Human Vaccines & Immunotherapeutics

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/khvi20

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To cite this article: Caitlyn Kellogg & Ozlem Equils (2020): The role of the thymus in COVID-19 disease severity: implications for antibody treatment and immunization, Human Vaccines & Immunotherapeutics, DOI: 10.1080/21645515.2020.1818519

To link to this article: https://doi.org/10.1080/21645515.2020.1818519

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Published online: 16 Oct 2020.

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HUMAN VACCINES & IMMUNOTHERAPEUTICS
https://doi.org/10.1080/21645515.2020.1818519

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MINI REVIEW

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The role of the thymus in COVID-19 disease severity: implications for antibody treatment and immunization

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ABSTRACT

The thymus is a largely neglected organ but plays a significant role in the regulation of adaptive immune responses. The effect of aging on the thymus and immune senescence is well established, and the resulting inflammaging is found to be implicated in the development of many chronic diseases including atherosclerosis, hypertension and type 2 diabetes. Both aging and diseases of inflammaging are associated with severe COVID-19 disease, and a dysfunctional thymus may be a predisposing factor. In addition, insults on the thymus during childhood may lead to abnormal thymic function and may explain severe COVID-19 disease among younger individuals; therefore, measurement of thymic function may assist COVID-19 care. Those with poor thymic function may be treated prophylactically with convalescent serum or recombinant antibodies, and they may respond better to high-dose or adjuvanted COVID-19 vaccines. Treatments inducing thymic regeneration may improve patients' overall health and may be incorporated in COVID-19 management.

ARTICLE HISTORY
Received 5 August 2020
Accepted 27 August 2020

KEYWORDS
COVID-19; thymus; inflammation; immunity; aging; immunosenescence; longevity

History of recognition of the thymus and its role in the immune system

A deeper understanding of the thymus is critical in combating COVID-19. Immune changes that occur with thymic aging (immune senescence) lead to an inflammatory environment that underlies the pathogenesis of diseases of aging (i.e. cardiovascular disease, hypertension, chronic obstructive lung disease and arthritis),[1–4] and people who develop these comorbidities are known to be at higher risk for severe COVID-19 infection and death.[5,6]

Although knowledge of the thymus has existed since the time of the ancient Greeks (130–200 AD), who called the thymus *thumos*, meaning "principle of life," or "heart, soul, passion, life"[7] there were few efforts to understand its function until the 1960s when removal of the thymus in a mouse model was shown to lead to immune deficiency.[8] In 1967, lymphocytes of thymic origin (T lymphocytes) were identified and recognized to enable bone marrow-derived B lymphocytes to differentiate into antibody-forming cells.[8] In the 1980s, the AIDS epidemic and the discovery of thymic involvement in human immunodeficiency virus (HIV) infection brought further attention to the thymus.[9,10] Treatments to boost thymic function were considered for HIV-infected individuals.[9] However, the development of effective anti-retroviral treatments and successful suppression of HIV replication to undetectable levels cooled the interest in the thymus.

In the early 2000s, infants who underwent thymectomy for congenital heart surgery were found to develop an immune profile similar to that seen in aged individuals.[11] In those children, repopulation occurred with lymphocytes of extra-thymic origin with limited breadth of immune responses; the number of naïve CD4+ helper and CD8+ suppressor T lymphocytes and T-cell receptor rearrangement excision circles (TRECs) were lower and the number of B lymphocytes was higher, though IgG1 and IgA levels were lower.[11–13] Despite these observations, even as recent as 2010, the surgical protocols to repair congenital heart defects required partial or complete thymectomy. Today, thymectomy is routinely performed to treat patients with myasthenia gravis and thymomas. The sternal defect pectus excavatum is corrected with the Nuss procedure, in which a metal rod is inserted between the thymus and sternum, which may affect thymic function.[14,15]

Factors influencing the development and function of the thymus

Genetic and environmental factors (prenatal and postnatal) influence thymic health. DiGeorge Syndrome (Chromosome 22q11.2 deletion syndrome) is the most common chromosomal microdeletion reported in humans, affecting approximately 1 in 4,000 individuals, and leads to cardiovascular defects and the absence or under-development of the thymus.[16] Males and females are affected equally regardless of their race and ethnicity.[17] However, the penetrance and disease severity varies among those affected, which is explained by novel genetic and epigenetic differences as well as differences in coding and non-coding genes including microRNAs (miRNA) and long noncoding RNAs (lncRNAs). For example, *DiGeorge Syndrome Critical Region 8, DGCR8*, is a gene on the long arm of chromosome 22, and it is required for miRNA biogenesis.[19–20] A 50% reduction in *DGCR8* expression due to 22q11.2del may modulate the expression of hundreds of micro RNAs (miRNAs).

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MicroRNAs are a family of approximately 2000 evolutionarily conserved small noncoding RNAs (18–22 nucleotides) found in many body fluids such as serum, plasma, saliva and amniotic fluid. These molecules bind to diverse mRNA transcripts that play a role in cell function and target mRNA transcripts for degradation.[20,21] MiRNAs play an important role in thymic organogenesis, maturation and involution,[22] and conversely, aging influences miRNA levels.[23] Interestingly, miRNAs not only regulate host cellular responses but also responses to infectious agents like viruses.[24] There is a decrease in T cell number and increased susceptibility to infection observed in DiGeorge syndrome;[16] miRNA dysfunction seen in this disease may be a contributor.

Environmental factors regulate thymic development both pre- and postnatally. Gestational diabetes has the potential to cause birth defects, and newborns born to women with gestational diabetes have congenital features overlapping with 22q11.2del.[17] Approximately 1 out of 5 infants with thymic aplasia with deletions on chromosome 22q11.2 and requiring a thymic tissue transplant were born to mothers with a clinical history of gestational diabetes.[17] Retinoic acid treatment of pregnant women (tretinoin, isotretinoin) for acne also leads to 22q11.2-like congenital malformations in their infants.[17]

Postnatally, acute stress such as emotional distress,[25] malnutrition,[26] and infections[27] may induce transient thymic involution characterized by a reduction in thymus size. This is postulated to be caused by an acute loss of cortical thymocytes and reduced output of naïve T cells to the periphery.[28]

Soluble factors released from lymphocytes and from non-lymphoid cells in the thymus, lymph nodes and at sites of inflammation regulate thymic function and T lymphocyte proliferation.[29] Interleukin (IL)-6 (previously called B cell-stimulating factor, BSF-2) is a costimulant for human thymocytes and T lymphocytes and plays a role in B lymphocyte differentiation.[29] At physiologic levels, IL-6 may promote thymocyte proliferation. However, during acute stress, elevated IL-6 levels may lead to thymic suppression.[30] One IL-6 family protein, leukemia inhibitory factor (LIF), has been shown to induce thymic suppression and is dependent both on intrathymic and systemic cortisol levels.[30]

Physical trauma to the chest is common among children, especially males, and may lead to thymic injury. Thymic injury during youth may lead to a chronic inflammatory state and premature immune-senescence and may increase the risk for obesity, insulin resistance and metabolic syndrome.[31] Research has shown that participation in American football may increase the risk for cardiovascular disease later in life, and repetitive blunt trauma to the chest may be a cause.[32] Defensive lineman football players endure repeated chest insults, this may explain the higher rates of obesity and metabolic syndrome even among collegiate lineman.[33] Long term, regular, strenuous exercise (-approximately 2 hours of daily swimming, running and cycling plus weight, interval or skills training) has also been shown to decrease thymic function among healthy young people.[34] These observations may explain COVID-19 deaths observed in some healthy, athletic young adults.

The metabolic hormones leptin and ghrelin influence thymic function and involution.[35] For example, leptin, the satiety hormone that regulates the energy balance by inhibiting hunger and diminishing fat storage in adipocytes,[36] plays a role in thymopoiesis and prevents corticosteroid-induced thymic atrophy.[37] There is a tight relationship between leptin levels and obesity, which is the most common comorbidity for severe COVID-19.[31,38]

Thymic development and thymus size are also under the control of hypothalamic, pituitary and sex hormones, whose levels change over time. Both thymocytes and thymic epithelial cells express sex hormone receptors.[39,40] The thymus is most active early in life but undergoes a steady decline in function over time,[41] a phenomenon that is evolutionarily conserved among vertebrates.[42] Thymic involution becomes most notable around the time of puberty when sex steroid production increases.[43] The increasing rate of childhood obesity and subsequent early start of puberty may initiate thymic senescence at a younger age. This may explain the high rate of obesity among pediatric and adult patients with severe COVID-19 disease.[44,45]

Although there are limited data on the effect of gender on thymic involution, most animal data suggest that females have a larger thymus compared to males.[42,43] In addition, the second X-chromosome in females encodes many immune proteins that play a role in thymic regulation of the immune system.[46] This may explain lower rates of severe COVID-19 in females. During pregnancy, under the influence of hormones, the thymus experiences dramatic changes, in which the cortex shrinks and there is an increase in cellularity in the medulla.[41] Those changes may influence COVID-19 disease course in pregnant women.

Thymus and aging

Aging is characterized by thymic involution and peripheral immunosenescence that leads to inflammaging, which is characterized by chronic inflammation.[47] Increased levels of IL-6, IL-1, TNF-α and C-reactive protein contribute to the enhanced low-grade inflammation characteristic of aging.[47] With aging, the thymus turns into strands of medullary and cortical cells surrounded by adipose and connective tissue, altering the thymic cytokine milieu.[48,49] Thymus-produced cytokines whose expression falls with aging include IL-2, IL-9, IL-10, IL-13 and IL-14.[49] Thymic cytokines that increase with aging include leukemia inhibitor factor (LIF), oncostatin M (OSM) and stem cell factor (SCF) (Table 1).[49] The thymic cytokine LIF also regulates adrenocorticotropic hormone (ACTH), which regulates cortisol release.[49] Cortisol in turn suppresses thymopoiesis, suggesting that overproduction of thymic cytokines may lead to thymic atrophy.[49]

As the productive capacity of the thymus lags, the frequency of naïve T cell production is reduced and the TCR repertoire contracts.[1] In young and even middle-aged adults, the naïve CD45RA+CD62L+CD4 positive T cell repertoire diversity has been estimated at 20 million different TCR-β chains; in the

Table 1. The effect of aging on thymus cytokine production.

Increase with aging	Leukemia inhibitor factor (LIF), oncostatin M (OSM) and stem cell factor (SCF).
Decrease with aging	IL-2, IL-9, IL-10, IL-13 and IL-14.

elderly (older than 70 years),[50] the pool has severely contracted to 200,000 TCR-β specificities.[51] The 95% decline in TCR repertoire diversity in CD4 + T cells in the elderly may limit functional response.[52] Nonetheless, the overall T cell levels are maintained by a variety of peripheral thymus-independent homeostatic mechanisms[53] where memory T cells stimulated by cytokines undergo proliferation and differentiation.[54,55] With the loss of critical cytokines and hormones from the thymic microenvironment, newly activated naive and memory cell populations expand in response to cognate antigenic stimulation and occupy increased fractions of the repertoire.[54–57] Overall, these changes confer older individuals relatively preserved immunity against previously encountered antigens, but decreased immunity against new antigens, infectious agents and vaccines.[58]

Interestingly, aging affects the immune system differentially between men and women. Inflammaging is accelerated among men; changes including a decline in naïve T cell numbers and increase monocyte and cytotoxic cell functions are greater in men than women, as is the decline in B-cell specific loci.[59] Also, older men have higher levels of pro-inflammatory cytokines (IL-6, IL-18) than women.[59] The genomic differences between sexes increase after age 65 years, with men having higher innate and pro-inflammatory immune activity and lower adaptive immune activity regardless of the decline of B cell frequencies.[59] These observations are persistent in different ethnic groups, which suggest that endocrine factors may be mediating these differences.[60–62]

Thymus and COVID-19 disease

Although COVID-19 mostly affects those with comorbid conditions, even among those without comorbidities, age is a significant risk factor, and there is a direct relationship between age and COVID-19 severity and mortality.[6] This may be explained by the inappropriate COVID-19-induced immune responses in the elderly who are already experiencing immune-senescence and inflammaging at baseline. Overall, there are many similarities between the blood cytokine profile of aging and that observed in severely ill COVID-19 patients, including an elevated IL-6, which appears to play a key role in poor COVID-19 prognosis (Table 2).[63–66]

Table 2. Immune profile in aging compared to that seen in COVID-19 patients.

	COVID-19 patients	Aging
Immune cell profile		
Total T cell number	↓	↓
Total CD8 + T cell number	↓ ↓	↓ ↓
Total CD4 + T cell number	↓	↓
T reg profile	↓	↑ naturally occurring, ↓ inducible
B cell number	Normal	↓
NK cell number	Normal	↓
Cytokine profile		
IL-2	↑	↓ or normal
IL-6	↑	↑ or normal
IL-8	↑	↑ or normal
IL-10	↑	↓ or normal
TNF-A	↑	↑ or normal
IFN-γ	↑	↑ or normal

Assessment of thymic function to determine the risk for severe COVID-19

Although an abnormal immune response plays a large role in the pathogenesis of many comorbid conditions and the thymus is the organ for T cell lymphopoiesis, since 1800s, the white blood cell count is the only laboratory test performed during routine doctor visits to assess the immune system.[67] Thymus function is not examined during routine health visits or during the medical management of chronic diseases, such as diabetes or atherosclerosis. However, there was a great interest in thymus during the early years of HIV epidemic and there is extensive experience on the measurement of thymic function. Thymic function can be quantified by measuring the nonreplicating circle of DNA, signal joint TCR excision circle (sjTREC), in naïve T cells by performing real-time polymerase chain reactions (PCR).[68,69] Higher TREC number is associated with better thymic function and repertoire diversity of the memory T-cell population.[69] Thymic output may also be monitored by conducting flow cytometry in the blood and measuring naïve CD45RA and CD62 ligand positive cells.[70]

Measurement of thymic function may help determine a patient's risk of developing comorbid conditions and severe COVID-19 disease and may also predict a patient's response to vaccines. The CD4 + T-cell population correlates with both the capacity to respond to vaccines and the resistance to opportunistic infections.[71,72] Decreased thymic function may affect the response to vaccines; although most children with DiGeorge syndrome respond to live viral vaccines, the duration of immunity is much shorter.[73]

Data on thymic health and function among patients with COVID-19 infection, including those who are younger (including children) and those without comorbidities, may help identify patients who may be at risk for more severe COVID-19 infection and who may not respond to the vaccines. The patients with low thymic function may be started on post-exposure prophylaxis or early treatment with convalescent plasma,[74] recombinant antibody[75] and/or anti-viral treatment. Patients with insufficient thymic response may better respond to high dose[76]or adjuvanted[77] vaccines.

Restoring thymus function to improve COVID-19 prognosis

The average life expectancy has increased substantially since 1900s.[78] Studies suggest that although there appears to be a maximum limit on lifespan, by targeting the biological/genetic and environmental causes of aging, humans can live longer. In the1900s, the primary cause of death was infection. With the advent of clean water, vaccines and anti-microbials, the current leading cause of death is cancer.[79] The COVID-19 pandemic may reverse this trend. Since COVID-19-related mortality is significantly higher among people 65 years and older, treatments that restore thymic function may suppress inflammaging, COVID-19 related inflammation, and prevent severe COVID-19 disease.

Treatment with recombinant human growth hormone (rhGH) and thymus transplantation was proposed to restore thymus function among HIV-infected patients[80] and patients with DiGeorge syndrome[81] respectively. Methods proposed to restore thymic function include administration of recombinant human keratinocyte growth factor (Palifermin), recombinant human hIL-7 (CYT107), recombinant human IL-22 (hrIL-22), rhGH and insulin-like growth factor-1 (IGF1), in addition to sex steroid inhibition by luteinizing hormone-releasing hormone (LHRH)-agonist (Lupron) or enzalutamide (nonsteroidal anti-androgen), adoptive transfer of precursor (pre-) T cells and thymus bioengineering.[82] Recently in a clinical trial to improve thymic function in 10 healthy men between the ages of 51 and 65 years treatment with recombinant human growth hormone (rhGH), dehydroepiandrosterone (DHEA) and metformin showed improved immune markers.[83] Zinc supplementation restored thymic function in aging mouse model.[84] Currently, Interleukin7, enzalutamide and ascorbic acid plus zinc supplementation are in clinical trials to treat COVID-19.[85–87] There is a need for concerted efforts to develop treatments targeting the thymus to improve the immune system and overall health.

Conclusions

Measurement of thymic function may help identify children and adults with immune dysfunction who are at risk of developing severe COVID-19 disease. Thymic function measurement may also be used to determine when to start convalescent COVID-19 plasma or recombinant antibody prophylaxis. Patients with low thymic function may respond better to high dose or adjuvanted vaccines, and strategies to interrupt thymic insult and restore thymic function may be incorporated in COVID-19 treatment regimens.

Disclosure of potential conflicts of interest

The authors declare no conflicts of interest.

Funding

This work was supported by MiOra public health education nonprofit.

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