# Thymus Gland

Subjects: Infectious Diseases | Medicine, General & Internal

Contributor: Ebtesam Al-Suhaimi

The thymus gland is the chief lymphoid organ that regulates the functions of the immune and endocrine systems by controlling the levels of hormones and cytokines. The thymus gland protects against various internal and external stresses through immunoregulatory properties, nerve systems, and endocrine pathways. The thymus gland controls cell proliferation, apoptosis, hormones, and neuropeptides, as well as regulating intrathymic T cell differentiation and production of a repertoire of the T cell.

Thymus Hassall interleukin antibody hormone coronavirus COVID- 19

## 1. Introduction

The coronavirus family was first identified in the late of 1960s [1]. In the decades since, the world has experienced many lethal episodes of the coronavirus family. Coronavirus diseases were noted with mild or severe infections in the respiratory tract [2]. In 2002, severe acute respiratory syndrome coronavirus (SARS-CoV) emerged and infected many populations worldwide [3]. In 2012, the Middle East respiratory syndrome (MERS-CoV) outbreak infected Middle Eastern countries, with symptoms of chronic respiratory syndrome [4]. In 2019, SARS-CoV-2 was identified in Wuhan, China, which affected a total of 30,524,214 people with a mortality of 952,240 at the time of drafting this paper. SARS-CoV, MERS-CoV, and SARS-CoV-2 involve serious respiratory tract infections followed by fever, cough, dyspnea, and fatigue [5].

The thymus gland is the chief lymphoid organ that regulates the functions of the immune and some endocrine systems by controlling the levels of their hormones as well as cytokines. The thymus gland protects against various internal and external stresses through immunoregulatory properties, nerve systems, and some endocrine pathways. The thymus gland controls cell proliferation, apoptosis, hormones, and neuropeptides, as well as regulating intrathymic T cell differentiation and production of a repertoire of the T cell. The thymus is located in front of the heart behind the sternum. It has two identical thymic lobes on each side, made up of the cortex and the central medulla, surrounded by an outer capsule [6]. The thymus gland is most actively functioning in fetal and neonatal life and starts shrinking in tissue mass and is replaced with fat during thymic involution [7]. In 1961, Jacques Miller discovered the immunoregulatory role of the thymus in newborn mice by studying involvement in a lymphocyte population [8].

The reason for children being less exposed to SARS-CoV-2 could be attributed to the significant capacity of children for maintaining the availability of rare T cell clonotypes that originate in the thymus and the variety of the T cell populations, which supposes a causative connection in the rising tendency of infection with age [9][10]. This clonotype is rare if it is not utilized, which leads to less proliferation and postpones presenting viral antigens to SARS-CoV-2-specific T cells, permitting more effects of virus damage and breakout. This late activation of the adaptive power in the immune system appears as lymphopenia in lack of effective virus-specific clonal growth specific to epitopes of the virus presented by the lymphatic nodes. It was suggested by Rousseau et al. (2020) [9] that stimulating the same approach will help in reducing the severity of this virus. Thymic hormones such as thymosin-α-1-Fc (TA-1) have been shown to increase the naive CD8 and CD4 cells that have recombined in the blood and stimulate thymopoiesis, then TA-1 adjusts a hyperinflammatory response via dendritic cells (DCs) for immunosuppressing and activating natural killer (NK) cell function. The absence of type 1 interferon (IFN) in alveolar cells and the presence of a lymphopenia response in SARS-CoV-2 diseases propose that incorporation of αβ-IFN and TA-1 may present the synergistic action to attract the adaptive immunity that helps significantly in a much-needed response.

The immune system is generally classified into innate immunity which provides the first line of defense against different stimuli, such as antigens and chemical, biochemical, physiological, and physical stresses. Cellular innate immunity mediates their actions through macrophages, granulocytes, NK cells, and DCs, either by engulfing the antigens in a process called phagocytosis or by acting as antigen-presenting cells to expose the antigens to the cells of the acquired immunity, which is a more specific type of immunity. B lymphocytes and T lymphocytes are interrelated cellular counterparts of the acquired immune system, expressed as surface receptors that recognize specific antigens and have the potential for long-term immunological memory. Lymphocytes are generated in the bone marrow, where only B lymphocytes mature and are exported to the periphery. However, T lymphocytes, as hematopoietic precursors, migrate to the thymus to grow, develop, and differentiate [11].

The thymus offers specialized conditions for developing various functional and self-tolerant T cells. Once in the thymus, precursor cells enter the subcapsular cortical region, undergoing several developmental stages to become thymocytes. In the differentiation process, thymocytes move from the cortex area to the medulla for negative and positive thymic selection [12]. Thymocytes interact with the thymic epithelial cells and trigger their differentiation into mature clusters of differentiation 4 (CD4+) and CD8+. Cytotoxic T lymphocytes (CTLs) undergo a process known as the positive selection, where thymocytes recognize and bind to self-peptides of the major histocompatibility complex (MHC). This process determines whether the T lymphocyte is CD4+ (helper) or CD8+ (cytotoxic/killer), depending on bonding to the type of MHC (class I or class II). When self-reactive thymocytes fail to recognize self-antigens and strongly bind to the self-peptide MHC, they undergo negative selection and are eliminated by the process of apoptosis [11]. The naive T lymphocytes disembark the thymus into the secondary lymphoid organs such as lymph nodes, where they are activated by foreign peptides of MHC that are found on the surfaces of the antigen-presenting cells (APCs). This type of activation results in the proliferation and differentiation of effector T lymphocytes into four types that can produce cytokines and respond to different pathogens. The thymus gland also secretes the thymosin hormone, which has a functional role in T lymphocyte differentiation and maturation to mediate immunological response [13]. T lymphocytes are the most fundamental components of cellular immunity. Besides humoral immunity, they also have featured roles as a complementary component to innate immunity, which cannot efficiently defend against all pathogens.

Some immunodeficiency viral diseases such as thymic lymphoid hyperplasia (thymitis), loss of Hassall's corpuscles, and dysinvolution have been associated with the malfunctioning of thymus or viral infections of Hassall's corpuscles [14]. Hassall's corpuscles were also found to be severely damaged upon infection with herpes simplex virus pneumonia and ependymoma [15]. SARS-CoV induces immune-mediated lymphocyte damage, bone marrow or thymus suppression, or cell programming death [16]. The SARS-CoV-2 infection causes lymphopenia in peripheral circulation, which is counterbalanced by the thymus to enhance lymphocyte recirculation between peripheral blood and SARS-specific IgG immunoglobulins release, with no elevation in the levels of interleukin (IL) 8 and tumor necrosis factor (TNF-α) [16][17]. The aim of the current study is to support the notion that a defect in thymic tolerogenic function is implicated as an essential factor in the pathophysiology of autoimmunity and virus-related diseases, including COVID-19. This piece of work underpins the reported literature on the physiology of the thymus and the biological role of different thymic hormones with regard to the modulation of inflammatory responses and involvement in the maturation and differentiation of immune cells, as well as advocating the clinical and biological application in the treatment of inflammatory disorders, including viral diseases.

## 2. Cellular Immunity and Role of T Lymphocytes

There is compelling evidence that the thymus is responsible for the development and differentiation of T lymphocytes. T lymphocytes mediate cellular immunity, providing a defense mechanism against intracellular microorganisms either through the direct killing of the cells that host microorganisms in their cytoplasm or the activation of other immune cells to destroy ingested microorganisms by the process of phagocytosis and productions of antibodies against specific antigens [18][19]. It has been reported that short chains of peptides that bind to MHC-I molecules are derived from degraded intracellular cytosolic proteins of microorganisms, including virus-mediated infections. On the other hand, peptides that bind to MHC-II molecules are derived from extracellular proteins of infectious agents [20]. The CD4+ T lymphocytes recognize antigens presented by

MHC-II molecules, readily expressed on DCs, macrophages, and B lymphocytes [20]. Consequently, CD4+ T lymphocytes are activated and differentiated into one of several subsets of effector T helper (Th) lymphocytes, including, Th1, Th2, Th9, Th17, and Th22, which regulate the immune responses by secreting cytokines [21]. Th2 lymphocytes also regulate the production of antibodies from B lymphocytes by secreting ILs such as IL-3, IL-4, and IL-5 and differentiation to antibody-secreting plasma cells [22]. Th17 has been reported to prevent mucosal respiratory viral infections in the lungs through recruiting macrophages and neutrophils, which ultimately clears pathogens, mediating inflammation, and maintaining tissue integrity [23]. Th17 lymphocytes have suppressed the detrimental tissue inflammations in viral infections. The exact underlying defensive mechanism of Th17 lymphocytes remains to be elucidated because lymphocytes-associated viral lung pathologies have been reported previously [24].

It is well known that inflammation is a central player in the pathogenesis of SARS-CoV pneumonia and edema [25]. Moreover, Th1 lymphocytes are responsible for the proliferation and differentiation of cytotoxic CD8+ T lymphocytes and other cells in response to intracellular pathogens, as well as latent viral infections and tumors, which are all weak innate immune response inducers. Various cytokines such as IL-2, IL-12, IL-15, and IL-21 are involved in CD8+ T lymphocyte differentiation and the generation of effector and memory lymphocytes. CD4+ Th lymphocytes promote CD8+ T lymphocyte activation, either directly by cytokine production or indirectly by enhancing the ability of APCs to stimulate the activation process [19]. CTLs recognize the cells presenting MHC-I molecules, which serve as legends to the T-cell receptors (TCRs) on their surfaces, targeting them for destruction. In this process, only antigen-expressing cells are affected and destroyed. CTLs activate macrophages through interferon gamma (IFNγ) production, which can phagocytose microorganisms [26]. The activity of Th lymphocytes and CTLs is regulated by the regulatory T lymphocytes (Treg), known as suppressor T lymphocytes, and a subtype of CD4+ T lymphocyte. Treg lymphocytes account for 5–10% of CD4+ T lymphocytes in the periphery and play an essential role in inhibiting autoimmune and chronic inflammatory diseases. Treg cells also eliminate self-reactive T lymphocytes that have escaped central tolerance (negative thymic selection) by the mechanism of peripheral tolerance [27]. Once a pathogen or a disease-causing agent is identified, naive T lymphocytes proliferate and differentiate into effector T lymphocytes, ultimately targeting and eliminating the foreign invaders. Effector T lymphocytes also serve as memory T lymphocytes, such as stem cell memory T lymphocytes (Tscm), central memory T lymphocytes (Tcm), and effector memory T lymphocytes (Tem), as well as terminal effector T lymphocytes and tissue-resident memory T lymphocytes, which can respond faster and more efficiently in the future against the same infection [28]. Compared with naive T lymphocytes, Tscm cells reveal higher expression levels of C-X-C motif chemokine receptor 3 (CXCR3), apoptosis antigen-1 (APO-1), IL-2 receptor (IL-2Rβ), and leukocyte function-associated antigen-1 (LFA-1). Tem and Tcm cells are differentiated by the function and expression of the C-C chemokine receptor type-7 (CCR7) protein. Tcm cells are occupied in the lymphoid system and have no direct role, while Tem cells are found in the non-organ lymphatic tissue and have a rapid and more significant function than Tcm cells [29].

## 3. Function of Hassall's Corpuscles in Viral Infection

There is compelling evidence that thymic stromal lymphopoietin (TSLP) is a cytokine, which stimulates B lymphocytes development derived from thymic stromal cell line Z210R.1. It has been reported that Hassall's corpuscles' epithelial cells produced TSLP, responsible for the activation of thymic DCs to induce and generate CD4+ CD25+ regulatory T cells within the thymus. In addition, Hassall's corpuscles are accountable for thymocyte development and removal of apoptotic thymocytes inside the thymus [30]. The primary extravillous trophoblast (EVT) expressed the cytokine TSLP and TSLP receptors. Studies have shown that TNF-α and IL-4 or pregnancy-associated hormones lead to a substantial rise in TSLP-mediated primary human EVT propagation and invasion in vitro. TSLP has a crucial role in human EVT invasion and regulation of the placenta in the first trimester of pregnancy [31].

Transforming growth factor alpha (TGF-α) is associated with medullary human thymic epithelial cells (TECs) and thymic Hassall's corpuscles, whereas epidermal growth factor (EGF) receptor was concentrated only in TEC cells through the thymus tissue [32]. Both TGF-α and EGF are crucial regulatory precursors for synthesizing TEC-derived cytokines in the thymus and

act as essential modulators for developing T lymphocyte proliferation in humans [33]. TGFβRII was found to mediate TEC signaling and reduce their improvement in Hassall's corpuscles in mice [34].

Hassall's corpuscles are composed of terminally differentiated medullary TECs with properties of cellular senescence and release inflammatory cytokines and chemokines, such as CXCL5, that employ and activate neutrophils to release IL-23 in the thymic medulla. Thymic plasmacytoid DCs express IL-23 receptors essentially produce IFNγ, which functions in cell maturation [35]. The human thymus expresses antibodies IgG, IgA, IgM, IgD, and IgE, and light chains, in the cells of Hassall's corpuscles. In the thymic medulla, the production of IgG, IgA, and IgM by plasma cells is controlled.

IL-1α/β enhances IgM and recruitment of CD4+ T cells at the site of infection but does not contribute to killing the virus-infected cell [37]. Additionally, CD4+ but not CD8+ Treg cells were suppressed by IL-6, allowing pathogen clearance and host survival in virus-induced infection [38]. In H1N1 influenza, IL-6 levels elevated in severe cases of virally infected patients [39] and activated CD4+ CD8+ thymocytes and a large amount of IFNγ [40]. While IL-32 is a part of a negative feedback loop, inhibiting sIL-6R and upregulating IL-6 is essential for the survival of an influenza A virus infection [35][41]. Few immunodeficiency viral diseases have been linked with the thymus in childhood, including thymic lymphoid hyperplasia (thymitis), loss of Hassall's corpuscles, and dysinvolution [14]. Hassall's corpuscles were found to be altered and damaged in a 4-year-old boy infected with herpes simplex virus pneumonia and ependymoma [15]. Modulation in the size of the thymus has been associated with hyperactivation of dystrophic calcification of Hassall bodies, reflecting the decrease in the number of CD4+ cells in drug-addicted patients [42]. Lymphocytopenia is a noticeable portion of SARS-CoV contagion. It may be immune-mediated lymphocyte damage, bone marrow or thymus suppression, or cell programming death [16]. After a viral infection, lymphopenia is noticed in peripheral circulation [17].

## 4. Role of Thymic Hormones in Viral Infection

The thymus is a lymphoid organ involved in T lymphocyte maturation and differentiation. It is known that TECs can secrete IL-6 and granulocyte-macrophage colony-stimulating factor (GM-CSF) and thymic hormones in circulation, which promote thymocyte differentiation and proliferation and have anti-inflammatory effects. Thymic hormones such as thymopoietin, thymosin alpha 1 (Tα1), and thymuline have a potential role in the differentiation and functions of lymphocytes, thus they may have the potential for T lymphocyte-related diseases. In addition, the thymus mediates neuroendocrine interactions directly affected by pituitary hormones, consequently affecting the neuroendocrine function of the thymus [43]. The active biological thymic peptides have been extracted and purified in a process called Thymosin Fraction V, along with several main peptides such as prothymosin α (ProTα), Tα1, thymosin beta-4 (Tβ4), thymosin beta-10 (Tβ10), and thymuline, for the maturation and differentiation of immature thymocytes [44][45][46]. These peptides are biologically essential and known to activate the immune system through several mechanisms and signaling pathways, including stimulation of T cell differentiation and maturation, activation of NK cells, DCs, and induction of proinflammatory cytokine release [47]. The previous description indicates that thymic hormones can mediate anti-inflammatory effects, and future clinical trials are needed to translate them against inflammatory disorders and viral diseases [48]. In an experimental model of allergic asthma, a dose of DNA nanoparticles, including thymuline plasmids, could protect the lungs from some injurious inflammation and muscular hypertrophy, which recovered respiratory mechanical functions [49]. Mice were treated through intratracheal administration with a dose of thymuline-expressing plasmids administrated with nanoparticles to enable the thymuline to infiltrate the mucus barrier of the respiratory system [50].

The most important member of the thymosin family is Tα1 and its precursor ProTα [48].

Tα1 is highly expressed in the thymus and peripheral tissues and produced through cleavage of ProTα in the thymus, pituitary, and brain [51]. Thymus hormones are targeted to control viral infectious diseases and inflammatory and autoimmune diseases [46][52]. Tα1, Tβ4, and Tβ10 displayed positive immunomodulatory effects by inducing Th lymphocytes (CD4+) and activating cytotoxic T lymphocytes (CD8+), maintaining immune homeostasis in viral infection [53].

## References


1. Principi, N.; Bosis, S.; Esposito, S. Effects of Coronavirus Infections in Children. Emerg. Infect. Dis. 2010, 16, 183–188.
2. Abdul-Rasool, S.; Fielding, B.C. Understanding human coronavirus HCoV-NL63. Open Virol. J. 2010, 4, 76.
3. Meo, S.A.; Alhowikan, A.M.; Al-Khlaiwi, T.; Meo, I.M.; Halepoto, D.M.; Iqbal, M.; Usmani, A.M.; Hajjar, W.; Ahmed, N. Novel coronavirus 2019-nCoV: Prevalence, biological and clinical characteristics comparison with SARS-CoV and MERS-CoV. Eur. Rev. Med. Pharmacol. Sci. 2020, 24, 2012–2019.
4. Prompetchara, E.; Ketloy, C.; Palaga, T. Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. Asian Pac. J. Allergy Immunol. 2020, 38, 1–9.
5. Cao, M.; Zhang, D.; Wang, Y.; Lu, Y.; Zhu, X.; Li, Y.; Xue, H.; Lin, Y.; Zhang, M.; Sun, Y.; et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020, 395, 497–506.
6. Drljača, J.N.; Vejnović, A.-M.T.; Miljković, D.M.; Popović, M.J.; Rakić, D.B.; Sekulić, S.R.; Čapo, I.Đ.; Petković, B.B. Changes in mouse thymus after exposure to tube-restraint stress. Arch. Biol. Sci. 2020, 72, 5–11.
7. Young, B.; O'Dowd, G.; Woodford, P. Wheater's Functional Histology: A Text and Colour Atlas, 6th ed.; Elsevier: Philadelphia, PA, USA, 2013; pp. 204–206. ISBN 9780702047473.
8. Miller, J. The early work on the discovery of the function of the thymus, an interview with Jacques Miller. Cell Death Differ. 2019, 27, 396–401.
9. Rousseau, M.A.; Chindelevitch, L.; An, G.; Hu, L.; Thareja, R.; Stephens, D.; Rish, i. Understanding Thethymus with Applications to Covid-19 Pathophysiology and Susceptibility with Potential Therapeutics. 2020. Available online: https://www.researchgate.net/publication/342882478_UNDERSTANDING_THE_THYMUS_WITH_APPLICATIONS_TO_COV-2_PATHOPHYSIOLOGY_AND_SUSCEPTIBILITY_WITH_POTENTIAL_THERAPEUTICS_A_PREPRINT#fullTextFileCo (accessed on 29 July 2020).
10. Rehman, S.; Majeed, T.; Ansari, M.A.; Ali, U.; Sabit, H.; Al-Suhaimi, E.A. Current scenario of COVID-19 in pediatric age group and physiology of immune and thymus response. Saudi J. Biol. Sci. 2020, 27, 2567–2573.
11. Thapa, P.; Farber, D.L. The Role of the Thymus in the Immune Response. Thorac. Surg. Clin. 2019, 29, 123–131.
12. Naparstek, Y.; Holoshitz, J.; Eisenstein, S.; Reshef, T.; Rappaport, S.; Chemke, J.; Ben-Nun, A.; Cohen, I.R. Effector T lymphocyte line cells migrate to the thymus and persist there. Nature 1982, 300, 262–264.
13. Dembic, Z. The Cytokines of the Immune System: The Role of Cytokines in Disease Related to Immune Response; Academic Press: Cambridge, MA, USA, 2015.
14. Mishalani, S.H.; Lones, M.A.; Said, J.W. Multilocular thymic cyst. A novel thymic lesion associated with human immunodeficiency virus infection. Arch. Pathol. Lab. Med. 1995, 119, 467.
15. Inaba, H.; Rabah, R.; Meert, K.L.; Bhambhani, K. Herpes Simplex Virus Pneumonia in a Patient with Ependymoma. J. Pediatr. Hematol. 2004, 26, 108–111.

16. He, Z.; Zhao, C.; Dong, Q.; Zhuang, H.; Song, S.; Peng, G.; Dwyer, D.E. Effects of severe acute respiratory syndrome (SARS) coronavirus infection on peripheral blood lymphocytes and their subsets. Int. J. Infect. Dis. 2005, 9, 323–330.
17. Da Guan, W.; Mok, C.K.P.; Chen, Z.L.; Feng, L.Q.; Li, Z.T.; Huang, J.C.; Ke, C.W.; Deng, X.; Ling, Y.; Wu, S.G.; et al. Characteristics of Traveler with Middle East Respiratory Syndrome, China, 2015. Emerg. Infect. Dis. 2015, 21, 2278–2280.
18. Alberola-Ila, J.; Hogquist, K.; Swan, K.A.; Bevan, M.J.; Perlmutter, R.M. Positive and negative selection invoke distinct signaling pathways. J. Exp. Med. 1996, 184, 9–18.
19. Abbas, A.K.; Lichtman, A.H.; Pillai, S. Cellular and Molecular Immunology; Elsevier Health Sciences: Amsterdam, The Netherlands, 2017.
20. Budd, R.C.; Fortner, K.A. T lymphocytes. In Kelley and Firestein's Textbook of Rheumatology; Elsevier: Amsterdam, The Netherlands, 2017; pp. 189–206.
21. Rich, R.R.; Fleisher, T.A.; Shearer, W.T.; Schroeder, H.W., Jr.; Frew, A.J.; Weyand, C.M. Clinical Immunology E-Book: Principles and Practice; Elsevier Health Sciences: Amsterdam, The Netherlands, 2019.
22. Maddur, M.S.; Bayry, J. B cells drive Th2 responses by instructing human dendritic cell maturation. OncoImmunology 2015, 4, e1005508.
23. Rathore, J.S.; Wang, Y. Protective role of Th17 cells in pulmonary infection. Vaccine 2016, 34, 1504–1514.
24. Le Rouzic, O.; Pichavant, M.; Frealle, E.; Guillon, A.; Si-Tahar, M.; Gosset, P. Th17 cytokines: Novel potential therapeutic targets for COPD pathogenesis and exacerbations. Eur. Respir. J. 2017, 50, 1602434.
25. Hotez, P.J.; Bottazzi, M.E.; Corry, D.B. The potential role of Th17 immune responses in coronavirus immunopathology and vaccine-induced immune enhancement. Microbes Infect. 2020, 22, 165–167.
26. Chen, X.; Du, Y.; Lin, X.; Qian, Y.; Zhou, T.; Huang, Z. CD4+ CD25+ regulatory T cells in tumor immunity. Int. Immunopharmacol. 2016, 34, 244–249.
27. Swerdlow, S.H.; Jaffe, E.S.; Brousset, P.; Chan, J.K.; de Leval, L.; Gaulard, P.; Harris, N.L.; Pileri, S.; Weiss, L.M. Cytotoxic T-cell and NK-cell Lymphomas. Am. J. Surg. Pathol. 2014, 38, e60–e71.
28. Liu, Q.; Sun, Z.; Chen, L. Memory T cells: Strategies for optimizing tumor immunotherapy. Protein Cell 2020, 11, 549–564.
29. Zhou, Y.; Shi, X.; Chen, H.; Zhang, S.; Salker, M.S.; Mack, A.F.; Föller, M.; Mak, T.W.; Singh, Y.; Lang, F. DJ-1/Park7 Sensitive Na+/H+Exchanger 1 (NHE1) in CD4+T Cells. J. Cell. Physiol. 2016, 232, 3050–3059.
30. Fitzgerald, K.A.; O'Neill, L.A.; Gearing, A.J.; Callard, R.E. The Cytokine FactsBook and Webfacts, 2nd ed.; Academic Press: Cambridge, MA, USA, 2001.
31. Wu, H.-X.; Guo, P.-F.; Jin, L.-P.; Liang, S.-S.; Li, D.-J. Functional regulation of thymic stromal lymphopoietin on proliferation and invasion of trophoblasts in human first-trimester pregnancy. Hum. Reprod. 2010, 25, 1146–1152.
32. Sakaguchi, S.; Miyara, M.; Costantino, C.; Hafler, D.A. FOXP3+ regulatory T cells in the human immune system. Nat. Rev. Immunol. 2010, 10, 490–500.
33. Le, P.T.; Lazorick, S.; Whichard, L.P.; Haynes, B.F.; Singer, K.H. Regulation of cytokine production in the human thymus: Epidermal growth factor and transforming growth factor alpha regulate mRNA levels of interleukin 1 alpha (IL-1 alpha), IL-1 beta, and IL-6 in human thymic epithelial cells at a post-transcriptional level. J. Exp. Med. 1991, 174, 1147–1157.

34. Odaka, C.; Hauri-Hohl, M.; Takizawa, K.; Nishikawa, Y.; Yano, M.; Matsumoto, M.; Boyd, R.; Holländer, G.A. TGF-β type II receptor expression in thymic epithelial cells inhibits the development of Hassall's corpuscles in mice. Int. Immunol. 2013, 25, 633–642.
35. Wang, J.; Wang, Q.; Han, T.; Li, Y.-K.; Zhu, S.-L.; Ao, F.; Feng, J.; Jing, M.-Z.; Wang, L.; Ye, L.-B.; et al. Soluble interleukin-6 receptor is elevated during influenza A virus infection and mediates the IL-6 and IL-32 inflammatory cytokine burst. Cell. Mol. Immunol. 2014, 12, 633–644.
36. Henry, L.; Anderson, G. Immunoglobulins in Hassall's corpuscles of the human thymus. J. Anat. 1990, 168, 185–197.
37. Schmitz, N.; Kurrer, M.; Bachmann, M.F.; Kopf, M. Interleukin-1 Is Responsible for Acute Lung Immunopathology but Increases Survival of Respiratory Influenza Virus Infection. J. Virol. 2005, 79, 6441–6448.
38. Longhi, P.; Wright, K.; Lauder, S.N.; Nowell, M.; Jones, G.; Godkin, A.; Jones, S.A.; Gallimore, A.M. Interleukin-6 Is Crucial for Recall of Influenza-Specific Memory CD4+ T Cells. PLoS Pathog. 2008, 4, e1000006.
39. Paquette, S.G.; Banner, D.; Zhao, Z.; Fang, Y.; Huang, S.S.H.; León, A.J.; Ng, D.C.K.; Almansa, R.; Martin-Loeches, I.; Ramírez, P.; et al. Interleukin-6 Is a Potential Biomarker for Severe Pandemic H1N1 Influenza A Infection. PLoS ONE 2012, 7, e38214.
40. Liu, B.; Zhang, X.; Deng, W.; Liu, J.; Li, H.; Wen, M.; Bao, L.; Qu, J.; Liu, Y.; Li, F.; et al. Severe influenza A(H1N1)pdm09 infection induces thymic atrophy through activating innate CD8+CD44hi T cells by upregulating IFN-γ. Cell Death Dis. 2014, 5, e1440.
41. Velazquez-Salinas, L.; Verdugo-Rodriguez, A.; Rodriguez, L.L.; Borca, M.V. The Role of Interleukin 6 During Viral Infections. Front. Microbiol. 2019, 10, 1057.
42. Edston, E. Thymus Involution and Intravenous Drug Abuse. Am. J. Forensic Med. Pathol. 2020, 41, 32–34.
43. Lunin, S.M.; Novoselova, E.G. Thymus hormones as prospective anti-inflammatory agents. Expert Opin. Ther. Targets 2010, 14, 775–786.
44. Goldstein, A.L. History of the Discovery of the Thymosins. Ann. N. Y. Acad. Sci. 2007, 1112, 1–13.
45. Rafie, C.; Campa, A.; Smith, S.; Huffman, F.; Newman, F.; Baum, M.K. Cocaine Reduces Thymic Endocrine Function: Another Mechanism for Accelerated HIV Disease Progression. AIDS Res. Hum. Retrovir. 2011, 27, 815–822.
46. Severa, M.; Zhang, J.; Giacomini, E.; Rizzo, F.; Etna, M.P.; Cruciani, M.; Garaci, E.; Chopp, M.; Coccia, E.M. Thymosins in multiple sclerosis and its experimental models: Moving from basic to clinical application. Mult. Scler. Relat. Disord. 2018, 27, 52–60.
47. Romani, L.; Bistoni, F.; Gaziano, R.; Bozza, S.; Montagnoli, C.; Perruccio, K.; Pitzurra, L.; Bellocchio, S.; Velardi, A.; Rasi, G.; et al. Thymosin α 1 activates dendritic cells for antifungal Th1 resistance through Toll-like receptor signaling. Blood 2004, 103, 4232–4239.
48. Goldstein, A.L.; Badamchian, M. Thymosins: Chemistry and biological properties in health and disease. Expert Opin. Biol. Ther. 2004, 4, 559–573.
49. da Silva, A.L.; Martini, S.V.; Abreu, S.C.; Samary, C.d.S.; Diaz, B.L.; Fernezlian, S.; de Sá, V.K.; Capelozzi, V.L.; Boylan, N.J.; Goya, R.G.; et al. DNA nanoparticle-mediated thymulin gene therapy prevents airway remodeling in experimental allergic asthma. J. Control Release 2014, 180, 125–133.

50. Da Silva, A.L.; De Oliveira, G.P.; Kim, N.; Cruz, F.F.; Kitoko, J.Z.; Blanco, N.G.; Martini, S.V.; Hanes, J.; Rocco, P.R.M.; Suk, J.S.; et al. Nanoparticle-based thymulin gene therapy therapeutically reverses key pathology of experimental allergic asthma. Sci. Adv. 2020, 6, eaay7973.
51. Palaszynski, E.; Moody, T.; O'Donohue, T.; Goldstein, A. Thymosin α1-like peptides: Localization and biochemical characterization in the rat brain and pituitary gland. Peptides 1983, 4, 463–467.
52. Camerini, R.; Garaci, E. Historical review of thymosin α 1 in infectious diseases. Expert Opin. Biol. Ther. 2015, 15 (Suppl. 1), S117–S127.
53. Jia, R.; Liu, S.; Xu, J.; Liang, X. IL16 deficiency enhances Th1 and cytotoxic T lymphocyte response against influenza A virus infection. Biosci. Trends 2019, 13, 516–522.