In Search of a Salient Marker of Immune Function for Population Health Research

Lydia Feinstein,ab Elizabeth McClure,b Jennifer B Dowd,c and Allison E. Aielloab

aCarolina Population Center, The University of North Carolina at Chapel Hill
bDepartment of Epidemiology, The University of North Carolina at Chapel Hill
cCUNY School of Public Health, Hunter College, City University of New York
Population-based longitudinal cohort study (N=2081)

5 study waves & 4 in-home blood draws (2008-2013)
Bio-social Integration in DNHS

**Psychosocial**
- Socio-demographics
- Neighborhood
- Social Support
- Mental Health
- Substance Use
- Trauma

**Biological**
- Anthropometry
- Inflammation
- Epigenetics
- Infections
- Immunological
Overview

Background: Stress, infection, and the aging immune system

Detroit Neighborhood Health Study

- Socioeconomic Status, Cytomegalovirus, and T-Cell Markers of Immunological Aging
- Characterizing Thymic Function in the Community Setting

Future directions and challenges
Why the Immune System?

Critical to multiple health outcomes

Target of public health and medical interventions
Immune Function Declines with Age

Age and the human T-cell repertoire

Understanding immunosenescence to improve responses to vaccines.
Variability in Immunological Aging

Pathogen exposure

Psychosocial stress
The Immune Risk Profile and Associated Parameters in Late Life: Lessons from the OCTO and NONA Longitudinal Studies

Anders Wikby, Jan Strindhall, Boo Johansson

Table 5 Characteristics of the Immune Risk Profile

<table>
<thead>
<tr>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased CD8+ and CD3+</td>
</tr>
<tr>
<td>Decreased CD4+ and CD19+</td>
</tr>
<tr>
<td>CD4/CD8 ratio &lt; 1</td>
</tr>
<tr>
<td>Increased lately differentiated CD8+CD28-CD27- cells</td>
</tr>
<tr>
<td>Depletion of naive CD8+CD45RA+CCR7+ cells</td>
</tr>
<tr>
<td><strong>CMV-seropositivity</strong></td>
</tr>
<tr>
<td>Clonal expansion of CD8+ cells carrying receptors for CMV</td>
</tr>
<tr>
<td>High proportion of dysfunctional cells among the CMV-specific CD8+ cells</td>
</tr>
</tbody>
</table>
### CMV Prevalence in the United States (1999-2004)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Low</th>
<th>Middle</th>
<th>High</th>
<th>&lt; High School</th>
<th>HS or GED</th>
<th>&gt; High School</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12-19</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-29</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-39</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CMV Reactivation Induced by Psychosocial Stress

Socioeconomic Status, Cytomegalovirus, and T-Cell Markers of Immunological Aging
Pilot Study Aims

**Aim 1:** Examine the associations between socioeconomic status and T-cell markers of aging

**Aim 2:** Assess whether CMV IgG antibody levels mediate the associations between socioeconomic status and T-cell markers of aging
T-cell Sub-Sample

T-cell phenotypes assessed in Wave 1 (n=85)

Median age 45 years (IQR: 35-56 years)

63% female

80% Non-Hispanic Black

48% ≤ High school education
Ascertainment of T-Cell Phenotypes

T-cell subsets analyzed using flow cytometry in cryopreserved peripheral blood mononuclear cell (PBMC) samples
Study Measures

Outcome: T-cell Markers of Immune Aging

↓ CD4:CD8 T-cell ratio

↑ CD4 Effector:Naïve T-cell ratio

↑ CD8 Effector:Naïve T-cell ratio

Exposure: Pre-tax annual household income
Mediator

CMV IgG Antibody Level

Income ➔ Immune Aging

CMV IgG antibodies quantified by ELISA
Statistical Analysis

Linear regression

Total Effect: Income $\rightarrow$ Immune Aging

Mediation Analysis (*Preacher and Hayes, 2008*)

Indirect Effect: Income $\rightarrow$ CMV $\rightarrow$ Immune Aging

Direct Effect: Income $\rightarrow$ Immune Aging
Income and T-cell Markers of Aging

Model 1: Adjusted for age, gender, and race/ethnicity
Model 2: Additionally adjusted for smoking, medication use, and mental health status.
Mediation Results

Income → CMV IgG → CD4 E:N ratio

- **Indirect effect**
  - CMV IgG: 0.22 (0.08, 0.39)**

Income → CMV IgG → CD8 E:N ratio

- **Indirect effect**
  - CMV IgG: 0.09 (0.02, 0.21)**

Income → CD4 E:N ratio

- **Direct effect**
  - 0.19 (-0.09, 0.47)

Income → CD8 E:N ratio

- **Direct effect**
  - 0.11 (-0.07, 0.29)

*P value <0.1
**P value <0.05

Adjustments: age, gender, race/ethnicity, smoking, medication use, and mental health status
Characterizing Thymic Function in the Community Setting
Thymic Involution Over Life Course

Newborn

Adult
Thymic Function Critical for Immune Response

Essential for maintaining supply of naïve T cells

Reduced thymic function predictive of poor health outcomes

Stress-induced thymic atrophy compromises immune system
Aims

**Aim 1:** Characterize thymic function in community setting

**Aim 2:** Examine whether economic stressors are associated with reduced thymic function
Thymic Function Sub-Sample

Thymic function measured in Wave 4 (n=390)

Median age 48 years (IQR: 38-62 years)

49% female

88% Non-Hispanic Black

53% ≤ High school education
Thymic Function Measurement

Signal joint T-cell receptor excision circles (sjTREC)

Nonreplicated extrachromosomal DNA by-products of TCR gene rearrangements evident in recently developed T cells

(Douek et al. Nature 1998)

Analyzed by PCR in genomic DNA
Thymic function in DHNS

Mean Thymic Function (sjTREC per Million Whole Blood Cells) by Age and Gender

Past-Year Economic Stressors and Thymic function

*Linear regression models adjusted for age, gender, race/ethnicity, and education*
Conclusions

Immune signatures provide clues about how social determinants influence biological pathways to health

Research gaps remain

Smaller-scale, yet still representative, studies offer opportunities more detailed immune phenotyping

Ability to measure thymic function in dried blood spots offers potential for larger-scale application
Acknowledgements

Aiello Research Group

Allison Aiello
Christian Douglas
Anissa Vines
Amanda Simanek

Rebecca Stebbins
Erline Miller
Libby McClure
Evette Cordoba
Julia Ward

Graham Pawelec and Evelyna Derhovanessian (University of Tübingen, Germany)

Sara Ferrando-Martínez and Manuel Leal (Laboratory of Immunovirology, Institute of Biomedicine of Seville, IBiS, Virgen del Rocío University Hospital, Sevilla, Spain)

Gregory Sempowski and Melissa Samo (Duke University)

Funding Support

NICHDD T32 HD007168 (PI: Halpern)
NICHDD P2C HD050924 (PI: Morgan)
NIDA R01 DA022720 (PI: Aiello)
NIDA R01 DA022720-S1 (PI: Aiello)
NIA AG013283 (PI: Aiello)
Questions?

Lydia Feinstein, PhD, MSPH
Department of Epidemiology & Carolina Population Center
The University of North at Chapel Hill
✉️ lfeinst@email.unc.edu