**Immunosenescence: ageing of the immune system**

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**Abstract**

“Immunosenescence,” or ageing of the immune system, is the term given to changes (in comparison with younger individuals) observed in the immune systems of elderly individuals. Elderly individuals are predisposed to more severe symptoms from certain infections than young adults, and they do not mount as an effective immune response to vaccination. In addition, the elderly suffer from more malignancies than younger individuals, which may be because of failure of the immune system to provide surveillance against diseases such as tumours. The decrease in immune function is paradoxically coupled with features of chronic inflammation in the elderly, termed “inflammaging.” The mechanisms of immune senescence are multiple, but seem to be driven largely by changes in T cell-mediated immunity. There are fewer antigen-naïve T cells in the peripheral blood of aged individuals than there are in younger individuals. The memory T-cell repertoire is not as broad as that in younger individuals, and the memory T cells demonstrate a poorer functional ability to respond to pathogens. It is likely that these T-cell changes result from the involution of the primary organ of T-cell development, the thymus. Thymic activity is maximal following birth, followed by thymic involution from as early as one year of age. By puberty, adults are left with only a small thymic remnant. While many investigators seek to counteract immune senescence in order to improve vaccine responses or ameliorate various diseases, thymic involution is evolutionarily conserved in vertebrates. Such conservation implies that immunosenescence is driven by natural selection, and may serve a particular biological function. Such a function may relate to immunity against infections or cancer, as well as to immune tolerance of commensal organisms or the foetus for reproductive compatibility.

**Introduction**

“Immunosenescence,” or ageing of the immune system, is the term given to changes (in comparison with younger individuals) observed in the immune systems of elderly individuals. Elderly individuals are predisposed to more severe symptoms from certain infections than young adults, as seen with influenza or varicella. Ninety per cent of influenza deaths in the USA occur in elderly patients.1 Despite recommendations in certain countries for the vaccination of the elderly against pathogens such as influenza, Streptococcus pneumoniae and tetanus, the elderly do not mount an effective immune response to vaccination as young adults.2-4 In addition, the elderly suffer from more malignancies than younger individuals, which may be because of failure to provide surveillance against immune system challenges, such as tumours. Taken together, these features of decreased functioning of the immune system raise the question of whether or not such changes are programmed and whether or not they respond to modifiable environmental triggers. Such triggers could pose therapeutic targets to delay age-induced frailty.

The term “senescence” is used to describe programmed biological ageing, such as the discoloration and death of autumn leaves. Prior to winter, leaves undergo an orderly degradation of cellular material, including chlorophyll, yielding typical autumn colours. While senescence in plants occurs, most often, at organ level it can also, be seen at the level of the whole organism, such as in rice, corn or wheat fields at harvest time.5 There are clues that ageing of the human immune system may similarly be a form of programmed senescence.

**The immune system**

The immune system comprises innate and adaptive arms. The adaptive immune system comprises two separate lineages, T and B lymphocytes. The innate immune system comprises myeloid cells (monocytes, macrophages and neutrophils), natural killer cells, physical barriers (the skin and mucosal surfaces), antibacterial and antiviral factors, as well as pattern recognition receptors which sense pathogen-associated molecular patterns. Developing T and B lymphocytes in the adaptive immune system undergo a random gene recombination of their T or
B cell receptors during development, to allow an almost infinite repertoire of individual T or B cells, all differing from one another within one individual and between different individuals. The genetic recombination giving rise to the T- or B-cell receptor is derived from the recombination of segmented variable, diversity and joining regions of the gene (termed V(D)J recombination), and is random, allowing a repertoire of millions of potential naïve T or B lymphocytes to be formed.6

B cells are produced in humans from common lymphoid progenitor cells in the bone marrow, undergo V(D)J recombination in the bone marrow, and exit to the peripheral blood as short-lived, naïve B lymphocytes. T lymphocytes in humans are produced similarly from lymphoid progenitor cells in the marrow, but travel to the thymus to undergo V(D)J recombination.7 Once a T or B lymphocyte has interacted with its antigen or target, it may be selected to proliferate, mature and become a long-lived memory cell. While changes in the innate and B-cell compartments have been described in ageing individuals,7,8 the most apparent changes during ageing occur in the T-cell compartment, responsible for cell-mediated immunity.

The thymus

Involvement of the thymus is the most frequently noted alteration seen in ageing vertebrates. The thymus is located at the bifurcation of the trachea, and is largest in foetal and neonatal life. The thymus in infants can often be visualised on a chest X-ray as thickening of the mediastinum. Major shrinking of the thymus occurs with time with replacement of the thymic epithelial cells with fat. The thymus is only a minor remnant of its earlier bulk by the onset of puberty. Thymic involution starts as early as one year of age, and relates to hormonal influences.2 By the age of 70 years, the thymic epithelial space shrinks to 10% of the total thymic tissue, with replacement by perivascular tissue comprising adipocytes and stroma.9 T cells are long-lived cells, and therefore most naïve T-cell specificities are generated during childhood before thymic involution. There is still some residual T-cell generation in adulthood, but most of the repertoire of naïve T cells in an adult derives from thymic output prior to thymic involution.

Total T-cell numbers in the peripheral blood appear to be relatively stable in the elderly, and seem to be maintained by homeostasis. However, the balance of naïve to memory T cells shifts with age.20 Approximately 50% of T cells are naïve in young adults, whereas most T cells are memory T cells in the elderly. Functional defects are exhibited in the remaining naïve T cells in the elderly.11 Antigen exposure converts naïve T cells into memory T cells, but naïve T cells cannot be replenished without youthful thymic function. Therefore, the adult T-cell repertoire shifts progressively from naïve to memory subsets as a person ages. This skewing of the T-cell repertoire results in the decreasing capacity to respond to novel antigens never previously encountered.

Particular pathogens may have a large impact on the repertoire of memory T cells, in particular latent viruses, such as cytomegalovirus or other herpes viruses, including herpes simplex virus, Epstein Barr virus and varicella-zoster virus.11,12 Contraction of the repertoire of diversity of memory T cells occurs in older adults, with up to 25% of the CD8+ T cells being specific for cytomegalovirus in certain older individuals.13 The cytolytic activity of CD8+ T cells also seems to be impaired in older adults, leading to poorer cell-mediated responses against pathogens like influenza.14 Thus, the memory CD8+ T cells that are present in the elderly are less diverse in repertoire and function less well than the CD8+ T cells of young adults.

Inflamaging

The term “inflamaging” has been used to describe common features of diverse clinical syndromes associated with ageing, all of which include some form of inflammation. These syndromes include atherosclerosis, insulin resistance and osteoporosis. Increased titres of autoantibodies are also apparent. Levels of interleukin-6 and C-reactive protein are often elevated. Many of these syndromes are thought to encompass an imbalance of pro-versus anti-inflammatory cytokines released by the cells of the innate immune system, such as macrophages.15 It is intriguing to reflect on whether or not the adaptive immune system may also be a key player in these age-related syndromes.

It is worth noting that the thymus is involved in the generation of naïve T lymphocytes, and also in testing out T lymphocytes for self-reactivity and only allowing certain T cells to exit the thymus into the periphery. The thymus tests the developing T cells (thymocytes) by expressing self-antigen on the thymic epithelial cells. Any T cells which bind too strongly to the self-antigen are actively eliminated in the thymus. Only 5% of thymocytes entering the thymus are allowed to exit into the periphery as naïve T cells.16 This process is one mechanism of central tolerance. T cells which exit the thymus may also fall into different functional lineages, one of which is termed “regulatory T” (Treg) cells.17 Tregs have a suppressive function and inhibit the immune responses of other cell types. Thus, the thymus is a generator of naïve T lymphocytes, and also a central organ which mediates tolerance to self-antigen to prevent autoimmunity. Whether age-related inflammatory diseases represent a loss of tolerance to self-antigens or foreign antigens remains speculative.18

Immune tolerance

Immune tolerance can be defined as a state of immune unresponsiveness specific to a particular antigen or set of antigens induced by previous exposure to those antigens. Such a state is dependent on active T-cell function. The repeated injection of a low-dose allergen, such as bee venom, is an example of the therapeutic induction of immune tolerance in order to desensitise patients with severe allergy.19,20 Immune tolerance is thought to result from both central and peripheral mechanisms. Central mechanisms of tolerance include clonal deletion or anergy induced by the thymus, as well as the generation of Tregs. These
cells are termed “natural Tregs” (nTregs). Peripheral mechanisms of tolerance are thought to occur when previously proinflammatory cells are converted to an immune-suppressive function. These are termed “induced Tregs” (iTregs). There is great interest in the role of nTregs and iTregs as therapeutic targets for chronic inflammatory diseases, allergy, transplantation, malignancy and infectious disease.\(^{21,22}\) However, unsolved mysteries remain regarding the exact mechanisms of tolerance induction and control.

One of those great mysteries is how a mother tolerates an allogeneic foetus comprising foreign antigen, and particularly the paternal human leucocyte antigen (HLA). This question has intrigued immunologists since the days of Medawar and Billingham’s classical work in the 1950s.\(^{23-25}\)

Multiple factors have been elucidated, including:
- The downregulation of polymorphic HLA-A and HLA-B by the trophoblast, while the expression of non-polymorphic loci (HLA-C and HLA-G) is maintained
- The expression of immunosuppressive factors, such as indoleamine 2,3-dioxigenase by the placenta
- The increased number or function of regulatory T cells
- Skewing of the cytokine repertoire away from proinflammatory mediators
- Antibodies directed at the foetus
- Foetal-maternal microchimerism.\(^{23,26,27}\)

However, the inability to predict or prevent clinical syndromes, such as pre-eclampsia or immunological infertility, suggests that our understanding of maternal-foetal tolerance is far from complete. It is interesting to note that the thymus undergoes chronic involution with age, as well as acute, reversible involution during certain conditions, including pregnancy\(^{16}\) or stressful situations.\(^{16}\) Thus, it is likely that additional studies are required on the role of the thymus in maintaining a successful human pregnancy and its role in pregnancy complications.

The way the body interacts with food antigens and gut commensal flora is another illustration of immune tolerance. The immune system is not “ignorant” of such antigens, but rather “tolerates” them, although the mechanisms remain only partially elucidated. The immunological “self” is in fact dynamic, comprising both internally and externally (ecologically) derived components which change over time – from prenatal life to old age. This concept has been described as the “liquid self”.\(^{29}\)

**Interventions to address immune senescence**

Whether or not ageing or its associated immune decline can be slowed by modifying the rate of thymic involution has been addressed experimentally by a number of researchers. The thymus does not function in isolation, but rather as part of a coordinated neuroimmunoendocrine axis. Sex hormones, such as adrenal and gonadal steroids, have an inhibitory effect on the thymus, while adrenalectomy or castration result in thymic hypertrophy in adult animals.\(^{15,30}\) The thymus secretes hormones, such as thymulin. Additionally, prolactin, growth hormone and glucocorticoids can be synthesised by the thymus. Thymulin has been shown to stimulate pituitary hormones, luteinising hormone and adrenocorticotropic hormone. In turn, growth hormone stimulates the production of thymulin, using insulin-like growth factor receptor-1 as an intermediate.\(^{21}\) Leptin, the hormone that mediates satiety, has also been shown to have an effect on thymic function.\(^{7}\)

Therapeutic modulation of the neuroimmunoendocrine axis has resulted in effects in animal and human models. Increases in circulating naïve T cells have been demonstrated in patients undergoing sex steroid ablation therapy for prostate cancer.\(^{12}\) The therapeutic administration of the growth hormone has had beneficial effects on thymic function in human immunodeficiency virus-infected adults.\(^{33}\) Transplantation of the thymic tissue has already played a role in the treatment of certain immune deficiencies, such as those associated with Di George syndrome.\(^{34}\) Thus, improved understanding of an interaction between the immune system and the traditional neuroendocrine system may allow targeted interventions to counteract age-induced senescence.

**Evolutionary medicine**

How long will it take before vaccines can be improved enough to effectively protect elderly individuals against common infectious diseases? Will we be able to take medication containing the correct hormones to rejuvenate our adaptive immune systems? Instead of Botox injections, will cultured thymus tissue transplants\(^{35}\) become the elixir of youth? Is ageing of the immune system a treatable disease? Addressing such questions requires contemplation and consideration to be given to the principles of evolutionary medicine.

There are two general theories of ageing – ageing by wear and tear, or ageing which is genetically determined by a biological clock.\(^{36,37}\) In support of the second, thymic involution is an ancient evolutionarily conserved process, conserved among vertebrates, including jawed vertebrates and most fish. Some species also show seasonal changes in thymus size, including amphibians.\(^{36}\) According to evolutionary or Darwinian medicine, the assertion is that understanding the principles of natural selection assists in our understanding of why we are vulnerable to disease. In particular, there is a need to understand that bodies are not machines built to plan, but rather organisms full of compromise, and selected to maximise reproduction, rather than health.\(^{38}\) Thus, a genetic trait tends to spread if it enhances reproduction, even it harms health.

Bearing in mind that a trait will spread if it enhances reproduction, an understanding of thymic function could be significantly enhanced by better understanding reproductive immunology. In fact, the concept of the immune system as a defense against invading microorganisms may merely be a bystander effect of the role of the immune system in enhancing reproduction. It
is likely that a major role of the thymus is tolerance induction, a process which remains only partly understood. Thymic involution with age, particularly occurring prior to puberty, may be better understood once maternal-fetal tolerance and its role in successful pregnancies is understood.

In order to understand immune senescence, further attention needs to be devoted to the physiological roles of the thymus at various ages, bearing in mind that the role of the thymus is at least threefold. In addition to its often-quoted role in mediating defense against invading organisms, more needs to be understood about the role of the thymus in mediating tolerance to the "liquid self," as well as its role in maintaining successful pregnancies. An evolutionary perspective is needed in order to design strategies for therapeutic interventions to prevent age-induced immune dysfunction, including suboptimal vaccine responses and inflamming.

Conflict of interest
The author declares that a conflict of interest did not inappropriately influence her when writing this article.

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