Humoral Responses in HIV-infected Individuals

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Immunological Battlefield of Mucosal Surfaces

Surface Area
400 m²

Bacteria
Viruses
Parasites
Food Antigens

Epithelium
Innate factors

Lymphoid Cells
B cell + plasma cells
T cells

Phagocytic Cells
MØ
PMN
EOS

~ $10^{14}$

~ $10^{11}$

Shedding $10^{11}$ cells/day
HIV-1 and SIV Infections: Mucosal Involvement

Virus entry: genital tract
intestinal
sexual contact, ingestion

Virus replication: intestinal tract

Early depletion of CD4+ T cells in mucosal tissues – especially gut

Altered mucosal immune responses:
decreased Ab responses to neoantigens decreased IgA responses to HIV-1 / SIV cell-mediated immune responses (?)

Infections with mucosal pathogens

Antibody-secreting Cells (ASC)

- Plasma Ab are produced in the bone marrow >>> spleen, lymph nodes by resident plasma cells

- Mucosal Ab are produced locally with a variable but usually very low (<1%) contribution from plasma
  Exception - genital tract, urine, bile, lungs

- Peripheral blood ASC - cells on their way to mucosal tissues and spleen and lymph nodes (homing receptors)
  transient (1-2 wks) appearance of specific ASC in peripheral blood
Paucity of HIV-1-Specific IgA Responses in HIV-1-Infected Patients

<table>
<thead>
<tr>
<th>Fluid</th>
<th>Isotype</th>
<th>Total Ig level (ng/ml)</th>
<th>Specific antibody level (ng/ml)</th>
<th>Specific Ab as % of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum (50)</td>
<td>IgG</td>
<td>15,513,000</td>
<td>108,000</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td>IgA</td>
<td>2,173,000</td>
<td>3,290</td>
<td>0.15</td>
</tr>
<tr>
<td>Rectal fluid (49)</td>
<td>IgG</td>
<td>4,500</td>
<td>106</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>IgA</td>
<td>165,000</td>
<td>26</td>
<td>0.02</td>
</tr>
<tr>
<td>Cervico-vaginal fluid (26)</td>
<td>IgG</td>
<td>108,000</td>
<td>3,148</td>
<td>2.9</td>
</tr>
<tr>
<td></td>
<td>IgA</td>
<td>31,000</td>
<td>69</td>
<td>0.2</td>
</tr>
<tr>
<td>Seminal plasma (18)</td>
<td>IgG</td>
<td>62,000</td>
<td>2,895</td>
<td>4.7</td>
</tr>
<tr>
<td></td>
<td>IgA</td>
<td>47,000</td>
<td>68</td>
<td>0.15</td>
</tr>
<tr>
<td>Peripheral blood antibody-secreting cells (47)</td>
<td></td>
<td></td>
<td></td>
<td>1.2</td>
</tr>
</tbody>
</table>

| Specific Ab as % of total | | | | 0.3 |
Immune Responses to HIV-1 in Infected Individuals

- Increased levels of total IgG in sera and some external secretions; less evident for IgA
- HIV-1-specific IgA – present at very low levels in sera > vaginal washes > seminal plasma > urine > nasal washes.
- HIV-1-specific antibodies present in sera and the majority of secretions – DOMINANT ISOTYPE - IgG
- Urine, vaginal washes, nasal washes and seminal plasma – highly reliable (94 – 100%) for the detection of IgG HIV-1-antibodies by ELISA
- Parotid saliva and rectal washes – unreliable, frequently false positive
- Chemiluminescence-enhanced WB more reliable than ELISA
- When present, IgA HIV-1 antibodies are specific for gp160

Selective IgA Hyporesponsiveness to HIV-1 Antigens in Sera, External Secretions and Peripheral Blood Antibody-secreting Cells
General Conclusions

• No significant change in total IgA levels in sera and secretions
• Antigen-specific IgA responses to HIV-1 absent or very low
• HIV-1-exposed but seronegative women have no IgG or IgA HIV-1-specific antibodies in external secretions
• Specific responses to other antigens (e.g., influenza virus) preserved in sera and secretions
• HIV-1-specific IgG responses in sera, secretions and ASC are dominant

SELECTIVE IgA HYPO- OR UN-RESPONSIVENESS TO HIV-1 IN MOST INDIVIDUALS

HIV Infection and Aging

• Alterations in the magnitude and Ig isotype responses in sera and external secretions
• Alterations of immune responses to chronically-encountered antigens (indigenous mucosal microbiota-exhaustion of the immune system)
• Alterations in humoral responses to systemic (e.g., pneumococcus, influenza virus) and mucosal (e.g., intranasal influenza virus) vaccines