

The Thymus Gland: From Immune Education to Clinical Disorders and Future Regeneration

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Abstract—The thymus gland, once considered vestigial, is now recognized as the central organ of T-cell development and immune tolerance. It educates T lymphocytes through positive and negative selection, thereby shaping the immune repertoire and preventing autoimmunity. Despite its crucial role in early life, the thymus undergoes progressive involution with age, leading to immune senescence, susceptibility to infections, malignancies, and reduced vaccine responses. Thymic pathology is clinically significant, encompassing autoimmune diseases such as myasthenia gravis, congenital immunodeficiencies like DiGeorge syndrome, and thymic tumors including thymomas and carcinomas. Recent advances in regenerative medicine—spanning cytokine therapy, stem cell approaches, and thymic bioengineering—offer hope for reversing thymic decline and restoring immune competence. This article reviews the thymus from anatomy and physiology to clinical disorders and emerging regenerative strategies, highlighting its pivotal role in bridging immunology, clinical medicine, and future therapeutic innovation.

Index Terms—Thymus gland; T lymphocytes; Immune tolerance; Thymic involution; Autoimmunity; Myasthenia gravis; Thymic tumors; DiGeorge syndrome; Immunosenescence; Thymic regeneration; Stem cell therapy; Bioengineered thymus.

I. INTRODUCTION

The thymus gland, a primary lymphoid organ situated in the anterior mediastinum, plays a central role in the development and education of T lymphocytes. Once regarded as vestigial, it is now recognized as the 'school of immunity,' responsible for establishing central tolerance and preventing autoimmunity (1–5). Despite its vital role in early life, the thymus undergoes progressive involution with age, contributing to immune senescence, susceptibility to infections, and malignancies (6–9). Understanding the physiology, pathology, and regenerative potential of

the thymus bridges basic immunology with clinical medicine and novel therapeutic frontiers.

II. PHYSIOLOGY OF THE THYMUS

The thymus originates from the third pharyngeal pouch and is composed of cortical and medullary compartments that coordinate T-cell development (2,3). Immature thymocytes migrate from the bone marrow and undergo positive and negative selection, ensuring the survival of T cells capable of recognizing self-MHC while eliminating autoreactive clones (4,5,28). Thymic epithelial cells, dendritic cells, and the autoimmune regulator (AIRE) gene play critical roles in central tolerance (29). In addition, thymic hormones such as thymosin, thymopoietin, and thymulin modulate immune maturation (15,16).

III. THYMIC INVOLUTION AND AGING

After puberty, the thymus gradually involutes, replaced by adipose tissue, though residual function persists throughout life (6,14,17). Thymic shrinkage is associated with decreased naïve T-cell output, reduced T-cell receptor diversity, and impaired vaccine responses in the elderly (8–13). This process, termed immunosenescence, contributes to infections, autoimmune phenomena, and cancer risk in aging populations (9,10,13). Hormones such as ghrelin, growth hormone, and fibroblast growth factor 21 have been shown to partially reverse thymic involution, offering therapeutic promise (15,16,18).

IV. THYMIC INJURY

The thymus is very much sensitive to various factors such as stress, acute infection, glucocorticoids,

cytoreductive therapies, and in chronic such as aging are most common

Acute Injury

Glucocorticoid is widely used. The thymus is an immune organ plays a significant role in the immune response during acute infection; however, the thymus is also a target of multiple pathogens. These pathogens usually enter the thymus through blood circulation, disrupting the thymic structure and altering the T-cell character. Studies showed that acute viral infections, including influenza virus and Epstein-Barr virus, not only affect the thymus microenvironments and cause thymic atrophy but also interference with thymocyte development and increased apoptosis of thymocyte subsequently leading to acute thymic injury

Chronic injury

Aging

Immune system functionality declines significantly with age, increasing susceptibility to infections and other chronic inflammatory disorders. Age-related involution is characterized mainly by progressive regression of thymic size and structure, resulting in impaired thymopoiesis, T cell characteristics ineffective central tolerance, and accumulation of senescent memory T cells, consequentially leading to innate immune cell-induced chronic inflammation. Generally, aging also affects various stages of T cell development, from age-related factors changes in key signaling molecules that modulate thymopoiesis, reduction of T cell differentiation activity, to the subsequent decline in T cell output and immune function.

V. CLINICAL DISORDERS OF THE THYMUS

Defective negative selection within the thymus can lead to autoimmunity. Myasthenia gravis, an autoimmune disorder of the neuromuscular junction, is strongly associated with thymic abnormalities including hyperplasia and thymoma (21,22). Thymomas and thymic carcinomas, though rare, are the most common tumors of the anterior mediastinum. They are frequently associated with paraneoplastic syndromes such as myasthenia gravis, pure red cell aplasia, and hypogammaglobulinemia (21,23,24). The 2021 WHO classification has refined the histopathological criteria for thymic epithelial tumors, aiding diagnosis and management (21). Congenital

thymic aplasia or hypoplasia, as seen in DiGeorge syndrome, results in profound T-cell deficiency and severe immunodeficiency (25,26). Thymus transplantation has emerged as a life-saving intervention for complete DiGeorge anomaly (26).

VI. ADVANCES IN THYMIC REGENERATION

Recent research focuses on reversing thymic involution and engineering functional thymic tissue. Approaches include cytokine therapy (IL-7, IL-22), stem cell transplantation, and bioengineered thymic organoids (18,19,20,30). These strategies hold potential for rejuvenating immunity in the elderly, restoring T-cell function after chemotherapy or bone marrow transplantation, and preventing age-related diseases.

VII. CONCLUSION

The thymus gland is more than an embryological relic; it is the foundation of adaptive immunity and self-tolerance. Its decline with age links directly to immune senescence, while its dysfunction manifests in autoimmunity, immunodeficiency, and neoplasia. Ongoing advances in thymic regeneration and bioengineering suggest that restoring thymic function may transform approaches to aging, vaccination, and autoimmune disease therapy. The story of the thymus highlights the intersection of basic science, clinical relevance, and regenerative medicine—a journey from immune education to therapeutic innovation.