Immune Activation and the Pathogenesis of HIV Infection

Michael M. Lederman, MD
Depletion of circulating CD4+ T cells results in progressive immune deficiency and AIDS.
HIV replication is necessary to drive the immune deficiency (CD4 depletion) that defines AIDS

– Is it sufficient?
– If not, what other factors contribute?
T cell homeostasis

Thymus

Bone Marrow

Lymph Node

Central memory cell

Effector cell

Naïve T cells

Homeostatic proliferation

Periphery

Thymus

Bone Marrow

T cell homeostasis

Presented at the 4th INTEREST Workshop
25-28 May 2010, Maputo Mozambique
# T cell maturation subsets

<table>
<thead>
<tr>
<th>Subset</th>
<th>TCR diversity</th>
<th>Homing Receptors</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naive</td>
<td>Broad</td>
<td>Lymph Nodes</td>
<td>Capacity for new responses</td>
</tr>
<tr>
<td>Effector</td>
<td>Current antigen exposures</td>
<td>Tissues</td>
<td>Protection: cytokines cytotoxicity</td>
</tr>
<tr>
<td>Central Memory</td>
<td>Prior antigen exposures</td>
<td>Lymph Nodes</td>
<td>Effector cell renewal</td>
</tr>
</tbody>
</table>
The CD4 lymphopenia of AIDS is due to:

- HIV infection of Effector Memory CD4 T cells
- Bystander activation, death (and infection) of Central Memory CD4 T cells
- Failure of Naïve CD4 T cell expansion capacity

- Some of this is related to inappropriate sequestration of Effector Memory CD8 T cells in lymphoid tissue
A tale of two monkeys

Rhesus

Sooty Mangabey
SIV replication - not sufficient to drive immune deficiency in the naturally adapted host

• Rhesus (pathogenic SIV infection) – model for HIV infection
  – High level viremia
  – Circulating CD4 depletion
  – OI risk and death
  – High level immune activation

• Sooty Mangabey (non-pathogenic SIV infection)
  – High level viremia
  – CD4 depletion extremely rare
  – No OIs
  – Low level immune activation
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>LEU 3/LEU 2 Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T10</td>
<td></td>
</tr>
<tr>
<td>per cent lymphocytes reactive with monoclonal antibodies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>45</td>
<td>57</td>
</tr>
<tr>
<td>2</td>
<td>47</td>
<td>52</td>
</tr>
<tr>
<td>3</td>
<td>49</td>
<td>57</td>
</tr>
<tr>
<td>4</td>
<td>67</td>
<td>47</td>
</tr>
<tr>
<td>Mean ±S.D.</td>
<td>52 *</td>
<td>53.3 †</td>
</tr>
</tbody>
</table>

Normal subjects (n = 16 [mean ± S.D.])

T10 = CD38
Immune activation predicts HIV disease progression

Janice Giorgi

- Immune activation (though related to VL) predicts HIV disease progression risk independently
  - CD38 expression a better predictor of disease progression than VL. (Liu JAIDS ’98, Giorgi JID ’99, Deeks ’04, Wilson ‘04)
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
How to measure cell cycling and turnover

Ki-67

BrdU labeling

www.med.unibs.it/~marchesi/dna.html
Circulating S phase T cells are more frequent in HIV infection than among controls

Sieg, *J Inf Dis* '05
What happens to circulating S phase T cells in HIV infection?

Circulating S phase cells express caspase 3

Circulating S phase cells die ex vivo

Sieg et al J Leuk Biol '08
Most circulating S phase cells in HIV infection are **Central Memory T cells**

- Though correlated with viremia, they are not HIV reactive and look to be activated by "**bystander**" mechanisms (ie – not through the T cell receptor)

  Sieg et al, *J Inf Dis ’05*

- Since central memory cells home to lymphoid tissues, perhaps this is where bystander activation takes place
The lymph node in HIV infection is enriched with effector T cells.

- Naïve T cells
- Effector cells
- Central memory cells
- Peripheral tissues

Tenner Racz '93
Cheynier '94
Altfeld '02
Brenchley '04
Biancotto '07
Cytokine expression is perturbed in the HIV infected lymph node

LN control n = 10
HIV+ LN n = 12

Are these cytokines driving bystander activation and turnover of central memory T cells?

Biancotto et al, Blood ‘07
Interval Summary

• Immune activation distinguishes pathogenic from non-pathogenic SIV infection
• Immune activation is an important predictor of HIV disease progression
• HIV infection is characterized by an increased frequency of activated central memory cells in cell cycle
• These activated central memory cells appear to be activated by bystander mechanisms and do not complete cycle ex vivo but tend to die
• Lymphoid tissue in HIV infection is enriched for effector memory T cells and for common gamma chain receptor cytokines IL-2 and IL-15 that can drive bystander T cell activation
HIV infection rapidly depletes gut effector memory CD4 T cells

HIV-  

HIV+

Veazey ’98, Guadalupe ‘03, Mehandru ‘04  
Matapallil ‘05  

Brenchley et al  JEM 2004
Plasma LPS levels are increased in chronic HIV infection

Brenchley et al, *Nat Med* 06
Plasma levels of bacterial 16s rDNA are increased in HIV infection

Jiang et al J Inf Dis ‘09
Levels of circulating microbial products correlate with indices of immune activation

Brenchley et al Nat Med ‘06  Jiang et al J Inf Dis ‘09
Levels of microbial products correlate inversely with magnitude of CD4 T cell restoration on HAART

Jiang et al J Inf Dis ‘09

Brenchley et al Nat Med ‘06

CC = -0.65, p = 0.007
How do these microbial products drive immune activation? (that’s their job!)

Kanzler et al. Nat Med ‘07

Presented at the 4th INTEREST Workshop
25-28 May 2010, Maputo Mozambique
Microbial TLR ligands activate CD4+ T cells to enter cell cycle and CD8+ T cells to express CD69.
Interval Summary  
- part II

- Injury to the gut in HIV infection is associated with heightened translocation of microbial products into systemic circulation
- Systemic levels of these microbial products are related to the magnitude of immune activation and predict CD4 T cell homeostasis on HAART
- Microbial TLR ligands drive bystander T cell activation *in vitro*
- Effector Memory CD8 T cells are activated to express CD69 (making them “sticky” via cytoplasmic retention of S1P1?)
- Central Memory CD4 T cells are activated to enter cell cycle and to die
Activation of adaptive and innate immune systems drives HIV pathogenesis in the lymph node
Presented at the 4th INTEREST Workshop
25-28 May 2010, Maputo Mozambique

Immune Deficiency → Immune Activation

HIV replication

Immune Activation → Gut Mucosal damage

Microbial Translocation → Immune Activation
Dramatis personae

CASE:
Scott Sieg
Benigno Rodriguez
Robert Asaad
Doug Bazdar
Nick Funderburg
Enrique Espinosa
Wei Jiang
Angel Luciano
Kathy Medvik
Clifford Harding
Gareth Hardy

NIH VRC
Jason Brenchley
Danny Douek

NICHD
Leonid Margolis
Angelique Biancotto
Jean-Charles Grivel

The BBC

Presented at the 4th INTEREST Workshop
25-28 May 2010, Maputo Mozambique
The “Bad Boys of Cleveland”

E. Haddad
G. Hardy
B. Rodriguez
R. Bosch

S. Sieg
T. Schacker
J. C. Grivel
R. Sekaly

S. Deeks
L. Margolis
D. Douek
A. Landay

A. Tenorio
M. Lederman
R. Kalayjian
G. Silvestri

J. Brenchley
C. Harding
Z. Grossman
P. Hunt

Not shown:
I. Sereti
A. Blancotto
M. Carrington
W. Jiang
N. Funderburg