control of the immune response and to provide a tolerance for antigens of its own tissues [36]. Subpopulation of T-killers belongs to the effector function for cell immunity, they destroy cells of the transplant, tumors as well as its own cells changed as a result of modifications [37, 38]. Another subpopulations of cells because of the humoral factors play the role of mediators of secular inflammation, and one part of T-cells, which lives longer provides an immunological memory. Thus, populations of T-cells of thymus that were described above carry collectively all types of immunological protection such as: antibodies production, RHZT, RHNT, tolerance and immunological memory, defining by these actions thymus as a central organ of immunity [39, 40].

As a characteristic feature for T-lymphocytes population we can differ presence of homeostatic mechanisms, which provide support of the sustainability of number, composition

and spatial organization of cells [41]. Sustainability of number can be provided by balance between cell formation and cell death. The spatial organization can be characterized by existing of different volume niches for specific populations of T-lymphocytes [42].

Because of the fact, that the thymus is an endocrine gland we should definitely consider its endocrine function. The main endocrine function of the thymus is immunogenesis regulation, which means: differentiation and maturation of pre-T-lymphocytes, re-circulation of the hormones and hormone-like substances, that are produced in the gland [43]. There are more than 20 extracts of gland among of which we can tell about 5, that can influence into the lymphoid tissue. This is thymozin-fraction 5, thymopoetin, thymic humoral factor, serum thymic factor, active factor of thymus - 6 (AFT-6). The impact of the main thymic hormones appears in such way. Thymopoetin affects on the pre-T-lymphocytes, stimulates immunogenesis and response of the lymphocytes to mutagens, as well as it blocks neuro - muscular transmission [44]. Thymic humoral factor activates T-cells stimulates a proliferation and differentiation, increasing at the same time mitosis in T-cells. Thymic X-factor restores the number of T-cells in blood, enhances RHZT. Thymic serum factor (thymulin) affects on the different stages of differentiation of T-cells as well as on the differentiation of the cytotoxic T-lymphocytes. Thymosin $\alpha 1$ affects on the earlier stages of differentiation of T-cells and T-helper cells. Thymosin $\alpha 7$ affects on the differentiation of T-suppressors, as well as on the later stages of the differentiation of T-lymphocytes [45]. Thymosin B-4 affects on the earlier stages of differentiation of T-lymphocytes. A-protymozin - the predecessor and $\alpha 1$ and $\alpha 2$ thymosin [46]. The active factor of thymus ATF-6 is situated closer to thymosin. V.H Khavinson, V. V. Zhukov differ a homeostatic thymic hormone as well. Besides hormones, which stimulate lymphoid tissue and immunogenesis, in thymus we can differ also suppressor factors of the lipid nature, that are depress a mitotic activity of thymocytes; as well as we can differ a group of humoral factors of the gland, that can affect on blood sugar regulation (hypoglycemic effect), which also reduce the content of the organic phosphorus in skeletal muscles and which show also a hypopotassium activity. As being an endocrine gland, the thymus can also affects on metabolism, hematopoiesis, growth and puberty [47].

As a structural and functional part of thymus we can name a particle, which consists of lymphocytes, macrophages and neighboring areas of inter particles perivascular spaces of vessels and cells of mesenchymal origin. In the particle we can differ a subcapsular zone, inside cortical zone, medullary zone, inter particles perivascular spaces of the cortex and medulla.

Subcapsular zone is located immediately under the basal membrane of particles and it is represented as a network of light epithelial cells, in the middle of which lymphoid cells are situated. In the subcapsular zone we can differ two types of cells: cells of the first type are located as a continuous layer on the basal membrane, they are light subcapsular and perivascular cells and, in addition, they contain many thymic hormones ($\alpha 1$, $\beta 3$, $\beta 4$ - thymosins). This layer of cells is a major component of the hematochemical barrier. Cells of the second type - (light cells of the cortex and medulla) - are cells "breadwinners" or cells "nurses", which have deep intussusceptions. In this intussusceptions like in the cradle are situated lymphocytes. The second type of cells bears antigens of cytochromes of Thy-11-Go (FAA) and the second (DR) classes of the system HLA. They are able to produce thymosins and thymopoetyn. Cells, that are located inside of cells "nurses" can be characterized by presence of antigens (CD1, CD2, CD7 and CD5) [48]. Some of them have the phenotype of T-helpers CD4, as well they are able to produce IL-4. The role of the subcapsular zone can be described as a creation of conditions of the proliferation and primary stages of maturation of pre-T-lymphocytes. The main factors of micro-environment are thymic hormones and IL-4, which are released by lymphocytes [49, 50].

Cortical substance (cortex) - is a peripheral portion of particles, which contains densely located small and medium lymphocytes surrounded by macrophages and epithelioreticulocytes as well as T-lymphoblasts. Epithelial cells of this zone are characterized by expression of antigens of the first (A, B, C) and the second (DR) grades of the HLA system. The inner cortical zone contains from 60% to 80 % of all thymus' lymphocytes. Lymphocyte population of this zone is diverse and contains a couple of a bit specific and different subpopulations, among of which some subpopulations carry antigens T10, CD2, CD7, CD1, CD4, CD8 [18, 51]. Among of them we can also differ "double positive" CD4+ and CD8+, and "double negative" CD4- and CD8- ones [8, 12, 52]. This mature lymphocytes are carrying homing receptors for the migration to T-dependent areas of peripheral lymphoid organs [53]. Precursors of T-lymphocytes are transferred from red bone marrow to cortical substance. Here is sampling their proliferation and selective phagocytosis of newly created cells by macrophages. After that selected and "educated" T-lymphocytes, that brought a specific cytochromes for foreign antigens, migrate to the medulla [16, 28, 41]. Cells of the cortical substance are separated from blood by hematothymus barrier, which protects them from an excess of antigens [53].

Medulla - is lighter because of the fact, that it consists of dense network of epithelial cells, which form cells and contain fewer lymphocytes. Medullary zone can be differed from

cortical one, by lack of the hematohymical barrier, because of the fact, that epithelial cells in it are not created a continuous layer along the basal membrane around inter particles perivascular spaces, as well as because of the presence in medullary zone fenestral capillaries. Medullary zone contains from 15% to 20 % of thymus' lymphocytes. Among of them we can differ mature lymphocytes with markers CD3, CD5, CD4, CD8 and antigens of HLA of the first and second class; lymphocytes with immature cortical phenotype, among of which one part carries antigens CD2, CD7, CD5, CD3, CD4, CD6, which means helpers-inducers, and the second one carries antigens CD2, CD7, CD5, CD3, CD8, CD6, which means cytotoxic suppressors [54]. Lymphocytes of this zone are the pool of recirculation of T-lymphocytes and they can come in to blood and come out blood flow through postcapillary venules. Medullary zone is characterized by presence of a large number of cells and macrophages. In the medullary zone are located thymic bodies (corpusculum thymicum), formed because of the degeneration and later stratification of stellate of epithelioreticulocytes of the medulla. It is believed, that this bodies, in the period of embryogenesis already, are consist of finally differentiated epithelial cells and also, that the Hasal's bodies, which contain a horny mass, are the kind of stimuli for reticuloepithelium, by causing by itself accelerated proliferation of him, increasing the size of the thymus and its settlement by lymphocytes. The number of cells increases till the period of puberty and then decreases. According to the meaning of T. E. Ivanowska, T. F. Kogoi, L. I. Pokrowska, Z. E. Khohlov [55] in the period of maturing a thymic body is a corpuscle, filled with lipids, nucleoprotein and mucopolisaccharides. The wall of the corpuscle is represented as a one layer, thinned by flattened retikoepithelium. When the wall of corpuscle ruptures, the secret of the thymic body flowing into the deep lymphatic network, it means, that it falls directly into the internal environment according to principles of incretor secretion. The authors suggest, that the secret of the thymic body is those accurately humoral factor, which regulates limphopoiesis and immunogenesis as well as such thing, that cells of the retikuloepithelium are not functionally active out of thymic body.

IPS (internal particles perivascular spaces) - are parenchymes, reaching deep into the gland. They are narrow or wider branches of the interlobular septum, inside of which are located inside of blood vessels. On the one side, IPS are separated by basal membrane of blood vessels, from an other side - by a basal membrane of epithelium cells, strictly by cells of thymus' parenchyma. The function of the IPS in different zones of thymus is not similar. In the cortex, this function can be described by telling about creation of structural basis of the

hematothymic barrier. In the marrow the function of IPS includes also transports of T-lymphocytes [21].

In the fetal period there are few peaks of growth can be marked, speaking about thymus as well as different components of thymus. The mass of thymus on the 12th week is 0,0245h, till the 13th week it reaches to 0,131h and continues to grow until birth, but, what is important, the period of the fastest growth is the time between 19th and 24th weeks. Till the 30th week the mass of thymus reaches to 4,63h. Moreover, if till the 22nd week the cortical substance dominates under the brain one, the peak of growth of the gland at the next period caused by presence of two active zones of cell proliferation already it means: subcapsular and medullary, where subcapsular epithelial cells were entered. This period is connected with growing of number and volume of thymic bodies, what provides to peaks of growth at the age of 18-20 and 27-28 weeks.

Infants' thymus is the largest lymphoid organ in their organism [28, 33]. Until the time of birth of the full-term fetus, thymus of this fetus is already structurally and functionally developed. Moreover, this organ by this time has such characteristics: this glands in the girls' organism are bigger than in the boys' ones; the weight of the gland (as a maximum mass) is in average 15-20 h (it depends on the weight of the newborn), particles of the parenchyma are large and, in addition, they are differentiated on a wider cortex and relatively narrow medulla, that contain thymic cells. Moreover, there are narrow interlobular septums and runways, that are expanding in the area of cortico - medullary limit [53].

Thus, if the fetus is cherished in relatively good conditions and by healthy woman, till the time of childbirth thymus will be fully formed. All structural and functional components of thymus (lymphoid and epithelial) will be harmoniously and sufficiently developed; thymocytes will be differentiated and immunologically "trained".

Pathology of pregnancy and the process of childbirth are undoubtedly adversely affect on the embryogenesis and fetogenesis of the fetal thymus.

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