The Role of B Cell Follicles in HIV Replication and Persistence

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Conflicts

Dr. Connick has served as a member of data monitoring committees for Sangamo Biosciences-sponsored clinical trials.
Most HIV Replication Occurs In Secondary Lymphoid Tissues


Lymph Node Structure

- Paracortex (EF)
- Follicle (F)
- Germinal Center (GC)
Two Patterns of HIV RNA are Found in Lymph Nodes

HIV RNA in situ+ (red); CD20 (white), FDC (green)

Intracellular HIV RNA In CD4+ Cells

Virions Bound to Follicular Dendritic Cells (FDC)

HIV Replication is Concentrated in CD4+ cells in B Cell Follicles


A CD4+ cell in F had a 31-fold (range, 6- to 155-fold) greater likelihood of being HIV RNA+ as a CD4+ cell in EF.

Are T Follicular Helper Cells (TFH) More Permissive to HIV than Other CD4+ T Cells?

Tonsil Infection with HIV GFP Reporter Virus

GFP Expression in Tonsil Subsets

% GFP+

MFI of GFP

GFP Expression in Sorted Tonsil Cell Subsets

GC TFH are highly permissive, but alter their phenotype during productive infection.

Why Are CTL Unable to Suppress HIV Replication in B Cell Follicles?

Hypothesis: B cell follicles are immune privileged sites.
CD8+ Cells and Many Antiviral Proteins Are Less Abundant in B-cell Follicles

HIV-1 seropositive subjects (N=15)

<table>
<thead>
<tr>
<th>Protein</th>
<th>Median Cells/mm² (range)</th>
<th>EF Median Cells/mm² (range)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>INF-α</td>
<td>0.4 (0.0 - 40.4)</td>
<td>2.7 (0.4 – 29.0)</td>
<td>0.0186</td>
</tr>
<tr>
<td>α-Defensins 1, 2, 3</td>
<td>2.5 (1.4 - 12.4)</td>
<td>4.9 ( 0.8 - 8.5)</td>
<td>0.0127</td>
</tr>
<tr>
<td>RANTES</td>
<td>282 (63 – 1122)</td>
<td>1025 (213 – 3065)</td>
<td>0.0007</td>
</tr>
<tr>
<td>MIP-1α</td>
<td>32 (6 - 132)</td>
<td>105 (21 – 577)</td>
<td>0.0054</td>
</tr>
<tr>
<td>MIP-1β</td>
<td>14 (0 – 299)</td>
<td>23 (9 -244)</td>
<td>0.4251</td>
</tr>
<tr>
<td>Interferon-γ</td>
<td>1.0 (0.0 – 21.0)</td>
<td>2.7 ( 0.7 – 25.6))</td>
<td>0.1257</td>
</tr>
<tr>
<td>Perforin</td>
<td>4.7 (1.1 – 30.5)</td>
<td>4.1 (1.0 - 21.8)</td>
<td>0.7736</td>
</tr>
<tr>
<td>Granzyme A</td>
<td>158 (15 – 444)</td>
<td>465 (39 – 1246)</td>
<td>0.0018</td>
</tr>
<tr>
<td><strong>CD8</strong></td>
<td><strong>11.8 (3.1 – 32.5)</strong></td>
<td><strong>56.7 (32.8 - 72.3)</strong></td>
<td><strong>&lt;0.0001</strong></td>
</tr>
</tbody>
</table>

Are HIV-Specific CTL deficient in B cell follicles?


Dr. Pamela Skinner
CTL Fail to Accumulate in F of Untreated HIV+ Lymph Node

HLA-A*0201 gag

CD20

SIV RNA+ Cells Are More Frequent in F Compared to EF

SIV-Specific Tetramer Staining Cells Are Concentrated in EF

Red = Mamu B*08/Vif RL8 tetramer
Green = CD20     Blue = CD3

Frequencies of SIV RNA+ Cells in F and EF by Disease Stage


14 Day Acute

Chronic

S AIDS

F : EF GM 0.91 3.2 1.9
95% CI 0.66, 1.26 2.1, 4.9 1.1, 3.4

p = 0.99
p = 0.0001
p = 0.39
CD8 depletion largely abrogates the F concentration of SIV replication.

Few SIV-Specific CTL Exhibit a Follicular Homing Phenotype

Multiple factors promote HIV replication in B cell follicles:

- FDC-bound virions
- Heightened permissivity of TFH
- Paucity of CTL in B cell follicles
Increasing Evidence That B Cell Follicles are a Reservoir for HIV in Treated Disease

- **FDC Reservoir**

- **T Cell Reservoir**
Acknowledgments

Study Participants

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