Aging & the Immune System

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The above presenter has no relevant financial relationships with commercial interests and will not reference unlabeled/unapproved uses of drugs or products in his presentation.
Presentation outline

• The aging imperative
• The immune system and immune function
• Aging of the immune system and its clinical implications
Aging: A Global Imperative

Figure 1-1.
Percent Population Aged 65 and Over: 2008

The Age Wave

is upon us -

We are living longer and remaining functional for a greater time.
Aging in China
- The Tsunami -

The largest aging population in the world:

- > 60 yrs: 247 m in 2017; projected 487 m by 2053
- > 80 yrs: 27 m in 2017 at 1 m/yr until 2025
- Empty nesters: 50%
- Disease prevalence: HTN 53%, depression 1/3, ¼ dementia, 500,000 go missing every year
International collaboration: Geriatrics program development in China

- Develop a leadership geriatrics program at PUMC:
  - “Training the trainers” program at Hopkins
  - Geriatrics demonstration ward at PUMC Hospital
  - Faculty exchange and on-site consultation

- Promoting quality geriatrics care throughout China

- Development of aging research

Funded by China Medical Board

Leng SX, et al. J. Am Geriatr Soc. 2010
Leng SX. Chinese J Geriatr 2012
Young Children and Older People as a Percentage of Global Population: 1950 to 2050

Source: United Nations Department of Economic and Social Affairs, 2007b.
### Rank Order of the World's 25 Largest Older Populations: 2008

(In millions)

<table>
<thead>
<tr>
<th>Rank</th>
<th>Country</th>
<th>Population aged 65 and over</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>China</td>
<td>106.1</td>
</tr>
<tr>
<td>2</td>
<td>India</td>
<td>59.6</td>
</tr>
<tr>
<td>3</td>
<td>United States</td>
<td>38.7</td>
</tr>
<tr>
<td>4</td>
<td>Japan</td>
<td>27.5</td>
</tr>
<tr>
<td>5</td>
<td>Russia</td>
<td>19.9</td>
</tr>
<tr>
<td>6</td>
<td>Germany</td>
<td>16.5</td>
</tr>
<tr>
<td>7</td>
<td>Indonesia</td>
<td>13.9</td>
</tr>
<tr>
<td>8</td>
<td>Brazil</td>
<td>12.3</td>
</tr>
<tr>
<td>9</td>
<td>Italy</td>
<td>11.7</td>
</tr>
<tr>
<td>10</td>
<td>France</td>
<td>10.4</td>
</tr>
<tr>
<td>11</td>
<td>United Kingdom</td>
<td>9.7</td>
</tr>
<tr>
<td>12</td>
<td>Ukraine</td>
<td>7.4</td>
</tr>
<tr>
<td>13</td>
<td>Spain</td>
<td>7.3</td>
</tr>
<tr>
<td>14</td>
<td>Pakistan</td>
<td>7.2</td>
</tr>
<tr>
<td>15</td>
<td>Mexico</td>
<td>6.7</td>
</tr>
<tr>
<td>16</td>
<td>Thailand</td>
<td>5.5</td>
</tr>
<tr>
<td>17</td>
<td>Bangladesh</td>
<td>5.4</td>
</tr>
<tr>
<td>18</td>
<td>Poland</td>
<td>5.1</td>
</tr>
<tr>
<td>19</td>
<td>Turkey</td>
<td>5.1</td>
</tr>
<tr>
<td>20</td>
<td>Vietnam</td>
<td>5.0</td>
</tr>
<tr>
<td>21</td>
<td>South Korea</td>
<td>4.9</td>
</tr>
<tr>
<td>22</td>
<td>Canada</td>
<td>4.6</td>
</tr>
<tr>
<td>23</td>
<td>Argentina</td>
<td>4.4</td>
</tr>
<tr>
<td>24</td>
<td>Nigeria</td>
<td>4.3</td>
</tr>
<tr>
<td>25</td>
<td>Philippines</td>
<td>3.9</td>
</tr>
</tbody>
</table>

THE ABSOLUTE NUMBER OF OLDER AMERICANS IS INCREASING EXPONENTIALLY, 1940–2080

Moen, 1996
HUMAN SURVIVAL CURVES FOR 1900-1980

Fries and Crapo, 1981
The immune system

• Organ level:
  – Thymus, bone marrow, spleen, lymph nodes
  – Skin, mucosa

• Cellular level:
  – T, B, NK, neutrophils, basophils, eosinophils, dendritic cells, monocytes, macrophages, etc

• Molecular level:
  – Antibodies, cytokines, chemokines, complements, etc.
Immune function

• Immune protection from Infections:
  – Natural (innate vs adaptive)
  – Vaccination

• Immune surveillance:
  – Tumor immunology

• Self recognition

• Inflammatory response
Consequences of immune dysregulation

- Allergy and hypersensitivity
- Inflammatory/autoimmune diseases
- Organ transplant and rejection
- Age-related chronic diseases?
Aging of the immune system

• Immunosenescence *versus* immune remodeling
• Aging *per se* *versus* disease processes
• Heterogeneity of the older adult population
Adaptive (antigen-specific) Immunity

Cell-mediated immunity
- Thymus involution
- Decrease in naive T-lymphocyte production
- Altered memory T-cell function
- Increase in peripheral memory T lymphocytes
- Decrease in proliferative responses to antigens and mitogens
- Th1 to Th2 cytokine shift
- Increase in HLA-DR expression
- Decrease in diversity of T-lymphocyte receptor repertoire
- Decrease in Fas-mediated T-cell apoptosis

Humoral immunity
- Decrease in B cell number
- Decrease in germinal center formation
- Altered antibody responses to specific antigens
  - Decrease in B-lymphocyte receptor repertoire
  - Dysfunctional generation of primary B lymphocytes
  - Impaired production of memory B cells
  - Decrease in generation of protective antibodies with high affinity for antigen
- Increase in IgA and IgG
- Increase in autoantibodies

Innate Immunity
- Decrease in natural killer activity in association with impending morbidity
- Decrease in γδ T cell proliferation and number
- Decrease in efficiency of antigen presentation by dendritic cells
- Dysregulated cytokine production
- Decrease in macrophage and neutrophil function
Decreased naïve peripheral T cells
(from \(\sim 3 \times 10^9\) to \(\sim 7 \times 10^8\))

Decreased repertoire diversity
(from \(\sim 10^8\) to \(\sim 10^6\))

Increased numbers of memory T and B cells

Oligoclonal expansion of memory lymphocytes
Age-associated changes of CD8 T cells at molecular level
Immunosenescence and clinical implications

**Features of immunosenescence**
- Thymus involution with alterations in T cell subsets
- Decline of naïve T cell rates
- Compensatory proliferation of memory T cells
- Decreased IL-2 production, IL-2 receptor expression and poor T cell response to IL-2
- Loss of co-stimulatory signal CD28
- Increased telomerase activity in CD28− T cells
- Diminished B cell function
- Lower levels of TREC containing naïve T cells

**Clinical implications of immunosenescence**
- Low antibody response to vaccination
- Lost ability to recognize “self” and “foreign” antigens
- Increased autoantibody levels
- Oligoclonal expansion of CD8+ T cells e.g. caused by chronic viral infections
- Changes in the cytokine profiles to a chronic inflammatory cytokine state
- Increased susceptibility to infections with increased morbidity and mortality
Consequences of the immune system aging

• Decreased immune protection from infections:
  – Increased incidence and severity of infections
  – Decreased effectiveness of immunization

• Impaired immune surveillance – cancer

• Immune dysregulation
  – Autoimmune and inflammatory diseases
  – Role of inflammation in chronic diseases

• “Inflamm-Aging” theory
Risk factors for bacterial pneumonia in older adults

<table>
<thead>
<tr>
<th>Category</th>
<th>Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysfunctional immune defense</td>
<td>Immune suppression</td>
</tr>
<tr>
<td>mechanisms</td>
<td>Drugs (e.g., corticosteroids)</td>
</tr>
<tr>
<td></td>
<td>Systemic disease (e.g., malignancy, renal failure)</td>
</tr>
<tr>
<td></td>
<td>Age-associated decline</td>
</tr>
<tr>
<td>Predisposition to aspiration</td>
<td>of upper airway or oral secretions</td>
</tr>
<tr>
<td>of upper airway or oral secretions</td>
<td>Central nervous system dysfunction</td>
</tr>
<tr>
<td></td>
<td>Swallowing disorders</td>
</tr>
<tr>
<td></td>
<td>Sedating medications</td>
</tr>
<tr>
<td>Depressed clearance mechanisms</td>
<td>Mechanical reflexes (cough)</td>
</tr>
<tr>
<td></td>
<td>Oral clearance (salivary flow)</td>
</tr>
<tr>
<td></td>
<td>Mucociliary clearance</td>
</tr>
<tr>
<td>Admission to a medical care</td>
<td>Medical care facility</td>
</tr>
<tr>
<td>facility</td>
<td>Recent hospitalization</td>
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<tr>
<td></td>
<td>Long-term care facility</td>
</tr>
<tr>
<td>Organ system dysfunction</td>
<td>Parenchymal lung disease</td>
</tr>
<tr>
<td></td>
<td>Other (cardiac, renal, hepatic)</td>
</tr>
<tr>
<td></td>
<td>Chronic disease (diabetes, rheumatologic)</td>
</tr>
<tr>
<td>Protein-calorie malnutrition or</td>
<td>hypoalbuminemia</td>
</tr>
<tr>
<td>hypoalbuminemia</td>
<td>Tobacco smoking</td>
</tr>
<tr>
<td></td>
<td>Alcoholism</td>
</tr>
<tr>
<td></td>
<td>Viral infection</td>
</tr>
</tbody>
</table>
The aging immune system and frailty in older adults

• Frailty Phenotype:
  – Slow walking speed by gender and height
  – Low grip strength by gender and BMI
  – Subjective exhaustion
  – Low levels of physical activity
  – Unintentional weight loss

• Frail = 3-5/5; Pre-frail = 1-2/5; Non-frail = 0

Inflammation: Classic Definition

INFLAMMATION

- Heat
- Redness
- Swelling
- Pain
- Loss of Function
Acute *versus* chronic inflammation

**Acute Inflammatory Reaction**

- IL-6
- CRP

**Age-Related Pro-Inflammatory State**

**Dysregulated Chronic Inflammation**

- IL-6
- CRP

- Stress/Infection
- Response
- Healing
- Time
Chronic inflammation: Obvious reasons


<table>
<thead>
<tr>
<th></th>
<th>WBC (14.2 x 10^3/mm^3)</th>
<th>WBC (18.5 x 10^3/mm^3)</th>
<th>WBC (8.2 x 10^3/mm^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td>16.7ng/ml</td>
<td>25.7ng/ml</td>
<td>2.2 ng/ml</td>
</tr>
<tr>
<td>6 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

“auto Girdlestone”
Chronic Inflammatory State

- Elevated levels of IL-6 and CRP
- Increased IL-6 production by PBMCs
- Increased white blood cell (WBC) counts
- Other pathophysiological intermediaries: decreased hemoglobin and IGF-1 levels

Walston JD, et al. *Arch Intern Med* 2002
Leng SX, et al. *Aging Clin Exp Res* 2004 (2)
Molecular mechanism: LPS-induced monocytic gene expression

LPS-challenged ex vivo expression of specific genes with average frail-over-nonfrail ratio of 2-fold or higher by CD14+ monocytes from 16 study pairs.

<table>
<thead>
<tr>
<th>Genes</th>
<th>A. GEArray&lt;sup&gt;a&lt;/sup&gt; (mean ± S.D.)</th>
<th>B. QPCR (mean ± S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Transcription factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hic-5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5.4 ± 2.1</td>
<td>3.4 ± 1.2</td>
</tr>
<tr>
<td>GRLF1</td>
<td>26.7 ± 21.9</td>
<td>1.6 ± 1.5</td>
</tr>
<tr>
<td>FADD</td>
<td>7.9 ± 4.8</td>
<td>1.7 ± 1.0</td>
</tr>
<tr>
<td><strong>Signal transduction proteins</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAPK10</td>
<td>4.6 ± 1.9</td>
<td>3.4 ± 1.3</td>
</tr>
<tr>
<td>MAP2K7</td>
<td>2.9 ± 0.9</td>
<td>4.4 ± 2.2</td>
</tr>
<tr>
<td><strong>Chemokines &amp; receptors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CXCL10</td>
<td>3.8 ± 0.8</td>
<td>4.2 ± 1.1</td>
</tr>
<tr>
<td>XCL1</td>
<td>12.6 ± 7.5</td>
<td>2.8 ± 0.7</td>
</tr>
<tr>
<td>VCAM-1</td>
<td>10.5 ± 6.4</td>
<td>1.8 ± 1.7</td>
</tr>
<tr>
<td>CCR10</td>
<td>4.3 ± 1.8</td>
<td>U.D&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Cytokines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGF-β</td>
<td>2.9 ± 0.6</td>
<td>3.1 ± 0.9</td>
</tr>
<tr>
<td>LTA</td>
<td>4.5 ± 2.4</td>
<td>4.3 ± 2.1</td>
</tr>
<tr>
<td>IL-11</td>
<td>5.1 ± 2.9</td>
<td>U.D&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Molecular mechanism: Monocytic gene expression – CXCL10

**Ex vivo** CXCL-10 expression

Frail (16) | Non-frail (16)
---|---
1.05 ± 0.88 | 0.53 ± 0.39

P < .05

Frail-over-non-frail Ratios of IL-6 Levels

Frail-over-non-frail Ratios of CXCL10 Expression Levels

r = 0.93 (P < .0001)

Qu T, et al. *Cytokine* accepted
Potential etiologic mechanisms leading to the pro-inflammatory state of aging

• Age-related decline in gastrointestinal (GI) immune defense and disturbed GI microorganism symbiosis?
  – Gut leakage?

• Cellular senescence *in vivo*?
  – Inflammatory mediators from senescent cells?*

• Impaired mechanisms for resolution?

• Persistent subclinical viral infections?
  – Cytomegalovirus (CMV), HIV, etc?

Why chronic CMV infection?

- Persistent viral infection with reactivations
- Monocytes/macrophages – primary reservoir
- Modulating monocyte/macrophage function
- Chronically stimulating the immune system
- Clonal expansion of CMV-specific T cells
- Associations of CMV seropositivity and absolute anti-CMV IgG antibody titers with frailty, disability, and mortality
- May be preventable by immunization

Strandberg TE, et al. *JAMA* 2009
CMV seroprevalence: NHANES III

Chronic CMV infection in older adults: Diagnostic challenge

- Extremely high seroprevalence
- Conflict data on CMV-specific T-cell clonal expansion in seropositive older persons
- Conflict data on relationship between anti-CMV IgG titers and frailty or disability
- Positive anti-CMV IgG serology merely suggests prior exposure to the virus

Leng SX. Editorial J Am Geriatr Soc. 2011
Laboratory diagnosis of CMV infection

- Serology: IgM or IgG
- CMV DNA detection in plasma/serum by PCR: clinical CMV infection
- CMV viral DNA detection in cell components by nested PCR
Chronic CMV infection in Older Adults: Beyond Serology

All CMV seropositive (n=16)

- pp65 (NLV) 22%

Leng SX, et al. AGE 2011
CMV Monocyte DNA and Serum IL-6

Neopterin: Immune activation

Activated T-cell

IFN-γ

Non-self

huMΦ
DCs

GCH-I

Neopterin

Interferon-γ

GCH-I

Guanosine triphosphate

Dihyrdroptiner triphosphate

Neopterin

Biopterin

(hu MΦ)

(other cells)

log(neopterin)

ANOVA p < 0.05

Post test for linear trend across status
p < 0.05

nonfrail prefail frail

Leng SX, et al. Age Ageing 2011
Influenza infection

- A common viral infection:
  - Annual rate: 5-20%
  - Pandemic threat
- Annual hospital admissions ~ 300,000
- Annual deaths ~ 50,000, 95% in older adults
- The 4th leading cause of death for older Americans
- Annual vaccination: recommended for all older adults
# Influenza immunization

| Characteristics of immunization studies conducted in the elderly population since 1955 (N=48) |
|---|---|---|---|---|---|

## Study design

| Author* | Study Year | Co* | Young control group under 65 years | No. of subjects | Age range | Mean age | Vaccine type | Vaccine dosage (μg)* | SENEUR Protocol | Vaccination status prior to study* | Living situation | New strain year |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Zeit [16] | 1989 IT | Y | 24 | 60-77 | 70 | 60-77 | Split | 10 | 77%* | C | H3, B |
| Zeit [16] | 1989 IT | Y | 60 | 61-83 | 68 | 61-83 | Sub-unit | 10 | 77%* | C | H3, B |
| Chernsky [17] | 1990 CA | Y | 90 | >65 | 73.7 | Whole | 15 | 88%** | C | H3 |
| de Bruijn [18] | 1990 NL | Y | 57 | >80 | Whole | 15 | Y | 80%* | C | H3 |
| McElhaney [19] | 1990 CA | Y | 13 | 60-64 | Whole | 15 | Y | 80%* | C | H3 |
| de Bruijn [18] | 1991 NL | Y | 55 | >70 | Sub-unit | 15 | Y | 80%* | C | H3, B |
| de Bruijn [18] | 1992 NL | Y | 26 | >70 | Whole | 15 | Y | 80%* | C | H3 |
| De Donato [27] | 1993 IT | Y | 98 | 64-74 | Whole | 15 | Y | 80%* | C | H3 |
| Iorio [31] | 1995 IT | Y | 51 | 60-84 | Whole | 15 | Y | 80%* | C | H3 |
| Iorio [31] | 1995 IT | Y | 80 | 60-84 | Whole | 15 | Y | 80%* | C | H3 |
| Muzykutat [33] | 1997 IL | Y | 90 | 60-85 | Whole | 15 | Y | 80%* | C | H3 |
| Baldo [34] | 1998 IT | Y | 93 | 65-100 | Whole | 15 | Y | 80%* | C | H3 |
| Baldo [34] | 1998 IT | Y | 93 | 65-100 | Whole | 15 | Y | 80%* | C | H3 |
| Squerione [37] | 1998 IT | Y | 65 | >65 | Whole | 15 | Y | 80%* | C | H3 |
| Stepasava [38] | 1998 SE | Y | 11 | 58-93 | Whole | 15 | Y | 80%* | C | H3 |
| Belshe [40] | 2001 US | Y | 50 | 61-91 | Whole | 15 | Y | 80%* | C | H3 |
| Frecz [41] | 2002 CH | Y | 55 | >60 | Whole | 15 | Y | 80%* | C | H3 |
| Stuf [43] | 2002 DE | Y | 273 | >60 | Whole | 15 | Y | 80%* | C | H3 |
| Stuf [43] | 2002 DE | Y | 272 | >60 | Whole | 15 | Y | 80%* | C | H3 |

---

*Authors and references are provided in Goodwin K, et al. Vaccine 2006.
Discordant harmony. Why have U.S. influenza rates in the elderly risen in synchrony with vaccination rates?

The Beeson Project: Vaccine-induced immunity against influenza in frailty 2007-2008 Season

Screening:
- Age: ≥ 70 yrs
- Frailty screening
- Community-dwelling
- Exclusions
  
  (N=78 screened)

Visit 1:
- Brief history & physical
- Pre-vaccination blood draw for evaluation
- Vaccine administration
  
  (N=78)

Visit 2:
- 3-4 wks after Visit 1
- Brief history
- Post-vaccination blood draw for evaluation
  
  (N=71)

Post-vaccination monitoring:
- Bi-weekly phone contacts
- Influenza-like illness (ILI)
- Serology evaluation of ILI
  (4-6 weeks after ILI)
  
  (N=71 completed)

Timeline
- Early October, 2007
- Early - mid November, 2007
- November, 2007 – May 2, 2008

The 2007 – 2008 influenza season

Vaccine-induced antibody response

H1N1

Post-/pre-vaccination GMT Ratios

H3N2

B

Post-vaccination rates of influenza-like illness and laboratory-confirmed influenza infection

R01 project: Influenza vaccine failure in adults over 75 >> Role of chronic CMV infection <<
**In vitro human CMV studies – INTERVENTION**

**WI38 human fibroblasts**

<table>
<thead>
<tr>
<th>WI-38 Young</th>
<th>CMV alone</th>
<th>RES (20 μM)+CMV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ctrl 4 24 48 72</td>
<td>24 48 72 (h)</td>
<td></td>
</tr>
</tbody>
</table>

CMV Immediate Early (IE)

β-Actin

**Young**

**Old**

**Young+CMV**

**Young+RES+CMV**

**RES: Resveratrol**

Current working model

Human CMV

- T-cell Clonal Expansion
- Weakened Immune Surveillance
- T-cell Immunosenescence
- Monocytes /МФ Activation dysregulation
- Chronic Inflammation

Influenza Vaccine Failure → HIV & Aging → Frailty, Disability, Mortality

Leng SX. Editorial J Am Geriatr Soc. 2011
Li HF. et al Exp Geontol. 2014
Compression of Vulnerability and Frailty

- **Hypothetical Present State**
- **Scenario I: Extension**
- **Scenario II: Compression**
## Acknowledgements

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