NK cell and viral dynamics within lymph nodes during pathogenic and non pathogenic SIV infection

Les Pensières – Fondation Mérieux Conference Center - May 2016

Unité « HIV, Inflammation and Persistence »
Virology Department
Institut Pasteur, Paris, France
More than 30 years of HIV Science
Rapid progress but still no vaccine and no cure

Highly active anti-retroviral therapy (HAART)

HIV persistence in lymph node follicles

**American Journal of Pathology, Vol. 144, No. 6, June 1994**
Early Stages of Simian Immunodeficiency Virus Infection in Lymph Nodes

**Evidence for High Viral Load and Successive Populations of Target Cells**


B cell follicle sanctuary permits persistent productive simian immunodeficiency virus infection in elite controller:

Yoshinori Fukazawa1,2, Richard Lum1,2, Afam A Okoye1,2, Haesun Park1,2, Kenta Matsuda3, Jin Young Bae1,2, Shoko I Hagen1,2, Rebecca Shoemaker4, Claire Deleage5, Carissa Lucero6, David Morcock6, Tonya Swanson1,2, Alfred W Legasse1,2, Michael K Axthelm1,2, Joseph Hesselgesser7, Rimas Grizaitis5, Vanessa M Hirsch8, Paul T Edlefsen9, Michael Piatak, Jr1, Jacob D Estes3, Jeffrey D Lifson4 & Louis J Picker1,2.
African NHP  
Natural hosts of SIV  
Non pathogenic infection

Asian NHP  
Experimental hosts of SIV  
Pathogenic outcome

<table>
<thead>
<tr>
<th>Natural host</th>
<th>Human/MAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic inflammation</td>
<td>-</td>
</tr>
<tr>
<td>Viral mutation rate</td>
<td>+++</td>
</tr>
<tr>
<td>Viremia (blood)</td>
<td>+++</td>
</tr>
<tr>
<td>Viral load in gut</td>
<td>+++</td>
</tr>
</tbody>
</table>

Rapid control of SIVagm replication in lymph nodes in AGM

Diop et al, JVI, 2000
SIVagm, SIVmac: similar high replication levels during acute infection but opposite profiles in blood and lymph nodes in chronic infection.

6 AGM (sabaeus), SIVagm.sab\textsubscript{92018}, high dose IV
6 MAC (cynomolgus), SIVmac\textsubscript{251}, high dose IV

**Blood samplings**
**Lymph node biopsies**

**Blood**

![Graph showing SIVagm RNA copies/ml over time]

**Lymph nodes**

![Graph showing SIVagm RNA copies/10^6 cells over time]
Chronic SIVagm infection in AGM: Strong control of viral replication in T zone and no virus in follicles

Blue: DAPI
Red: SIV
Green: B cells

SIV RNA in follicles

Number of SIV RNA positive cells per follicle section

0 50 100 150 200

AGM
MAC
AGM/SIV: no evidence for CD8$^+$ T cells in lymph node follicles

Diop et al, JVI, 2000
### Blood cytokine profiles during HIV/SIV infections

<table>
<thead>
<tr>
<th>Marker</th>
<th>AGM</th>
<th>HUMAN MAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-15</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>IFN-α</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>IP-10</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>MCP-1</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>IFN-g</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>IL-18</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>TNF-a</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>IL-8</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>sTrail</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>IL-6</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>IL-12</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Mip-1a</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>MIP1-b</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>TGF-b</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>IL-10</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>IP-10</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>sCD14</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

Order of appearance in HIV and SIV infections

*Jacquelin et al, JCI, 2009*

*Jacquelin et al, Plos Path 2014*
Innate Immune Responses and Rapid Control of Inflammation in African Green Monkeys Treated or Not with Interferon-Alpha during Primary SIVagm Infection

Béatrice Jacquelin¹, Gaël Petitjean¹, Désirée Kunkel¹, Anne-Sophie Liovat¹, Simon P. Jochems¹,², Kenneth A. Rogers³, Mickaël J. Ploquin¹, Yoann Madec⁴, Françoise Barré-Sinoussi¹, Nathalie Dereuddre-Bosquet⁵, Pierre Lebon⁶, Roger Le Grand⁷, François Villinger⁸, Michaela Müller-Trutwin⁹

NK cells
- Ki-67 in Blood
- CD69 in LN
- CD107a in LN

Trafficking to lymph nodes?
Tissue trafficking of NK cells

Rapidly recruited in a CCR7-independent, CXCR3-and CD62L-dependent manner to lymph nodes on stimulation by the injection of mature DCs


Early viral replication in lymph nodes provides HIV with a means by which to escape NK-cell-mediated control

Rutger Luteijn*1, Gaia Sciaranghella*2, Jan van Lunzen2, Anne Nolting1, Anne-Sophie Dugast1, Musie S. Ghebremichael1,3,4, Marcus Altfeld1 and Galit Alter1


Simian Immunodeficiency Virus Infection Induces Expansion of α4β7+ and Cytotoxic CD56+ NK Cells

R. Keith Reeves,1 Tristan I. Evans,1 Jacqueline Gillis,1 and R. Paul Johnson1,2*

J Virol. 2010 Sep;84(17):8959-63
Before SIV infection: most of NK cells in paracortex (MAC and AGM)

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Before SIV infection: most of NK cells in paracortex (MAC and AGM)
Frequent decrease of NK cells with lymph node homing markers
Similar between pathogenic and non-pathogenic SIV infection
Thank you