Immunosenescence Overviews and Review Articles
Handbook on Immunosenescence: Basic Understanding and Clinical Applications
Springer, 2009, 1656 pages

Tamás Fülöp, Claudio Franceschi, Katsuiki Hirokawa

"Immunosenescence" is an imprecise term used to describe deleterious age-associated changes to immune parameters observed in all mammals studied so far. It represents a rapidly progressing science in the aging field, with a vertiginous volume of new data, knowledge and concepts concerning these changes. We are poised to be in a position to translate these accumulated data into the clinical setting via better understanding of the contribution of immunosenescence to age-associated pathologies, and their prevention by appropriate interventions. This authoritative handbook seeks to encompass the current state of our knowledge on the multitude of those changes to immunity related to aging, with contributions from experts in the research and clinical areas. This book therefore considers methods and models for studying immunosenescence; cellular immunosenescence of T cells, B cells, neutrophils, antigen presenting cells, NK, NKT and stem cells; genetics; mechanisms including receptors and signal transduction; mitochondria; proteasome; cytokines; neuro-endocrine-immune networks; inflammation; thymus; clinical relevance in disease states including infections, autoimmunity, cancer, metabolic syndrome, neurodegenerative diseases, frailty and osteoporosis; modulation by nutrition, lipids, vaccination and the question "can interventions to influence immunosenescence be realistically proposed based on our current state of knowledge?"

http://books.google.com/books/about/Handbook_on_immunosenescence.html?id=VY_8YfZHKWgC

See also “Handbook_on_Immunosenescence.pdf” link on the Background Science page for abstracts of relevant chapters.
Can the immune system still be efficient in the elderly? An immunological and immunoendocrine therapeutic perspective

Pfister G, Savino W.

Abstract - The continuous global increase in life expectancy represents a central challenge for our society and impacts public social security systems, families and individuals. One of the most striking changes that occur during normal human aging is immunosenescence, a progressive and overall diminution of immune functions that affect all cells and organs of the innate and adaptive immune system. As a hallmark of human aging, the progressive involution of the thymus leads to a disturbed balance and function of naïve, memory and effector T cells, thus promoting a latent pro-inflammatory status in the elderly. Together with chronic infections such as cytomegalovirus, that accumulate during life, this situation manifests in clinically relevant implications such as poor overall immune responses, decreased ability to control infectious disease and diminished response to vaccinations. Interestingly, this process parallels changes in the hormonal balance of aging subjects. In this review, we summarize recently published intriguing results from a very active and growing field of biomedical research and discuss some clinical consequences as well as possible ways of immune- and/or hormone-based interventions to delay or reverse immunosenescence.


- Excellent summary and overview of the multiple changes the contribute to immune deterioration, and their clinical implications

**Table 1. Impact of immunosenescence on immune responses**

<table>
<thead>
<tr>
<th>Innate immunity</th>
<th>Impact</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phagocytes and phagocytosis</td>
<td>decreased</td>
<td>21, 22</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>decreased</td>
<td>20</td>
</tr>
<tr>
<td>Membrane fluidity</td>
<td>decreased</td>
<td>23</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adaptive immunity</th>
<th>Impact</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>T cell maturation</td>
<td>decreased</td>
<td>3, 15, 57, 153</td>
</tr>
<tr>
<td>Treg output</td>
<td>decreased</td>
<td>3, 15, 77, 154, 78</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical implications</th>
<th>Impact</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunological memory</td>
<td>decreased</td>
<td>3, 7, 8, 103, 126, 161, 162</td>
</tr>
<tr>
<td>Vaccination efficiency</td>
<td>increased</td>
<td>3, 7, 103, 126, 163, 164</td>
</tr>
<tr>
<td>Risk of infection diseases</td>
<td>increased</td>
<td>3, 7, 125</td>
</tr>
</tbody>
</table>

APC = Antigen-presenting cell; TCR = T cell receptor, BCR = B cell receptor.
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Age-related changes in lymphocyte development and function

Phyllis Jean Linton & Kenneth Dorshkind

The effects of aging on the immune system are widespread and extend from hematopoietic stem cells and lymphoid progenitors in the bone marrow and thymus to mature lymphocytes in secondary lymphoid organs. These changes combine to result in a diminution of immune responsiveness in the elderly. This review aims to provide an overview of age-related changes in lymphocyte development and function and discusses current controversies in the field of aging research.

One reason cell-mediated immunity decreases with age is the substantial reduction in the representation of naive T lymphocytes with a concomitant increase in memory T cells. This shift in populations is thought to be the consequence of compensatory homeostatic proliferation in response to the reduced numbers of naive cells generated by the thymus or in response to chronic antigen exposure and foreign pathogens and environmental antigens. The effect of a reduction in naive T cells in the peripheral pool is the contraction of the T cell repertoire, which leads to an increased incidence of poor responsiveness to new antigens.

http://www.nature.com/ni/journal/v5/n2/full/ni1033.html

• Good Overview

Age-related changes in lymphocyte development and function.
Linton PJ, Dorshkind K.
Sidney Kimmel Cancer Center, San Diego, California 92121, USA.
Abstract - The effects of aging on the immune system are widespread and extend from hematopoietic stem cells and lymphoid progenitors in the bone marrow and thymus to mature lymphocytes in secondary lymphoid organs. These changes combine to result in a diminution of immune responsiveness in the elderly. This review aims to provide an overview of age-related changes in lymphocyte development and function and discusses current controversies in the field of aging research.

http://www.nature.com/ni/journal/v5/n2/full/ni1033.html
As humans age, immune cell numbers remain constant, but this masks decreases in naïve T cells and shrinkage of T cell diversity, while effector memory CD8 T cells accumulate.

Active T cell depletion (would be reasonably expected to) exacerbate this decline in functionality without affecting absolute T cell numbers.


Human immunosenescence: the prevailing of innate immunity, the failing of clonotypic immunity, and the filling of immunological space.

Franceschi C, Bonafè M, Valensin S.

Abstract - According to the remodeling theory of aging we proposed several years ago, the current data on human immunosenescence depicts a complex scenario where clonotypical immunity deteriorates, while ancestral innate/natural immunity is largely conserved or even up-regulated with age. Under an evolutionary perspective, antigens are the cause of a persistent life-long antigenic stress, responsible for the accumulation of effector CD8+/CD28- T cells, the decrease of naïve T cells (CD95-) and the marked shrinkage of T cell repertoire with age. Concomitantly, NK cytotoxicity, chemotaxis, phagocytosis and complement activities remain unaffected or negligibly affected, in comparison to clonotypical immunity. Thus, immunosenescence is not a random deteriorative phenomenon but appears to inversely recapitulate an evolutionary pattern. On the whole, immunosenescence can be envisaged as the result of the continuous challenge of the unavoidable exposure to a variety of potential antigens (viruses, bacteria, but also food and self molecules among others). From this perspective antigens are nothing else than a particular type of stressor and immunosenescence appears to be the price paid to immunological memory, i.e. one of the main characteristics of the most evolutionary recent and sophisticated type of immunity. Together with the age-related thymic involution, and the consequent age-related decrease of thymic output of new T cells, this situation leaves the body practically devoid of virgin T cells, and thus likely more prone to a variety of infectious and non infectious diseases.

• Good, comprehensive review of multiple effects of aging on immunity

Immunosupportive therapies in aging.

Abstract - The primary role of the immune system is to protect the organism against pathogens, but age-associated alterations to immunity increase the susceptibility of the elderly to infectious disease. The exact nature of these changes is still controversial, but the use of screening procedures, such as the SENIEUR protocol to exclude underlying illness, helped to better characterize the changes actually related to physiological aging rather than pathology. It is generally agreed that the most marked changes occur in the cellular immune response reflecting profound alterations in T cells. Much of this is due to thymic involution as well as changes in the proportions of T cell subpopulations resulting from antigen exposure, and altered T cell activation pathways. However, a body of data indicates that innate immune responses, including the critical bridge between innate and adaptive immunity, and antigen presenting capacity are not completely resistant to senescence processes. The consequences of all these alterations are an increased incidence of infections, as well as possibly cancers, autoimmune disorders, and chronic inflammatory diseases. The leading question is what, if anything, can we do to prevent these deleterious changes without dangerously dysregulating the precarious balance of productive immunity versus immunopathology? There are many potential new therapeutic means now available to modulate immunosenescence and many others are expected to be available shortly. One main problem in applying these experimental therapies is ethical: there is a common feeling that as ageing is not a disease; the elderly are not sick and therefore do not require adventurous therapies with unpredictable side-effects in mostly frail individuals. Animal models are not helpful in this context. In this chapter we will first briefly review what we think we know about human immunosenescence and its consequences for the health status of elderly individuals. We will then discuss possible interventions that might one day become applicable in an appropriate ethical environment.

Free Full Text: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2684090/?tool=pubmed
• Focus on impaired vaccine efficacy in the elderly


Immunosenescence: what does it mean to health outcomes in older adults?

McElhaney JE, Effros RB.

Department of Medicine, University of British Columbia, Vancouver, BC, Canada

Abstract - The most profound consequences of immune senescence with respect to human health are the increased susceptibility to infectious diseases and decreased vaccine efficacy. Changes in both innate and adaptive immune function converge in the reduced response to vaccination and protection against infection and related diseases. The decline in thymic output of naïve T cells diminishes responses to novel antigens, such as West Nile Virus, while clonal expansions leading to defects in the T cell repertoire are associated with blunted responses of memory T cells to conserved epitopes of the influenza virus. Recent studies on how immunologic mechanisms of protection change during aging have led to novel strategies for improving vaccine responsiveness and outcomes of infectious diseases in older adults.

Free Full Text: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2725188/?tool=pubmed
Focus on T Cells and B Cells

Tissue Antigens. 2007 Sep;70(3):179-89.

Immunosenescence: deficits in adaptive immunity in the elderly.

Hakim FT, Gress RE.

Experimental Transplantation and Immunology Branch, National Cancer Institute, NIH, Bethesda, MD, USA.

Abstract - Aging is associated clinically with increases in the frequency and severity of infectious diseases and an increased incidence of cancer, chronic inflammatory disorders and autoimmunity. These age-associated immune dysfunctions are the consequence of declines in both the generation of new naïve T and B lymphocytes and the functional competence of memory populations. These alterations collectively are termed immunosenescence.

Immune responses in the skin in old age.
Vukmanovic-Stejic M, Rustin MH, Nikolich-Zugich J, Akbar AN.

Abstract
A marked increase in the susceptibility to cutaneous infections and malignancies has been observed in older humans indicating that cutaneous immunity becomes defective with age. In this review we will focus on recent developments in the understanding of age-related changes in immune function of the skin with a particular emphasis on how alterations in the interaction between cells involved in innate and adaptive immunity leads to decreased cutaneous antigen-specific T cell immunosurveillance.

Conclusion
In older humans, there is increased incidence of certain cutaneous malignancies and infections that point to defective immunity in the skin. Immune ageing is a multifactorial process and in the skin there is evidence that various cells exhibit defects during ageing. The DTH reaction, a memory T cell response in the skin is also defective in older humans. However, the defect may not be in the memory T cells themselves instead, conditioning of the skin environment at the site of the antigenic challenge is defective, resulting in suboptimal endothelial activation that prevents circulating memory T cells from homing to the appropriate location in the skin. This decreased cutaneous response after antigenic challenge may be related to suppression of either the acquired or innate arms of the immune response by Tregs that are found at significantly higher numbers in the skin of older humans. These findings raise the question of whether modulating Treg activity in the skin may be a way to boost cutaneous immunosurveillance of older humans that may reduce the risk of developing malignancy or infections in these individuals.