Mucosal Immunity in AIDS Pathogenesis & Vaccines

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HIV/SIV infection and mucosal immunity: a drama in three acts

1. The first few DAYS
   Virus transmission through mucosal tissues

2. The first few WEEKS
   Early depletion of mucosal CD4+ T cells

3. The next few YEARS
   Mucosal immunodeficiency and progression to AIDS
Natural SIV hosts are the origin of HIV-1, HIV-2, and SIVmac

Slide courtesy of Beatrice Hahn
“For this field to make progress, we need to become evolutionist and learn more about natural SIV hosts. We need to think about ways to harness the human immune system to adapt to the virus in the same way.”

(Dr. Warner Greene, Chair - Final Remarks of the NIAID Summit on AIDS Vaccines, Bethesda, March 25th 2008.)
Natural, non-pathogenic SIV infection:

1. Acute infection presents with high viremia, variable levels of T cell activation, and depletion of MALT CD4+ T cells.

2. Transition to the chronic phase of infection is associated with a **dramatic decline of immune activation** despite persistent viremia.

3. During chronic infection, mucosal immunity is preserved and CD4+ T cell homeostasis is maintained.

4. The bulk of virus replication is in short-lived CD4+ T cells.

5. Virus replication is not controlled by the host cellular or humoral immune system.
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2. In the case of HIV, these events may paradoxically favor virus expansion beyond a small founder population of infected cells via recruitment of CD4+CCR5+ T cells.

3. Systemic infection with broadcasting of infected cells is established within 2-3 days from the initial breakthrough.

(Slide courtesy of Drs. Haase and Estes)
Rapid accumulation of CD4+ T cells in the endocervix of SIV-infected macaques

(Slide courtesy of Drs. Haase and Estes)
Expansion of SIV RNA+ cells coincides with inflammatory infiltrate (CD4+CCR5+ T cells)

(Slide courtesy of Drs. Haase and Estes)
Immune responses to HIV: why “immunology 101” may not work

It is possible that the key for an immunization strategy that will successfully control HIV transmission and/or early replication is the ability to induce persistently low levels of activated CD4+CCR5+ T cells in mucosal tissues.
Mucosal CD4+ T cells from natural SIV hosts express low levels of CCR5.

This finding represents a striking difference between natural hosts and humans / macaques.

Pandrea et al., Blood 2007
What is the pathophysiologic meaning of the low CCR5 expression on CD4+ T cells of natural hosts?

1. Does not protect from virus replication in infected animals.

2. May protect naïve and central memory CD4+ T cells from SIV.

3. May decrease immune activation, as CCR5 mediates homing of activated CD4+ T cells to inflamed tissues.

4. Does low CCR5 expression on CD4+ T cells protect natural SIV hosts from vertical transmission? (Silvestri et al., J Clin Invest 2007; Pandrea et al., J Virol 2008)

This latter possibility has huge theoretical and practical implications. Understanding the reason why natural SIV hosts are exquisitely resistant to vertical transmission should be an ABSOLUTE PRIORITY in AIDS vaccine research.
HIV/SIV infection and mucosal immunity

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Rapid and severe depletion of MALT CD4+ T cells during SIVmac infection of rhesus macaques

Mattapallil et al., Nature 2005

Veazey et al., Science 1998

- It is unclear to what extent the early mucosal CD4+ T cell depletion is due to direct virus killing as opposed to “bystander” death of non-productively infected cells.
HIV swiftly guts the immune system

Two studies show that SIV directly kills massive numbers of immune cells in the gut within days of infection. The results come on the heels of similarly dramatic findings for HIV, and could radically shift the focus of HIV research and therapy.

HIV pathogenesis: the first cut is the deepest

HIV pathogenesis is thought of as a chronic infection involving slow degradation of immunity that ultimately leads to AIDS. This scenario, however, could reflect the decay of an immune system mortally wounded during acute HIV infection.

Viral blitzkrieg

R. Paul Johnson and Amitinder Kaur

It takes years for AIDS to develop from the damage inflicted on the immune system by HIV or its simian counterpart. Surprisingly, as many as half of the body’s memory T cells may die at a very early stage of infection.

HIV disease: fallout from a mucosal catastrophe?

Jason M Brenchley, David A Price & Daniel C Douek

Pathogenesis of HIV infection: what the virus spares is as important as what it destroys

Zvi Grossman, Martin Meier-Schellersheim, William E Paul & Louis J Picker
SIV-infected natural hosts also show an early, severe, and persistent CD4+ T cell depletion in MALT.

Very similar results observed in SMs and AGMs

Mucosal CD4+ T cell depletion during ACUTE SIVagm infection of rhesus macaques

- Massive (>90%) acute depletion of mucosal CD4+ T cells.
- Total recovery during the follow-up.
- Mucosal immunity can be restored if virus replication is controlled.

Pandrea et al. J Immunol. 2007,
What is the pathophysiologic meaning of the early CD4 depletion during HIV/SIV infection?

1. Similar in pathogenic vs. non-pathogenic models.

2. Does not seem to be sufficient to cause AIDS in-and-of-itself, and does not represent an irreversible injury to the immune system.

3. Is the early depletion of mucosal CD4+ T cells a mechanism to achieve dissemination, establishing a large reservoir of latently infected cells, thereby ensuring chronicity?

4. Is this “once in a lifetime” destruction of a highly susceptible population of mucosal CD4+ T cells responsible for the peak and post-peak decline of viremia (in conjunction with CTL responses)?
HIV infection and mucosal immunity

1. The first few DAYS
   HIV transmission through mucosal tissues

2. The first few WEEKS
   Massive depletion of mucosal CD4+ T cells
   An opportunity for vaccine-induced CTL responses?

3. The next few YEARS
   Mucosal immunodeficiency and progression to AIDS
Can SIV-specific CTL protect from the early mucosal CD4 depletion?

At day 28 post SIV infection macaques immunized with a DNA prime / Ad boost vaccine show higher levels of CD4+ memory T cells (Mattapallil J Exp Med 2006).
Emory IPCAVD -- Experimental Design:

Pre-clinical study (immunization AND challenge) in three groups of 5 MamuA*01-positive rhesus macaques:

Group 1. MVA expressing SIV\text{mac239}-gag-tat
Group 2. MVA \text{“}\Delta\text{UDG}\text{” expressing SIV\text{mac239}-gag-tat}
Group 3. Unvaccinated controls

Protocol:
Three immunizations (2x10^8 PFU i.d and i.m.) at day 0, 42, 84.
Challenge with SIV\text{mac239} (10,000 TCID50 i.v.) at day 365
Follow up through 365 dpi or simian AIDS
Sample Peripheral Blood, LN, BAL, RB
After challenge, mucosal SIV-specific CD8+ T cells increase faster and to higher levels in vaccinated RMs.
Vaccinated animals show a ~1 log reduction of both peak and set-point viral load.
Vaccinated and unvaccinated RMs show similar kinetics of MALT CD4+ T cell decline after challenge


More work is needed to understand the relationship between HIV/SIV specific CTLs and protection from mucosal CD4 depletion.
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Progressive mucosal CD4+ T cell depletion during chronic infection is associated with AIDS

SIV-infected SMs vs RMs

SIV-infected RM Controllers vs RM Progressors

Similar data in Picker’s lab (J Exp Med 2007)
How can natural SIV hosts maintain mucosal immunity despite the rapid depletion of MALT CD4+ T cells?

1. Are natural SIV hosts less dependent on mucosal CD4+ T cells?

2. Do additional factors (i.e., lack of local immune activation) protect the CD4+ T cell-depleted MALT of natural hosts?

3. Is the depletion of mucosal CD4+ T cells “qualitatively” different from that observed during pathogenic HIV/SIV infections?
A “new” T-helper-cell differentiation model

QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.
SIV infection of SMs, but not HIV infection of humans, is associated with preservation of $T_{h17}$ cells in GALT.

Preferential depletion of intestinal CD4+ Th17 cells may be involved in the loss of the mucosal immunological barrier in pathogenic HIV/SIV infections (Brenchley et al., Blood 2008).
Normal plasma levels of LPS in the chronic phase of natural SIV infection of SMs

Brenchley et al., Nat. Med., 2006
Mucosal immunity in pathogenic and non-pathogenic SIV infections

1. The early depletion of mucosal CD4+ T cells is a common event in pathogenic and non-pathogenic HIV/SIV infections.

2. The key differences in mucosal immunity between pathogenic and non-pathogenic HIV/SIV infections emerge during CHRONIC infection.

3. Pathogenic HIV and SIV infections show:
   i) progressive decline of MALT CD4+ T cells
   ii) preferential loss of CD4+ Th17 cells
   iii) chronic mucosal immune activation
   iv) microbial translocation
Final thoughts:

1. The unique ability of HIV to hijack and exploit antiviral mucosal immunity at multiple levels (DC-CD4+ T cell interaction, CCR5-mediated recruitment of activated CD4+ T cells, etc) is a key obstacle to any AIDS vaccine based on “conventional” effector antiviral immunity (NAb and/or CTLs) AND introduces a major safety issue (i.e., could HIV vaccines do worse by inducing excessive mucosal immune activation and/or creating more targets for the virus?)

2. The design of an effective AIDS vaccine may require “non-conventional” concepts (i.e., interfering with the DC-CD4+ T cell interaction; uncoupling the CD4+ T cell “helper” effect from CCR5 expression and/or mucosal homing). To this end, studies of the mechanisms that protect natural SIV hosts from vertical transmission may provide crucial information.
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Small founder populations in endocervix in all positive RMs
Endocervix Day 7
Viral Spread

Day 4

Day 7

Day 10

SIV RNA+ cells
What Accounts for the Limited Initial SIV-Infected Founder Population?

and

What Accounts for the Expansion of SIV-Infected CD4+ T cells at the Portal of Entry?
CD4
Nuclei
Collagen

(Slide courtesy of Dr. T. Hope)
SIV RNA+ cells Initially Limited & Focal