Chapter

Introductory Chapter: Thymus - The Central Self-Tolerance System

Amene Saghazadeh and Nima Rezaei

1. Where, when, and why of the thymus

The pharynx is regarded as a part of the digestive system. It is, however, attached to the respiratory system and, thus, is referred to as the conducting zone of the respiratory system as well. The pharyngeal apparatus groups together five pharyngeal arches, four pharyngeal pouches, four pharyngeal clefts, and pharyngeal membranes that occur during 4–5 weeks of human development [1]. Within the developmental context, the thymus is closely related to parathyroid glands [2] since both are derived from the endodermal-lined pharyngeal pouches—the thymus develops from the ventral portion of pouch 3, and the inferior and superior parathyroid glands arise from the dorsal portions of pouches 3 and 4, respectively.

Late in the 4th week, the primordia of the thymus begin to form but remain attached to that of the inferior parathyroid glands for a time [3]. By the 7th week, they migrate to the position where they should reside and be functional—the thymus is located midline in the upper chest just behind the sternum between the lungs and above the heart, and the inferior parathyroid glands descend along the inferior border of the thyroid. However, it takes about 12 weeks to form the definitive structure of the thymus, a bilobed organ that is covered by a mesenchymal capsule and is composed of two internal layers: the cortex and the medulla. The cortex is the outer layer of the thymus in which cortical thymic epithelial cells (cTECs) are found. The medulla is located in the center of the thymus. It is where medullary thymic epithelial cells (mTECs) and Hassall's (thymic) corpuscles are present.

The thymus is seen as of high value, due to its functions as a part of the neuroendocrine system in addition to its actions to provide a primary lymphoid microenvironment that efficiently carries T cell differentiation and selection. The first evidence that the thymus can have immune and endocrine functions was provided from athymic nude animals and/or animals undergoing thymectomy showing impairments in their cell-mediated immunity, growth pattern, and puberty and developing organ-specific autoimmune diseases. These impairments were consistent with their relative reduction in levels of thyroxin, testosterone, progesterone, and 17-β-estradiol, whereas corticosterone levels were elevated. Of particular note was that the passive transfer of lymphocytes and thymus implantation at birth were effective in transferring cell-mediated immunity to nude mice [4]. The endocrine defects could be, in part, healed by thymus implantation at birth as well but remain stable following passive transfer of lymphoid cells [4].

2. How does the thymus teach T lymphocytes self-tolerance?

2.1 Immunological tolerance

To keep the body healthy, the immune system is expected to entail invading pathogens while avoiding reactivity to self-tissues. This so-called immunological tolerance engages both central and peripheral modes of action (for review, see [5]).

2.1.1 Central tolerance

It is referred to immature B and T cells when they are present in the primary lymphoid organs—B cells in the bone marrow and T cells in the thymus. Mechanisms of central tolerance are, for example, clonal deletion and elimination of self-reactive cells.

2.1.2 Peripheral tolerance

This one is for mature B and T cells as detached from the primary lymphoid organs into the bloodstream, lymph, and secondary lymphoid organs such as spleen and lymph nodes. There are various mechanisms that can promote tolerance in the periphery, including clonal deletion, clonal anergy, clonal ignorance, deviation, helplessness, and suppression.

2.2 Thymopoiesis: the result of cross-talk between thymic stromal cells and precursor T cells

T cell progenitors that lack both CD4 and CD8 receptors are termed as double-negative (DN) cells. These cells separate from the bone marrow, enter the thymus through the large venules located at the corticomedullary junction (CMJ), and settle into the cortex of the thymus. In the thymic cortex, the rearrangement at T cell receptor (TCR) α and β genes makes the cells turn into double-positive (DP) stage, when cells express both CD4 and CD8. Then, a positive selection process directs DP cells into either CD4+ or CD8+ T cells depending on their affinity for either major histocompatibility complex (MHC) protein class II or I, respectively. The thymus selects single-positive (SP) immunocompetent T cells to export them out of the thymus. In the periphery, these naïve self-restricted T cells eventually home to secondary lymphoid organs. To bear the name of its creators, i.e., thymocytes, this process of manufacturing mature functional T cells is generally recognized as thymopoiesis.

2.3 Thymic mechanisms of central self-tolerance

2.3.1 Positive selection takes place in the thymic cortex

The positive selection is defined as a process through which SP T cells expressing either CD4 or CD8 are selected. The thymic cortex carries gene rearrangements that make precursor T cells co-express CD4 and CD8. These DP T cells are then engaged by a ligand bound to an MHC class II or I molecule that is present on cTECs and will be differentiated into SP T cells that express either CD4 or CD8, correspondingly [6].

2.3.2 Negative selection takes place in the thymic medulla

The negative selection is simply a process by which autoreactive T cells are removed. After positive selection is done, the transfer of SP T cells from the cortex to the medulla occurs. The expression of chemokine receptor CCR7 by T cells is

essential to the transfer process—since antigen-presenting cells (APCs) including mTECs and dendritic cells in the medulla express CCR7 ligands, e.g., CCL19 and CCL21. In this manner, SP T cells can engage in interaction with medullary APCs that present a variety of tissue-restricted antigens (TRAs). Medullary APCs are responsible for finding autoreactive T cells that recognize self-antigen—MHC complexes and their removal. Such selection would permit SP T cells that are not reactive to self to shift from the thymus to the periphery [6].

2.3.3 Agonist selection takes place in the thymic medulla

The agonist selection is also undertaken by the thymic medulla to allow a portion of autoreactive CD4+ T cells to differentiate into regulatory T (Treg) cells that express forkhead box P3 (Foxp3). These regulatory T cells that are derived from the thymus are referred to as tTreg cells and move from the thymus to the peripheral tissues. They constitute the majority of all Treg cells and play the central role in immune tolerance. So, the thymus must be precisely effective in the generation of Treg cells. If this could not be achieved, then we see the process of autoimmunity. However, there are Treg cells derived from peripheral tissues referred to as pTreg cells. This type of Treg cells is especially accumulated at sites of inflammation and consequently regulates inflammatory responses [6].

3. If peace is in the hands of the thymus, then what would happen if that does not work?

The thymus-mediated effects including the production of neuropeptides and also development of T cell repertoire are what may be called the function of the pacemaker [7]. However, the thymus is vulnerable to be exposed to both acute and chronic injuries. A variety of pathological conditions that range from infections and immunodeficiency to inflammatory and autoimmune disorders and tumors may cause the thymus to turn into malfunctioning or functionless. In a broader sense, the thymus undergoes physiological changes that occur with age and during pregnancy. Below is to represent dysregulation of immune homeostasis as the inevitable consequence of a failure in central self-tolerance system, i.e., the thymus.

3.1 The effects of thymic infection on thymopoiesis

3.1.1 The thymus gets sick

The thymus is not immune-privileged, but rather invading pathogens can adversely affect its structure and/or function, thymopoiesis, through indirect (systemic) and direct (local) ways. Pathogens that are able to penetrate into the different thymic location(s), e.g., cortex, CMJ, or medulla, and thereby directly infect thymic cells, include a number of viruses (human immunodeficiency virus, *Simian immunodeficiency virus*, influenza virus, lymphocytic choriomeningitis virus, *Murine leukemia virus*, mouse hepatitis virus, human cytomegalovirus, measles virus, coxsackievirus, Epstein-Barr virus, Junin virus, and poliovirus), bacteria (*Mycobacterium avium*, *Mycobacterium tuberculosis*, *Francisella tularensis*, and *Salmonella enterica*), fungi (*Paracoccidioides brasiliensis* and *Cryptococcus neoformans*), and parasites (*Trypanosoma cruzi*, *Plasmodium berghei*, and *Toxoplasma gondii*). In addition, pathogens can act indirectly by altering the systemic expression of glucocorticoids, cytokines, chemokines, and antigens. Then, these soluble factors can reach the village of the thymus and readily result in changes of its microenvironment [8].

Without regard to the nature of its invading pathogens, the infected thymus may encounter atrophy and architectural changes. The infected thymus is consequently liable to induce apoptosis, pathogen-specific immune responses, T cells that are tolerant to pathogens, and self-reactive T cells [8].

3.1.2 The thymus can cope with infection

Less is understood for mechanisms of thymic escape from infection and/or survival after being infected. However, it is suggested that the thymus may be affected by seeding of cells from other peripheral sites of infection. Therefore, elimination of infection from other peripheral sites might help in the prevention of seeding and development of infection in the thymus. When it gets infected, there is evidence on the presence of antigen-specific CD4+ or CD8+ T cells of other peripheral organs. This would imply that the thymus might in time profit from responses mediated by effector T cells that recirculate between peripheral tissues [8].

3.2 The role of thymic involution in the aging immune system

3.2.1 The thymus gets old

Older individuals have higher rates of diseases, e.g., infections, malignancies, and autoimmune diseases, demonstrate lower responsiveness to vaccines, and are less capable of immune restoration following chemotherapy, radiotherapy, and infections. This is plainly a reflection of the aging immune system, referred to as immune senescence, related to increased mortality and morbidity in the aged population. The immune cells mostly affected by aging are naïve T cells [9]. Yet the number of memory cells is proportionally increased. The process of T cell-mediated immunity becoming deteriorated gradually occurs, and both extrinsic and intrinsic factors may play a role [10].

Rather than being influenced by bone marrow aging, age-related deterioration of T cell-mediated immunity is influenced by the thymic involution. Both are, however, seated to serve as co-directors of this process. When the thymus undergoes aging, its architecture does not remain well defined. Cellular changes associated with thymic involution include reduction in the number of thymic epithelial cells and thymocytes in contrast to an increase in perivascular spaces and adipose tissue. Aging will affect the bone marrow in parallel to the thymus, making the quantity and quality of progenitor T cells that migrate from the bone marrow to the thymus go down. When "progenitor T cells" are not inputted to the "thymus" machine, then the output "naïve T cells" would not be logic anymore. In this manner, aging causes a decline in naïve T cells exported from the thymus to the periphery, and consequently memory T cells will predominate in the periphery.

3.2.2 The thymus has the ability to sustain life

Thymic involution is characterized by a continuous flow from the first year of life that gets pronounced at puberty and during pregnancy. After puberty, the thymus gradually decreases in size, weight, and cellularity as we age, and by the seventh decade of life, the thymic epithelial space drops to less than 10 percent of total tissue. This fact that the thymus feels old when the levels of sex steroids and hormones rise [9] provides, as a result, a role for sex steroids in the aging of the thymus. It also will open our eyes to see sex steroid ablation as a potential means of regenerating the thymus and consequently reversing immune senescence. There is reasonable evidence to believe that the prevention and/or reversal of thymic

function associated with aging is possible with sex steroid ablation using surgical and pharmaceutical approaches [11].

Thymopoiesis is an active complex process. Growth-stimulating factors, such as hematopoietic cytokines (interleukin-1, interleukin-3, interleukin-6, interleukin-7, interleukin-21, and interleukin-22, stem cell factor, and FMS-like tyrosine kinase 3 ligand), growth factors (transforming growth factor beta, oncostatin M, keratinocyte growth factor, bone morphogenetic protein 4, leukemia inhibitory factor), and hormones (growth hormone, insulin growth factor 1, and ghrelin), are, thus, needed to facilitate the cooperation between the two parties, i.e., thymocytes and T cells, involved in thymopoiesis. There are reports that the age-associated defects in the immune function and/or structure of the thymus could be returned by the administration of these factors (for review, see [11–13]). In particular, interleukin-21 has provided the most interesting results, as explained in preclinical studies [12].

Similarly, bioengineering thymus organoids [14], thymus transplantation, and cell-based therapies have been effective in immune reconstitution and establishing immune tolerance to allografts.

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