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NORMAL STRUCTURE, FUNCTION AND HISTOLOGICAL FEATURES OF THE THYMUS

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Abstract

The thymus is a primary lymphoid organ and, in immunological terms, serves as the source for the development of T-lymphocytes. It is also characterized by morphological diversity in its structure. Undoubtedly, the thymus is an epithelial organ in which epithelioreticulocytes form specialized structures that ensure the development and maturation of T-cells, along with other cells of the lymphoid lineage. The presence of symbiotic interactions between the thymic microenvironment and developing thymocytes has been established. It is also recognized that T-lymphocytes matured under thymic control subsequently enter the systemic circulation. The cortical substance of the thymus is densely populated with thymocytes, against which epithelioreticulocytes are relatively sparse. In the medullary substance of the thymus, more mature cells are located, while epithelioreticulocytes and other cell types are represented more abundantly. Understanding the normal morphological characteristics of the thymus, as well as the changes that occur under the influence of environmental factors, is of key and decisive importance for assessing the systemic immune function of the organism.

Keywords: thymus, T-cells, epithelioreticulocytes, morphology, histology, epithelial-free areas, rodents.

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Development

The thymus of rodents develops from the endoderm of the III and IV pharyngeal pouches as well as from the surrounding mesenchyme [6]. The pharyngeal pouch is connected to the pharynx via the thymopharyngeal duct, and its remnants within the developing thymic parenchyma may give rise to various epithelial structures (Figs. 1, 2). During development, the thymus migrates caudally (downward) together with the thyroid and parathyroid glands, which share a common origin. As the thymus descends into the thoracic cavity, these organs separate from one another. Embryonic remnants of the thymus may be found in the cervical tissues (Fig. 2), as well as show ectopic development within the thyroid (Fig. 1) and parathyroid glands [22]. After completion of organ migration, epithelial cells form a reticular network together with the developing blood vessels. Due to the rapid colonization of the organ by migrating lymphocyte precursors from developing hematopoietic tissues (in mice, on gestational days 11–12), the thymus becomes a lymphoepithelial organ. Cases of thyroid and parathyroid tissue development within the thymic parenchyma have also been described in the literature, which is explained by their common embryological origin (Figs. 1, 2). By the time of birth, the thymus is considered the first fully formed lymphoid organ and undergoes rapid development in response to postnatal antigenic stimulation. Genetic factors also significantly influence the characteristics of the thymus-associated immune response. In rats and mice, the thymus reaches its maximum development during sexual maturity and subsequently undergoes gradual involution (regression).

Fixation and histological processing of the thymus. Usually, after removal of the surrounding adipose and connective tissues, the thymus is weighed prior to fixation. Blood supply, innervation, and lymphatic drainage. Arteries supplying the thymus pass within the interlobular connective tissue septa and penetrate the organ parenchyma at the corticomedullary junction.

The arterioles then branch into capillaries that enter both the cortex and the medulla. In the cortex, they form a complex of capillary loops which, together with perivascular lymphocytes, macrophages, and peripheral epithelioreticulocytes, constitute the blood–thymus barrier [2]. According to Cooper et al., fenestrated capillaries are rare in the cortical region [13]. This limits the contact of developing lymphocytes with antigenic molecules circulating in the bloodstream. In contrast, the capillaries of the medulla are fenestrated and are freely permeable to antigens.

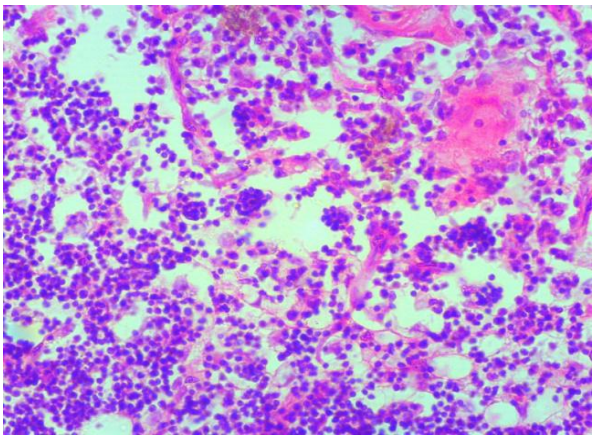


Figure 1. Hassall's corpuscles located in contact with surrounding reticuloepithelial cells. Staining method: H&E (hematoxylin and eosin). Ocular: 10×10.

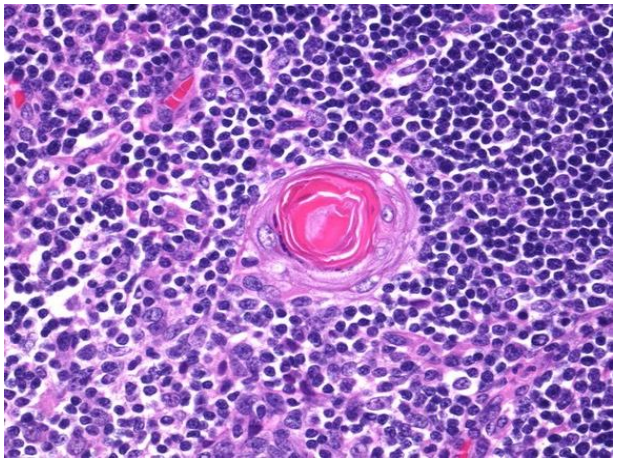


Figure 2. Histological structure of a thymic lobule, medullary region, and Hassall's corpuscle. Staining method: H&E (hematoxylin and eosin). Ocular: 10×40.

As a result, blood flows into the postcapillary venules and then into the veins of the medulla at the corticomedullary junction [2]. The structure of the microcirculatory bed in the mouse thymus was described by Kato [16]. It is believed that prothymocytes enter the thymic parenchyma through large venules in the corticomedullary region and return to the circulation via postcapillary venules. Phenotypically mature T lymphocytes expressing the Mel-14 marker accumulate in the perivascular spaces of these vessels. This marker is a receptor involved in lymphocyte migration through lymphatic vessels [18]. The efferent lymphatic vessels drain into nearby paired lymph nodes. There are no afferent lymphatics in the thymus. The rodent thymus possesses strong noradrenergic innervation, and some authors have also demonstrated a partial cholinergic component [5]. Nerve fibers accompany blood vessels within the capsule and interlobular septa. Their highest concentration is observed in the corticomedullary region.

Histology. Among all lymphoid organs, the thymus is considered the most unique and structurally diverse histologically [11]. It contains both lymphoid and epithelial components simultaneously, which makes it distinctive among immune defense organs. The epithelial cells form a structural framework containing mainly T lymphocytes, as well as small numbers of B lymphocytes, plasma cells, and other cell types (e.g., neuroendocrine cells). Morphologically, a thymic lobule consists of cortex and medulla separated by a vascular-rich corticomedullary zone.

Epithelial Stroma. Most of the supporting structure of the thymus is formed by a network of epithelioreticulocytes [2]. In the subcapsular zone of the cortex, epithelial cells form 1–2 deep layers. Epithelioreticulocytes differ in shape, location, and function. For example, flattened cells located in the outer cortical zone form the blood–thymus barrier. Stellate epithelioreticulocytes are widely distributed throughout the thymic parenchyma. Epithelial cells are divided into several types based on antigen expression, ultrastructure, and their ability to synthesize thymic hormones (thymulin, thymosin, thymopoietin, and thymic humoral factor) [5]. Immunohistochemically, four types of epithelioreticulocytes are distinguished: subcapsular cortical, true cortical, medullary epithelioreticulocytes, and Hassall's corpuscles. The main antigenic determinants of human thymic epithelioreticulocytes have been identified [22]. Detailed information about their immunohistochemical markers is provided in the works of Greaves, Kuper et al., and Suster and Rosai [10, 17, 22].

Capsule. Each lobe of the thymus is surrounded by a thin connective tissue capsule that sends septa into the organ parenchyma, dividing it into lobules of various sizes and shapes. The capsule consists of outer and inner layers of collagen and reticular fibers, between which occasional single lymphocytes may be found. The inner layer penetrates into the parenchyma, forming septa. Distinct trabeculae often extend from the capsule toward the center of the lobules. Special staining methods reveal a small amount of connective tissue in the capsule, trabeculae, and perivascular spaces; however, unlike other lymphoid organs, the stromal connective tissue component in the thymus is minimal. As noted above, the principal supporting structure of the thymic parenchyma is the epithelioreticulocyte network. In the subcapsular zone of the cortex, areas lacking epithelioreticular stroma—called "windows"—are identified [7, 8].

Cortex. Histologically, the thymic cortex stains darker and consists of densely packed immature lymphocytes at various stages of differentiation. Among them are relatively pale and fewer epithelioreticulocytes and a minor population of bone marrow–derived phagocytic macrophages (Fig. 9). Large mitotically active lymphoblasts are found in the subcapsular zone; they have round or oval nuclei and basophilic cytoplasm. Moving from the subcapsular zone toward the corticomedullary junction, smaller cells with reduced mitotic activity become more numerous. Rapidly dividing, short-lived lymphocytes are located in the subcapsular and cortical regions, and their cell cycle ends in apoptosis. Therefore, the presence of apoptotic bodies in this area is considered physiological. These structures are phagocytosed by macrophages and are visible within their cytoplasm ("tingible-body macrophages") (Fig. 2).

Corticomedullary Zone. This zone is characterized by numerous blood vessels, mainly arterioles; perivascular connective tissue is poorly developed. Both mature and maturing T lymphocytes are located here. Dendritic cells and a certain number of B lymphocytes and plasma cells are also present, and their number increases with age.

Medulla. Common to all lobules, the medulla extends from one lobule to another and may occasionally border the capsule (Fig. 3) [11]. It stains lighter than the cortex and contains fewer cells overall, but a higher proportion of mature T lymphocytes. Epithelioreticulocytes, Hassall's corpuscles, macrophages, non-phagocytic bone marrow–derived dendritic cells, B lymphocytes, and a small number of myoid cells are well distinguished (Fig. 4). T lymphocytes in the medulla are larger and stain paler than those in the cortex. Hassall's corpuscles are less common in rodents than in humans and primates. In mice, they are small and often detectable only by immunohistochemical methods. They react with antibodies against high molecular weight keratin (AE2), a marker of fully differentiated epithelial cells, but do not react with antibodies against other thymic epithelial markers. Cells of thymic corpuscles are large and polygonal, staining pale. Sometimes granules are present in their cytoplasm; it may be vacuolated and show dystrophic calcification. In rats, these cells form concentric layers around cellular debris or organized keratin (Fig. 3). In mice, these structures are poorly developed and do not form central keratin accumulations. Myoid cells are rare in the medulla of both humans and rodents [22]. Ultrastructurally and immunohistochemically, they exhibit features of striated muscle tissue and stain positively for desmin and myosin. Their histogenesis is not fully clarified, though some researchers suggest a common origin with epithelioreticulocytes. A small number of neuroendocrine cells are also found in the medulla. Their physiological function is unclear, but they may serve as a source of malignant tumors. Small populations of basophils and eosinophils are also present.

Cortex–Medulla Ratio. The ratio between cortical and medullary areas in thymic lobules can be easily assessed at low and medium magnification and is widely used in comprehensive histopathological evaluation of the thymus [7]. Since this ratio may vary depending on organ orientation during sectioning, standardized orientation is recommended (Fig. 3). Tryphonas et al. performed morphometric studies of histological sections of the thymus in intact Sprague–Dawley rats [19]. According to their data, the mean cortical–medullary ratio ranged from 4.4–4.7 in 30- and 90-day-old male rats and from 3.9–6.3 in 30- and 60-day-old female rats.

Electron Microscopy. Electron microscopy shows that epithelioreticulocytes possess long cytoplasmic processes, are connected to adjacent cells via desmosomes, and are covered by a basal membrane. Medullary epithelioreticulocytes are oval and large, with short cytoplasmic processes and numerous secretory organelles. The features of the thymic microcirculatory system in mice were described in detail by Kato [16].

Functions. The thymus is a primary lymphoid organ in which T-lymphocyte precursors originating from the bone marrow develop and differentiate within the thymic microenvironment. This process results in the formation of a fully functional immunocompetent cell population. Comprehensive reviews of immune system function have been provided by Abbas, Brown et al., as well as Tizard, Lebish et al. [1, 4, 15, 23]. Prothymocytes migrate from the red bone marrow to the thymus through the microcirculatory system of the corticomedullary zone and undergo a four-stage maturation process while moving from the subcapsular zone through the cortex toward the medulla. Finally, they return to the bloodstream as mature T lymphocytes. During intrathymic migration, developing T cells (thymocytes) undergo proliferation and differentiation, reflected by changes in cell size and expression of various antigen and interleukin receptors [18]. Phenotypic changes are associated with rearrangement of the T-cell receptor (TCR) gene, which is necessary for

immunological competence. This issue has been thoroughly studied by Perryman [20]. Intermediate stages of thymocyte maturation are characterized by immunological phenotype, assessed according to expression of the TCR-CD3 complex and its coreceptors CD4 and CD8 [13]. Thymocytes transition from a “double-negative” (CD4–/CD8–) phenotype to an intermediate “double-positive” (CD4+/CD8+) phenotype, characteristic of most cortical thymocytes. Successful interaction between TCR and major histocompatibility complex (MHC) class I molecules leads to the development of T-killer (cytotoxic T lymphocytes) or T-suppressor (CD4–/CD8+) cells. Interaction between TCR and MHC class II molecules stimulates the development of T-helper (CD4+/CD8–) cells. These single-positive mature phenotypes are mainly found in the medulla [5].

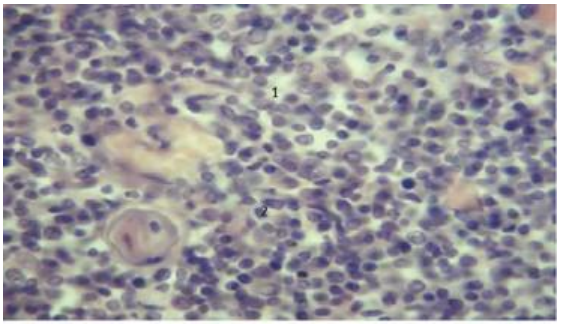


Figure 3. Medulla of the thymus (1). Epithelial cells (2), reticular cells. Objective 40×, ocular 20×.

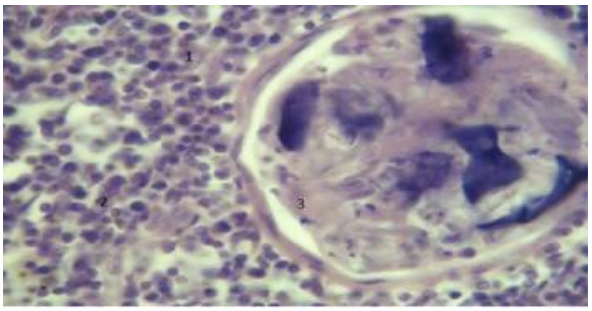


Figure 4. Medullary layer of the thymus (1). Epithelial and reticular cells (2). Scattered macrophages and Hassall’s corpuscles (3). Objective 40×, ocular 20×.

The thymus regulates the release of T-lymphocytes into the bloodstream through positive and negative selection. Positive selection involves MHC restriction and permits only those cells that recognize the body’s own MHC class I and II molecules to undergo clonal differentiation. In this process, thymic “nurse” cells expressing MHC I and II play an important role. During negative selection, developing T cells bearing receptors for self-antigens (autoreactive cells) undergo apoptosis, eliminating potentially dangerous clones. Therefore, the number of lymphocytes in the cortical substance is significantly higher than the number of cells that migrate to the medulla and subsequently enter the general circulation. The presence of apoptotic bodies and abnormal macrophages known as “tingible-body macrophages,” especially in young animals, is considered a normal histological feature of the thymic cortex. However, an excessive number of apoptotic bodies in the thymus may be interpreted as a disruption of positive selection [5]. Epithelial-free areas (“windows”). These zones contain solitary macrophages and lymphocytes with high mitotic activity (Fig. 4). It is assumed that these “windows” represent a specific pathway for thymocyte migration without direct contact with stromal elements responsible for selection [8]. Thus, cortical and medullary epithelial reticular cells, macrophages, and dendritic cells participate in the processes of thymocyte development and differentiation. Epithelial reticular cells play a crucial role in both positive and negative selection; they synthesize MHC class I molecules and, depending on their localization within the thymic parenchyma, strictly differentiated MHC class II molecules. “Nurse” cells are located in the subcapsular zone and form close intercellular contacts with numerous developing lymphocytes [4]. These cells are important in the early stages of thymocyte differentiation. Subcapsular and medullary epithelial reticular cells synthesize several thymic hormones. For example, thymosin stimulates thymocyte development at later stages; thymopoietin, thymic humoral factor, and serum thymic factor are important in

regulating lymphocyte reactivity [2]. Dendritic cells perform antigen-presenting functions (via MHC I and II) and are considered more effective than epithelial reticular cells in the process of negative selection. Genetically modified animals. The symbiotic relationship between the thymic microenvironment and developing T-lymphocytes is widely recognized. Various experimental mouse models have been developed to demonstrate the role of the microenvironment in positive and negative thymocyte selection, as well as the potential influence of T cells on it [5, 24]. SCID mice. Severe Combined Immunodeficiency Syndrome (SCID) is a genetic disorder characterized by impaired development of T- and B-lymphocytes. A critical stage in T-lymphocyte differentiation is the rearrangement and expression of genes encoding antigen-specific T-cell receptors (as well as surface immunoglobulin receptors of B-lymphocytes). Failure of complete rearrangement of these genes leads to the elimination of lymphocyte precursors and to the near absence of mature, functionally active cell forms. In mice, this process depends on DNA-dependent protein kinase. Deficiency of this enzyme results in a spontaneous autosomal recessive mutation in C.B-17 mice of the BALB/c strain. Animals homozygous for this allele almost completely lack functional T- and B-lymphocytes. In such mice, the thymus is often difficult to detect. Van Ewijk demonstrated that in mice with this syndrome the thymic microenvironment is also impaired [23]. In these animals, stromal elements exhibit a cortical phenotype, whereas medullary epithelial reticular cells are almost absent. Histologically, the thymus consists of small dysplastic lobules containing very few lymphocytes (Fig. 4). In some mice (“leaky SCIDs”), partial restoration of T-lymphocyte differentiation occurs over time, accompanied by focal reorganization of medullary epithelial reticular cells. In children, SCID most commonly results from mutations in the recombination-activating genes (RAG1 and RAG2) involved in lymphocyte DNA synthesis.

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