ISSN: 2378-3672

Ukaegbu. Int J Immunol Immunother 2024, 11:070
DOI: 10.23937/2378-3672/1410070
Volume 11 | Issue 1
Open Access

International Journal of
Immunology and Immunotherapy

REVIEW ARTICLE

The Ageing Immune System- Implications for COVID-19

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Keywords

SARS-CoV-2, Ageing, Senescence, Thymus

Introduction

Ageing is a slow and continuous process that is associated with the decline in the functioning immune system. These changes are now recognized and appreciated under the canopy term 'Immuno-senescence' [1]. Immuno-senescence is not due to a lack of immune cells but reduced diversity in the repertoire - with reduced naive cells and increased memory cells. Secondly, the ageing immune system is subject to inflammaging, elevated self-reactivity leading to chronic low-grade inflammation [2].

A healthy functioning immune system is needed for survival and crucially to defend against foreign antigens and pathogens. Immuno-senescence results in the reduced ability to fight infections, diminished vaccine immunity and reduced tumour clearance [3]. This is correlated with the increased mortality in the elderly population. Such issues with the immune system were not clear when the life expectancy of humans was lower. However, in the last century, we have experienced advances in both health care and public health that has led to increased longevity [4].

One of the key events in the ageing immune system is the involution of the thymus. The word thymus originates from the Greek word thymos which means 'principle of life' [5].

In 1985 the morphology of the thymus was described and it was apparent that the immune organ started to decrease in size and function from the first year of life. This has been documented in all vertebrae that have a thymus, which would suggest the involution is an evolutionary and conserved event [6].

There are several diseases associated with thymus decline and increasing age such as diabetes and hypertension [7]. COVID-19 is the most recent pandemic which has a higher prevalence and severity in the elderly compared to young adults and children [5]. The thymus' role in immune regulation and ageing could be key to understanding a range of pathologies including COVID-19. Furthermore, it can lead to the discovery and development of therapeutics to support healthy ageing.

The thymus is a primary lymphoid organ needed to produce self-restricted, self-tolerant immunocompetent T cells [6]. It is pyramidal in shape and consists of 2 lobes connected by areolar tissue enclosed in a fibrous capsule. It is located in the mediastinum between the sternum and pericardium. Thymopoeisis - the development of new T cells, takes place in the thymic epithelial space (TES), here certain positive thymic epithelium enables the development of thymocytes, the thymus also contains the perivascular space/ stroma (PVS), which is keratin negative and where no thymopoiesis takes place. During thymopoiesis, pluripotent stem cells leave the bone marrow and enter the thymus. These cells are triple-negative (CD3-CD4-CD8-) thymocytes. They enter the thymus where based on the microenvironment they differentiate into double-negative cells (CD3+CD4 -CD8-). These early progenitors migrate through different double negative subsets: DN I (CD44+CD25-) DN II (CD44+CD25+), DN III (CD44-CD25+) DN IV (CD44-CD25-). They then become double-positive thymocytes expressing CD4 and CD8, this is followed by rearrangement of their T cells antigen receptor genes [8]. Following this, central tolerance, where positive or negative selection takes place - so that

Citation: Ukaegbu K (2024) The Ageing Immune System- Implications for COVID-19. Int J Immunol Immunother 11:070. doi.org/10.23937/2378-3672/1410070

Accepted: March 02, 2024; **Published:** March 04, 2024

thymocytes become single positive naive T cells that can enter the periphery - then ensues. Negative selection leads to T cells that recognise self-antigens too strongly being removed from circulation through apoptosis [9]. Positive selection is where T cells recognise self-proteins with moderate strength and are allowed to continue developing.

There is also the generation of single-positive CD4 T regulatory (T reg) cells which function to suppress self-reactivity and compensate for imperfections yielded from negative selection [10].

There were several theories regarding the mechanisms of the ageing immune system, including reduced and/or defective stem cells from the bone marrow, with a consequently diminished number of early T cell progenitors entering the thymus. However, it was studies such as those that demonstrated mice had increased susceptibility to infections, impaired immune response following thymectomy was crucial in highlighting the role of the thymus in immune function [11]. Furthermore, the importance of the thymus is evident in congenital disease states such as DiGeorge Syndrome, which is due to deletions of the 21q11.2 chromosome, which leads to an underdeveloped or absent thymus. The result is a decrease in T cell number and increased infection risk. Malnutrition [12] and emotional stress [13] can also cause acute strain on the thymus and make the host more susceptible to infection.

The thymus is under the influence of the hypothalamic-pituitary-gonadal system; this association is identified by the presence of receptors for sex hormones found on thymocytes and thymic epithelial cells (TECs) [14]. There is evidence to suggest that the female thymus is larger than the male, moreover, during puberty, the thymus may be subjected to more sex hormones and it is during this period that thymic involution is very apparent [15]. These sex differences are also illustrated with the finding of Williams, et al., whereby male rodents experienced an increase in the size of their thymus following castration [16].

As research has progressed it is apparent that morphological and histological changes in the thymus play a significant role in thymic involution. Steinmann, et al., showed that the lymphoid cells within the TES began to decrease and involute shortly after birth, during the middle ages (35-45 years) it decreases at a rate of 3% per year, decreasing to 1% per year for the rest of the life course [17]. There is an expansion of the PVS shifting the ratio of TES to PVS, with the TES shrinking to less than 10% by the age of 70 [18]. With the decrease in TES, there is a decreased output of naive T cells. Single joint T cell receptor excision circles (sjTRECs) can be used to follow the creation of naive cells. A decline in sjTRECs has been found with increasing age. When extrapolated, it is estimated that the thymus would fail to produce new T cells at around the age of 105 years [19].

The ageing thymus has reduced the output of naive T cells and an increase in senescent peripheral memory cells. There is an overall decrease in TCR diversity and variation in T cell antigen receptors.

With increasing age, the involuted thymus has lower levels of T reg cells thus reducing the ability to control central tolerance and increasing the number of self-reactive T cells entering the periphery. These are T cells that would have normally been removed through negative selection. The latter promotes inflammaging. These cells can enter non-lymphoid tissue and lead to tissue damage. Inflammaging is also influenced by the increase in senescent cells which can change their phenotype/expression making them less likely to apoptose, instead increasing the release of cytokines [20].

There is also the release of pro-inflammatory cytokines mainly driven by the innate immune system with an upsurge of IL1, 6, TNF alpha and C reactive protein which spurs more cells to go into senescence [21].

Overall, the compromise is such that these changes preserve immunity against previously encountered antigens but weaken the response to new insults and vaccines.

Immuno-senescence and inflammaging are linked to several disease states that are associated with increasing age, including metabolic and cardiovascular diseases and may explain the higher mortality with the recent pandemic.

COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is a disease that has high mortality in the elderly, males and those with comorbidities such as obesity, diabetes and cardiovascular disease [20]. The virus is enveloped and made of single-strand RNA attacking the host through angiotensin-converting enzyme 2 receptors in the respiratory system [22]. Normally the immune system responds to viral infections through the innate system, via natural killer cells and macrophages which can produce cytokines and attract more immune cells. The adaptive system mainly responds through CD8 cytotoxic cells.

The exact role of the aged immune system in the pathogenesis of COVID-19 is not clear, yet all theories point towards the aged involuted thymus. This is notably characterized by the mechanisms explained above - immuno-senescence with senescent memory cells in the periphery and reduced naive T cells. Also, alterations in the T reg cells lead to reduced surveillance of self-reactive cells. Lastly, there is inflammaging which could potentiate the inflammation and damage and reduce the ability to mount a T cell response to vaccination. The

immune system can have a protective role, but also be at risk of promoting deleterious inflammation itself.

Severe COVID is characterised by a cytokine storm, an immune cell-induced phenomenon with high levels of IL1, 6 and TNF alpha [23]. The high levels of the latter correlate with lower levels of T cell function. There are many similarities between the inflammatory profile of patients with COVID-19 and the elderly, namely raised IL6, 8 and TNF alpha, as well as reduced total T cells [5]. Within the pathogenies of COVID-19, this could cascade into severe organ failure and could even be fatal.

Epidemiology suggests that there is sexual dimorphism, with men being more affected by severe COVID-19 than females, as well as, higher mortality. This may be due to older men having more elevated levels of IL1 and 18 [24]. In addition, Pido-Lopez, et al. reported that females had higher levels of sJTRECs which may result in a higher level of naive T cells compared to males. This would allow them to evoke a more effective immune response to the virus [25].

There has been the emergence of potential therapeutic targets to help deficits in the elderly and immunodeficient. The main aim, to improve the quantity and quality of naive T cells, the peripheral T cells and reduce basal inflammation. One option is bone marrow transplantation, however, the risk of graft versus host disease and graft versus leukaemia is a major limitation. Interestingly, mice studies have found that the addition of growth and transcriptions factors may further enhance the immune system.

FOXN1 a transcription regulator for the development of TECs is the most promising target to rejuvenate the thymus. Its declined expression leads to thymic atrophy [26]. Oh, et al. conducted a mouse model and showed that thymic injections of FOXN1 resulted in embryonic fibroblast which was able to regenerate the thymus and reduce inflammaging [27].

IL7 is a cytokine crucial for both T and B cell development, specifically early thymocyte development as evidenced by mice studies showing that lacking IL7 or the IL7 receptor leads to decreased thymus size and reduced cellularity. Laterre, et al., found patients with severe COVID-19 treated with IL7 had a return in CD4 and CD8 levels, the mechanisms of this are yet to be elucidated [28].

There may be a link between growth hormone and IL7, growth hormone (which also declines as age progresses) acts on thymic stromal cells and leads to increased IL7 production. This suggests that vulnerable groups should receive growth hormone supplementation during the pandemic [29].

Specifically related to COVID-19 Thymosin alpha-1 a synthetic polypeptide hormone that aids T cells initiation, maturation and survival has been used in COVID 19 trials. So far results have shown that it may reduce the mortality of patients with severe disease by up to 60%. It has exhibited restoration of CD4 and CD8 in patients with severe COVID disease [30].

A simple, less invasive way of rejuvenating the thymus may be diet and exercise to reduce adiposity. Obesity has been implicated in thymic involution and also comorbidity related to COVID-19; Dixit reported that increased thymic adiposity may decrease the function of the thymus [31]. Furthermore, a study by Yang, et al. demonstrated that inducing obesity in rodents increased thymic involution, decreased naive T cells and increased memory cells [32]. This may be because the adipose tissue acts as a reserve for cytokines and inflammation. The reverse effect was seen when rodents were subjected to caloric restriction which revealed increased cellular density in the thymus and less deterioration of the TCR repertoire diversity in older animals [33].

In addition, Duggal, et al. found a correlation between physical exercise and healthy thymic function in the elderly. Older individuals who cycle had higher numbers of naive T cells, IL7, and lower IL6 compared to non-active controls [34].

Conclusively, age-related changes in the immune system, specifically the thymus is one is thought to contribute to immuno-senescence and inflammaging, placing the elderly at risk of being in a pro-inflammatory state and at risk of several diseases, including COVID-19. Understanding the thymus and its decline may provide useful therapeutic targets and help the plight of rejuvenating the immune system.

Conflicts of Interest

The author declares no conflict of interest.

Funding

None applicable.

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