Does the immune system grow old gracefully?

Donald B. Palmer
and Tamar Freiberger
(Royal Veterinary College,
University of London, UK)

‘You don’t stop laughing when you grow old, you grow old when you stop laughing’.
George Bernard Shaw

The immune system consists of an array of cells and soluble factors that are designed to protect the host from pathogens and infectious diseases, and therefore represents a vital entity for an organism’s survival. Moreover, with increasing age, the immune system undergoes dramatic changes resulting in a decline in immune function, which is seen in humans as well as in many other species. Such changes, collectively termed immunosenescence, often lead to increased susceptibility and severity of infections, cancers and autoimmune diseases, together with the reduced ability to respond to vaccination, which is often seen in older individuals. Given the direct correlation between immune function and health, the increased morbidity and mortality seen in older individuals following infection are due, in large part, to the age-associated changes in the immune system. This is of great concern since, according to the Office of National Statistics, the population of individuals over the age of 65 in the UK is steadily increasing, standing at 18.2% in mid-2017 and estimated to rise to 20.7% by 2027 and 24% by 2037 (Figure 1); a trend that is also seen globally. Although this area of research is relatively new in comparison to other fields of immunology, investigations have identified several differences between the young and aged immune system which has helped shed light on the possible mechanisms associated with immunosenescence.

Involution is a general term for the shrinkage of an organ in old age, or due to inactivity (e.g., post-birth reduction in the size of the uterus). Age-associated thymic involution (Figure 2) is one of the most recognizable features of the aging immune system. This regression of the thymus is associated with a reduction in tissue mass, loss of tissue structure and a decline in the number of thymocytes (T cell precursors). Ultimately, this leads to a reduced production of new (naive) T cells, the consequence of which has major ramifications on functional immunity.

Why the thymus involutes with age is still unclear. One suggestion is that thymocyte development is highly energy demanding and once the T cell pool is established (as T cells are long-lived), the thymus regresses, so that energy can be redirected to other cellular systems. Nevertheless, this process occurs in all species that possess a thymus, which not only indicates that age-associated involution is an evolutionary-conserved event, but also makes it a suitable biomarker of aging. The start of thymic involution is believed to occur during adolescence; however, there is significant evidence to suggest it may occur earlier in life. Furthermore, thymic activity does not decline at a steady rate, but instead appears to be phasic (Figure 2). The onset of thymic involution appears to be relative to the lifespan of...
the host, since studies from our laboratory on dog breeds with varying lifespans, showed that the thymus began to regress at an earlier age in short-lived breeds compared with long-lived breeds.

Although the exact causes of thymic involution are still unclear, evidence suggests the involvement of both cell-intrinsic abnormalities and defects from the extrinsic environment. For example, early thymocyte progenitors from an aged murine thymus have a reduced capacity to generate into T cells. This might be due to perturbations acquired from aged HSC since these cells have a reduced potential to differentiate into the lymphoid lineage. As previously mentioned, the thymic environment is essential for T cell differentiation and its components are also likely to contribute to thymic involution. In particular, thymic epithelial cells from aged mice have been shown to be defective in supporting thymocyte development.

**Knock-on effects of thymic involution**

The consequence of a decline in naive T cell output from the aging thymus has a major impact on the peripheral T cell pool. This includes a reduction of diversity due to the steady accumulation of T cells that exhibit a memory phenotype (Figure 2). In addition, with increasing age, T cells exhibit: (1) a reduced proliferative capacity, (2) an inability to provide support for other immune cells and (3) altered production of cytokines. Such modifications can indeed be detrimental to host survival. For instance, having a reduced diversity to recognize foreign antigens is likely to leave older individuals more susceptible to new pathogens. Furthermore, the inability to proliferate will cause inefficient T cell responses to antigens as well as reducing their capacity to provide help for B cells, which is one of the reasons why vaccine efficacy is often poor in older populations.

The age-associated alteration of the peripheral T cell pool also includes the presence of T cells that lack the co-stimulatory marker CD28. This marker is expressed in all T cells at birth and is essential for T cell activation by promoting division, survival and differentiation. However, with age there is an accumulation of T cells that have lost this molecule and are thus ‘CD28 negative’ (CD28-). This occurs more rapidly among CD8+ (cytotoxic) T cells compared with CD4+ (helper) T cells. These CD28- T cells exhibit similar features to replicative senescent cells as they have reduced proliferative capacity, telomere erosion and secrete pro-inflammatory cytokines. The latter characteristic resembles the senescence-associated secretory phenotype (SASP) (the SASP refers to senescent cells that secrete a variety of pro-inflammatory cytokines and contribute to tissue dysfunction). Furthermore, CD28- T cells appear to have a negative effect on the immune response and may therefore play a part in the decline of functional immunity in the aged. Interestingly, both the accumulation of CD28- T cells and the gradual increase

Figure 2. Age-associated thymic involution and how it impacts the peripheral T cell pool. a) A schematic diagram showing the rate of age-associated thymic involution (as measured by thymic size) recorded in a number of animals. The regression of thymic size is not linear, but phasic with the greatest loss occurring early in life followed by a steady decline. b) The thymus structurally consists of a cortex and a medulla, represented as I and X respectively. In young individuals, the cortex and medulla are distinct, the thymus has a high output of naive T cells and the T cell repertoire is diverse in the periphery. However, in the aged, the thymus is reduced in size and disorganized, and T cell output is reduced (as illustrated by the arrow). Furthermore, cells produced from the aged thymus may not be as robust as those from a young thymus. The number of peripheral T cells does not change with age, so the vacancy created by the reduction of naive T cells is filled by existing memory cells. Consequently, the peripheral pool in the aged is less diverse and contains cells with a reduced proliferative capacity.
of a memory T cell phenotype within the aged immune system appear to be driven in part by persistent viral infections. For instance, several studies have observed high proportions of cytomegalovirus (CMV)-specific CD8+ T cell clones in the blood of older individuals, which demonstrates a positive correlation between CMV and the presence of senescent T cells. It is believed that this virus has the ability to induce premature aging and exhaustion of T cells and is viewed as a risk factor for immune-related morbidity and mortality.

Other contributors to T cell dysfunction in the aged

Thymic involution is not the only contributor towards peripheral T cell senescence; other lymphoid organs are also involved. Immune responses take place in secondary lymphoid organs (SLO), such as the spleen and lymph nodes. These organs have a unique structural organization and specialized environment that enables activation, proliferation and differentiation of immune cells. Interestingly, studies have shown that aged SLO in comparison to young SLO demonstrate a loss of tissue structure and increased disorganization. Furthermore, studies in mice show that aged SLO are poor at facilitating immune responses.

Let’s not inflame the situation

Another hallmark of the aged immune system is the increasing level of pro-inflammatory cytokines such as IL-1, IL-6, TNF-α and C-reactive protein. Described as ‘inflammaging’, it is proposed that these mediators contribute to the inflammatory pathogenesis that is a feature of many chronic ailments observed in older individuals such as osteoarthritis, diabetes and atherosclerosis. The accumulation of these cytokines is believed to be due to continual antigenic challenge, increased frequency of senescent cells and oxidative stress. Additionally, these mediators are known to disrupt T cell function and may therefore contribute to peripheral T cell senescence. Given the detrimental impact of pro-inflammatory cytokines on immune function and disease association, it is not surprising that their increased levels in older individuals are viewed as a risk factor linked to frailty and mortality.

What about the other players?

T cells are not the only ones affected in the aged immune system. In fact, almost every type of immune cell has been demonstrated to undergo age-associated changes. Innate immune cells, such as macrophages and neutrophils, have reduced migration and phagocytic activity in older adults. Furthermore, these cells express fewer recognition receptors, such as toll-like receptors. Other innate cells, natural killer (NK) cells, show an age-related increase in frequency, however they exhibit reduced cytotoxicity. As NK cells play a key role in viral immunity and the removal of cancer cells, their decline is likely to contribute towards the clinical signs of immunosenescence.

B cell function is also reduced with age, in part due to a decline in T cell help, but also their development from HSC is impaired. Similar to T cells, the age-related changes in B cell activity is a result of both intrinsic and environmental defects. With age, there is a loss of antibody diversity and affinity, together with an increase in autoantibody production. B cells also exhibit a poor response to vaccines and new antigens.

Can it be reversed (is it all doom and gloom)?

Having identified age-related changes of the immune system, studies are underway to produce potential therapies that can reverse or rejuvenate the impact of immunosenescence. Largely performed in mice, targeting the thymic environment using soluble factors proved successful in recovering thymus activity in older animals. Inhibition of a signalling pathway known as mechanistic target of rapamycin (mTOR) has been shown to influence longevity by increasing lifespan. Moreover, in a recent study, older individuals treated with a drug that inhibits mTOR showed improved vaccination response to influenza. Lifestyle is also viewed as a potential area of improving or maintaining immune function and a recent study revealed that physical activity throughout life appears to reduce some of the features of immunosenescence.

Concluding remarks

Globally, the human race is living longer, but the health status of older individuals is not improving at the same rate due to the impact of age-related diseases. It would seem that the immune system does not grow old gracefully after all, with the defects associated with immunosenescence contributing significantly to the increased morbidity and mortality seen in older individuals. It is therefore essential to dissect the mechanisms underlying immunosenescence with the aim of developing future therapies that can enhance or maintain immune function.
Further reading

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Donald Palmer is Associate Professor of Immunology at the Department of Comparative Biomedical Sciences at the Royal Veterinary College, University of London. His main research interests in the field of immunesenescence include age-associated thymic involution, the role of the stromal environment on immune function in the aged and comparative analysis of the immune system. Donald is also an Honorary Senior Lecturer at Imperial College London. Email: dpalmer@rvc.ac.uk.

Tamar Freiberger recently graduated with an MSci in BioVeterinary Sciences from the Royal Veterinary College, University of London. During her MSci she worked in Dr Palmer’s group investigating the effects of age on the phenotype and structure of murine secondary lymphoid organs, such as the spleen and lymph nodes. Tamar is also a member of the Royal Society of Biology. Email: tfreiberger4@rvc.ac.uk.