Immune Activation and Inflammation: Role in Co-morbidities in HIV Disease

Alan Landay, PhD
Professor and Chairman
Department of Immunology/Microbiology
Rush University Medical Center
Chicago, IL

Seema Desai, PhD
Assistant Professor
Learning Objectives:

At the conclusion of this presentation, learners should be better able to:

• Describe the relationship of immune activation and inflammation and how they can impact non HIV co-morbidities

• Discuss the potential pathways such as microbial translocation that can contribute to immune activation/inflammation in HIV subjects
Human Immune System

Innate Immunity
- pDC
- mDC
- iNKT
- NK
- Mast cells
- Complement

Adaptive Immunity
- CD4 T cells
- CD8 T cells
- B cells
Pneumocystis carinii pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired cellular immunodeficiency

MS Gottlieb, R Schroff, HM Schanker, JD Weisman, PT Fan, RA Wolf, and A Saxon

An outbreak of community-acquired Pneumocystis carinii pneumonia: initial manifestation of cellular immune dysfunction

H Masur, MA Michelis, JB Greene, I Onorato, RA Stouwe, RS Holzman, G Wormser, L Brettman, M Lange, HW Murray, and S Cunningham-Rundles

Table 3. Characterization of T-Lymphocyte Subsets.

<table>
<thead>
<tr>
<th>Group</th>
<th>Lymphocyte Subset</th>
<th>T10</th>
<th>LEU 3/LEU 2 Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LEU 1</td>
<td>LEU 2</td>
<td>LEU 3</td>
</tr>
<tr>
<td>Patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>45</td>
<td>57</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>47</td>
<td>52</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>49</td>
<td>57</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>67</td>
<td>47</td>
<td>2</td>
</tr>
<tr>
<td>Mean ± S.D.</td>
<td>52 ± 10.1</td>
<td>53.3 ± 4.7</td>
<td>3.0 ± 4.76</td>
</tr>
<tr>
<td>Normal subjects</td>
<td>71.0 ± 10.0</td>
<td>28.0 ± 8.0</td>
<td>46.0 ± 12.0</td>
</tr>
</tbody>
</table>

T10 = CD38
What is meant by “immune activation”?

- Activated cells express “activation markers”
- Activated cells make more stuff
  - B cells make Immunoglobulins
  - T cells, NK cells, monocytes and other APC make cytokines
- Activated cells also may enter cell cycle with an “intent” to divide
  - T cells enter cell cycle when their T cell receptors encounter antigen
  - T cells can also be induced to enter cell cycle by “bystander” mechanisms, e.g. via exposure to certain cytokines
Why Do We Still Care About Inflammation and Immune Activation in HIV?

• Most HIV-infected patients now achieve and maintain viral suppression on ART
• Abnormal immune activation and inflammation persist despite VL<75
• Inflammatory markers predict CAD and death during ART
• Strategies to decrease inflammation and immune activation are urgently needed.
T Cell Activation Declines with Lower Levels of Viral Replication

T Cell Activation Declines Further During ART-mediated VL Suppression

…but ART-suppressed Patients Have Persistently Abnormal T Cell Activation

High T Cell Activation Associated with Blunted CD4 Recovery

Spearman's rho: -0.40
P<0.001

Hunt et al, *JID*, 2003
Determinants of Accelerated Aging in HIV Infection

**Effects of treatment**
- Residual viral replication
- Persistent viral expression (in LN)
- Altered Th17/T<sub>reg</sub> ratio
- Collagen deposition
- Microbial translocation
- High pathogen load (cytomegalovirus, hepatitis C virus)
- Thymic dysfunction

**Non-AIDS events and premature mortality**

*Source: The Lancet 2010; 376:49-62*
Implications of Mucosal CD4 T Cell Depletion, Barrier Defect, and Inflammation

Brenchley

Nat Immun

2006
Markers of Microbial Translocation

- LPS – Lipopolysaccharide
- LBP - LPS binding protein
- Soluble CD14
- IFN-α
Microbial Translocation Correlates With Immune Activation and Inversely With Immune Reconstitution

Microbial Translocation Decreases with HAART but Persists for Years

Consequences of Microbial Translocation

- Inflammation
- Chronic Immune Activation
- Altered Microbiome

HIV disease progression
Non AIDS defining Co-morbidities
Early Aging
Unresolved Questions Around Persistent HIV-associated Inflammation

- Any interventions that actually improve clinical outcomes?
- How much non-AIDS morbidity is due to ongoing inflammation vs. irreversible damage accumulated prior to HAART?
- Does HIV cause irreversible aging of the immune system?
At 25 years into the HIV epidemic many HIV-infected patients have survived to older ages……by 2015, > 50% of the HIV-infected population will be > 50 years of age[1]

Late HAART Era Patients Have an Extended Life Expectancy though still Have a 10y Shorter Life Expectancy than HIV-Negative Controls[2]

Results from the SMART study showed that non-AIDS defining co-morbidities occur despite HAART[3]

Several immunological alterations such as activation/inflammation that characterize HIV-1 infection are similar to those associated with normal aging

Thus, immunological and physiological alterations along with co-morbidities suggests that advanced aging occurs in HIV disease

SMART: Inflammatory Markers Strongly Associated With Mortality and CVD Events

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>All-Cause Mortality (N=85)</th>
<th>Fatal or Non-fatal CVD (N=136)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>P-value</td>
</tr>
<tr>
<td>hs-CRP</td>
<td>3.5</td>
<td>0.004</td>
</tr>
<tr>
<td>IL-6</td>
<td>12.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Amyloid A</td>
<td>2.3</td>
<td>0.08</td>
</tr>
<tr>
<td>Amyloid P</td>
<td>1.1</td>
<td>0.90</td>
</tr>
<tr>
<td>D-dimer</td>
<td>13.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>F1.2</td>
<td>1.4</td>
<td>0.45</td>
</tr>
</tbody>
</table>

Mechanism Leading To End Stage Senescence

Clonal expansion

End stage senescent T cells

Adaption Effros RB
Senescent T cells affect organ Function

**Immune system**
- Proliferation, killing
- Pro-inflammatory cytokines function as suppressor cells
- Correlate with poor vaccine response

**Neurocognitive (Alzheimer’s disease)**
- Telomere length correlates with disease status

**Bone**
- Correlate with osteoporotic fractures
- IL-6, TNF-α correlates with bone loss

Source: CROI, 2008
A higher frequency of senescent T cells is associated with lower arterial distensibility (WIHS)

After adjustment for age and other factors, the frequency of senescent CD4+ and CD8+ T cells was strongly and consistently associated with arterial distensibility (P < 0.01 for CD4 and CD8)

Kaplan R et al, #709 17th Conference on Retroviruses and Opportunistic Infections, San Francisco, 2010
T-cell activation and carotid lesions
Multivariate analyses, HIV+ patients

<table>
<thead>
<tr>
<th></th>
<th>Prevalence</th>
<th>95% Conf Interval</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ratio ( \text{SD} )</strong></td>
<td><strong>Lesions</strong></td>
<td></td>
<td><strong>p</strong></td>
</tr>
<tr>
<td>CD4+ T-cell activation</td>
<td>1.6</td>
<td>1.1, 2.2</td>
<td>0.02</td>
</tr>
<tr>
<td>CD8+ T-cell activation</td>
<td>2.0</td>
<td>1.2, 3.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>1.0</td>
<td>0.6, 1.4</td>
<td>0.84</td>
</tr>
</tbody>
</table>

Adjusted for HIV medication use, age, race, education, income level, family history of MI, smoking, alcohol consumption, opiate use, injection drug use, study site, lipids, glucose, BMI

Kaplan R, et al. *JID 2011*
Causes & Consequences of Co-morbidities In HAART Treated HIV Infected Patients

Inflammation
Activation
Coagulation
Microbial translocation
Latent virus

Viral Replication

Co-morbidities

CVD Neurocog Cancers Liver Disease Metabolic Disease

Premature Aging

Seema Desai, Rush University
Modalities of De-accelerating Senescence

- **HAART**: reduces naive T-cell consumption and helps to restore their numbers, although sub-optimally
- **Inhibitors of pro-inflammatory cytokines** (eg, anti-IL-1β, anti-IL-6, or anti-TNF-α)
- **Controlling translocation**: Antagonists of TLR-4, antibiotic (Rifaxamin) to restore gut flora and prebiotic sugar to select good bacteria. Sevelamer to block endotoxin.
- **Adjuvant therapies** such as r-hIL-7 to stimulate recent thymic emigrant and increase the naïve pool.
- **Telomerase-based approaches** such as TAT2 (cycloastragenol) that activate telomerase could slow telomere loss
- **Others** targeting immune exhaustion need to be explored.
Immune Aging Model

What have we learned, a quiz
Which of the Following Can Contribute to Immune Activation/Inflammation in HIV+

1. Low level viral replication
2. Microbial translocation
3. Co-infections
4. All of the above
Chronic Immune Activation - quiz

1. Improves the clinical response to antiretroviral therapy
2. Is not important as long as patients are adherent to their medications
3. Associated with early aging
4. Effectively increases CD4 counts
Early Aging in HIV+ Patients

1. Associated with a normal immune response to vaccines
2. Characterized by development of non-AIDS comorbidities, i.e. cardiovascular disease
3. Improves with antiretroviral intensification
4. Does not impact life expectancy of HIV+ patients