Parallel session IVB
Biology of ageing and cancer

Chair: Hans Wildiers
IMMUNOSENESCENCE AND AGEING

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The immune system

adaptive (memory)

B cells (humoral via antibodies)

T cells (cellular effectors; cytokines)

antigen-presenting cells

non-adaptive (innate)

phagocytes

dendritic cells

NK cells

A.E. 1998
Cooperation between innate and adaptive immune responses

www.goodpsych.com/stress-psychology/
Immunosurveillance vs. immunoediting

- Innate + adaptive
- Adaptive + immunosenescence

Figure 1 | Relationship between cell-intrinsic and cell-extrinsic aspects of tumour progression. This figure illustrates the central concept that multistep carcinogenesis results from crosstalk of cancer-cell-intrinsic factors and host immune system (cell-extrinsic) effects.

Figure 53-2  Age and cancer susceptibility. This figure presents a model incorporating the various factors that may play a role in the increased incidence of cancer with age.
WHAT IS IMMUNOSENESCENCE?
IMMUNITY AND AGEING

• AGEING: Immune deregulation

• CAUSE: multifactorial
  - genetic
  - intrinsic
  - environmental: nutrition

• BASIC ALTERATION: cellular immunity

• MODULABLE
## Major changes in T cells with age

Many changes have been reported over the years but there is little agreement between cross-sectional studies.

<table>
<thead>
<tr>
<th>Decreased</th>
<th>Increased</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD3+ cells (slightly)</td>
<td>CD3+DR+ cells</td>
</tr>
<tr>
<td>TCR1 (γδ) cells (slightly)</td>
<td>TCR oligoclonality</td>
</tr>
<tr>
<td>CD4+CD7+ cells</td>
<td>TCR variants (mutants)</td>
</tr>
<tr>
<td>CD4+ cells (slightly or unchanged)</td>
<td>CD4+CD8 (αα)+ cells</td>
</tr>
<tr>
<td>CD45RA+ cells</td>
<td>CD45RO+ cells</td>
</tr>
<tr>
<td>CD28+ cells</td>
<td>CD28-negative cells</td>
</tr>
<tr>
<td><strong>i.e. naive T cells</strong></td>
<td><strong>CD95+ cells</strong></td>
</tr>
<tr>
<td><em>have never seen antigen</em></td>
<td><strong>CD152 (CTLA-4)+ cells</strong></td>
</tr>
</tbody>
</table>

Pawelec. G et al.
## Functions

<table>
<thead>
<tr>
<th>Decreased</th>
<th>Increased</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proliferation with mitogens</strong></td>
<td></td>
</tr>
<tr>
<td>TCR signal transduction</td>
<td></td>
</tr>
<tr>
<td>Nuclear transcription factor activation</td>
<td></td>
</tr>
<tr>
<td>(AP-1, NF-AT, NF-κB)</td>
<td></td>
</tr>
<tr>
<td><strong>IL 2 secretion</strong></td>
<td>IL 10 secretion</td>
</tr>
<tr>
<td>soluble IL 2R secretion</td>
<td>IL 6 secretion</td>
</tr>
<tr>
<td>IL 2R expression after activation</td>
<td>TNF-α secretion</td>
</tr>
<tr>
<td>CTL generation</td>
<td></td>
</tr>
<tr>
<td>CD40L (CD154) upregulation</td>
<td></td>
</tr>
<tr>
<td>and thus B cell help</td>
<td></td>
</tr>
<tr>
<td><strong>Telomere lengths</strong></td>
<td>DNA damage</td>
</tr>
<tr>
<td><strong>Telomerase induction</strong></td>
<td>hprt &amp; HLA mutations;</td>
</tr>
<tr>
<td>DNA repair</td>
<td></td>
</tr>
</tbody>
</table>

Pawelec. G et al
CELLULAR IMMUNITY: T Lymphocytes

CAUSES OF ALTERATIONS: INTRINSIC

- Chronic antigenic stimulation
- Changes in T lymphocytes sub-populations
- Thymic involution
- Alteration in T cell intracellular signalling
Chronic antigenic stress

It is suggested that many of these changes are caused by:

chronic antigenic stress and oxidative stress

- stimulation by tumour antigens in cancer patients
- stimulation by persistent viruses in the elderly.
  - CMV, Herpes
  - Varicella-Zoster Virus (VZV)

- The CD8 cells are characterised by increased resistance to apoptosis and the CD4 cells by increased susceptibility

- Hence dysfunctional CD8 cells accumulate and specific CD4 cells are clonally deleted;

- the CD4:8 ratio can become inverted
CMV infection is associated with accumulation of the most late-differentiated CD8 cells

Most age-associated changes are exacerbated by or even caused by, chronic antigenic stressors, commonly CMV

Derhovanessian 2008
Result: an accumulation of dysfunctional cells

Hypothesis: Because T cell homeostasis maintains constant numbers of T cells in the periphery, even if naive cells continue to be generated from the thymus, the T cell repertoire will be shrunken, contributing to increased susceptibility to infectious disease and cancer and Inflam-aging.

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Table 1
B lymphocytes in elderly.

<table>
<thead>
<tr>
<th>Age-related alterations</th>
<th>Functional effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ production of Ab with high affinity and</td>
<td>Lower efficiency of humoral immune response against</td>
</tr>
<tr>
<td>specificity</td>
<td>external antigens</td>
</tr>
<tr>
<td>↑ production of Ab with low affinity</td>
<td>Higher incidence of MGUS</td>
</tr>
<tr>
<td>↑ production of autoantibody</td>
<td>Higher frequency of autoimmune disorders</td>
</tr>
</tbody>
</table>

Ab: antibody; MGUS: monoclonal gammopathies of uncertain significance.
Figure 2
Age-associated changes to DCs. Reduced numbers and functions of DCs, together with reduced numbers of naïve T cells in the periphery of aged individuals further conspire to ensure that T cell function is depressed in the elderly due to the relative decrease in T helper cell activation.
Conceptual models of age-related changes in T cell–dendritic cell interactions

High et al. JAGS. 2010
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Stimulant</th>
<th>Changes</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of circulating neutrophils</td>
<td></td>
<td>↑</td>
<td>Chatta et al., 1993 (↔), Born et al., 1995 (↔), Cakman et al., 1997 (↑)</td>
</tr>
<tr>
<td>Number of PMN precursor cells in bone marrow</td>
<td></td>
<td>↔</td>
<td>Chatta et al., 1993 (↔)</td>
</tr>
<tr>
<td>Proliferative response of precursors to...</td>
<td>G-CSF</td>
<td>↓</td>
<td>Chatta et al., 1993 (↓)</td>
</tr>
<tr>
<td></td>
<td>GM-CSF</td>
<td>↔</td>
<td>Chatta et al., 1993 (↔)</td>
</tr>
<tr>
<td></td>
<td>IL-3</td>
<td>↔</td>
<td>Chatta et al., 1993 (↔)</td>
</tr>
<tr>
<td>Chemotaxis</td>
<td></td>
<td>↓</td>
<td>Biasi et al., 1996 (↔), Esparza et al., 1996 (↔), Niwa et al., 1989 (↓), Wenisch et al., 2000 (↓)</td>
</tr>
<tr>
<td>Expression of adhesion molecules</td>
<td>CD11a</td>
<td>↔</td>
<td>Esparza et al., 1996 (↔), Butcher et al., 2001 (↔)</td>
</tr>
<tr>
<td></td>
<td>CD11b</td>
<td>↔</td>
<td>Rao, 1986 (↔), Esparza et al., 1996 (♀), Butcher et al., 2001 (↔)</td>
</tr>
<tr>
<td></td>
<td>CD15</td>
<td>↑</td>
<td>Esparza et al., 1996 (♀)</td>
</tr>
<tr>
<td>CD16 expression</td>
<td></td>
<td>↓</td>
<td>Butcher et al., 2001 (↓)</td>
</tr>
<tr>
<td>Oxidative burst after fMLP stimulation</td>
<td></td>
<td>↓</td>
<td>Biasi et al., 1996 (↓), Braga et al., 1998 a,b (↓), Tortorella et al., 2000 (↓), Lord et al., 2001 (↔/♀), Butcher et al., 2001 (↔/♀)</td>
</tr>
<tr>
<td>Ca²⁺ mobilization after fMLP stimulation</td>
<td></td>
<td>↓</td>
<td>Varga et al., 1988 (↓), Fulop et al., 1989 (↓), Lipschitz et al., 1991 (↓)</td>
</tr>
<tr>
<td>Intracellular level of Ca²⁺ in resting PMN</td>
<td></td>
<td>↑</td>
<td>Varga et al., 1988 (↑), Mohacsy et al., 1992 (↑), Wenisch et al., 2000 (↑)</td>
</tr>
<tr>
<td>Capacity to be rescued by...</td>
<td>G-CSF</td>
<td>↓</td>
<td>Tortorella et al., 1998 (↓)</td>
</tr>
<tr>
<td></td>
<td>GM-CSF</td>
<td>↓</td>
<td>Fulop et al., 1997 (↓), Tortorella et al., 1998 (↓)</td>
</tr>
<tr>
<td>After Fas activation</td>
<td>IL-2</td>
<td>↓</td>
<td>Fulop et al., 1997 (↓)</td>
</tr>
<tr>
<td></td>
<td>LPS</td>
<td>↓</td>
<td>Fulop et al., 1997 (↓), Tortorella et al., 1998 (↓)</td>
</tr>
</tbody>
</table>

The immune system and aging

- Elimination of pathogen
- Control of inflammation
- Cell homeostasis
- Immune memory

mainly T lymphocytes

IMMUNOSENESCENCE

Is accompanied with a greater susceptibility to inflamm-aging, infections, autoimmune diseases, Alzheimer disease and cancers.
IMMUNOSENESCENCE

Immune stimulation

monocyte
macrophage

Functional deficit

lymphocyte

20% CD3 and CD4

60% capacities of proliferation

Inadequate response

Prolonged inflammatory syndrome: Inflam-aging

Groupe de travail sur la vaccination en gériatrie
# Table 2. Which Alterations in the Immune System with Aging Are the Most Susceptible to Favor the Increased Cancer Development?

| Networks of immune suppression in the old: | Increased regulatory T cells  
| | Increased myeloid-derived suppressor cells  
| | Increased production of indoleamine-2,3-dioxygenase  
| | B7 family molecules (B7-H1)  
| T cells: | Naive and CTL cells with contracted repertoire and activity  
| | Altered T helper 2 > T helper 1 balance  
| | Cytokines: increased IL-10, TGF-β, IL-6  
| | Altered T cell metabolism  
| | Altered T cell signaling  
| | Low grade chronic inflammation  

*Discovery Medicine, Volume 11, Number 61, June 2011* Fulop et al.
Figure 2. Leading causes of compromised immunosurveillance in the elderly.
AGING

Immune system dysregulation

Immunosenescence

- Endocrine function
- Neural function
- Cardiovascular health
- Muscle homeostasis
- Glucose metabolism
- Oxidative stress

Naïve CD4+ T cells
Immunosurveillance
Inflam-Aging
Loss of specificity
Nutrition

Infection
Cancer
Chronic inflammatory diseases: AD, CVD
Autoimmune disorders
Frailty

Immune Risk Phenotype

CD8+CD28-CD57+
CD4:CD8 < 1
CMV seropositivity
T-cell proliferation

Fulop et al. CIA, 2008
Conclusion

- Elderly are immunocompromised with few naive cells and dysfunctional (exhausted) memory cells, due to chronic antigenic stress (CMV, cancer antigens, ...) and thymic involution with altered innate immune response resulting in inflamm-aging as well as cancer development.
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Thank you!
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Paris, France

For more information, please visit: www.siog.org