Immune Defenses and HIV exposed
HIV uninfected – overview perspective

Michael M. Lederman
Winnipeg, Canada
November 16, 2009
Why do some apparently HIV exposed persons seem to remain uninfected?

• Dumb luck?
• Adaptive immune defenses?
  – Local antibody, CMI?
• Variable Susceptibility?
• Innate Defenses?
• Incidental events?
Some caveats

• Risk and protective determinants may vary according to the nature of exposure:
  – Parenteral vs. Mucosal
  – Mucosal vs Mucosal: Vaginal/Penile/Rectal/Neonatal Oral?

• Protective mechanisms may be:
  – Multiple
  – Additive
  – Relative
  – Inconstant over time

• It won’t be easy!
Adaptive defenses in protection among Exposed Seronegatives?

- T cell responses to HIV antigens detected in some ESNs.
- Magnitude of responses is lower than responses in challenged and unprotected non human primates
- Challenges not comparable
- No vaccine model yet
- Role of local humoral responses?
  - Neutralizing levels low
  - Are low levels sufficient in human exposures?
  - Can non-neutralizing Abs protect against low level challenge?
Altered intrinsic susceptibility to HIV infection: ΔCCR5
Some Innate Antiviral Defenses to consider

• Physical and Chemical barriers at mucosal sites
• Antimicrobial peptides
  – Human beta defensins
    • Elaborated by mucosal epithelial cells
    • Can block HIV replication in vitro
    • Variable gene reduplication (2-12) in human populations
    • Both constitutive (eg hBD-1) and inducible (hBD-2,3)

• Natural Killer Cells
  – Complex variabilities in activity in human populations
  – Can target virus infected cells (decreased MHC-1) directly
  – Can cooperate with non-neutralizing antibodies (ADCC)
Innate Antiviral Defenses

- Intrinsic cellular defenses
  - Trim 5α
  - APOBEC 3G Vif
  - Tetherin Vpu

- HIV is a host-dependent pathogen
  - Hundreds of cellular elements utilized for HIV replication
    (Brass et al Science ’08)
Type 1 Interferons

- Large family of related antiviral proteins
- Induced by microbial elements in numerous host cells
- IFN expression induces expression of hundreds of host genes including antiviral:
  - RNAse L, P-eIF2α
  - TRIM 5α, APOBEC3G, Tetherin
- Population variability in expression of IFN-inducible genes recognized
Can environmental determinants drive protective mechanisms?

- Do differences in the microbiome determine relative risk for infection?
  - Role of lactobacillus/vaginosis in “protection/heightened” risk for HIV acquisition
  - Microbes may differentially alter mucosal defenses against HIV acquisition
    - Different strains of *Porphyromonas gingivalis* increase or decrease expression of human beta defensin RNAs (Lu et al. Innate Immunity ’09)
Should we focus on “Exposed Seronegatives” (ESN)?

• Quantifying risk is difficult.
• Most single mucosal exposures confer relatively low risk
• Analysis of risk complicated by prevalence of infection
• Can we study “High Risk Seronegatives” (HRSN)?
Treatment intensity determines risk for HIV infection in Hemophilia

Kroner et al. JAIDS '94
How did HRSN hemophiliacs escape HIV infection? (MHCS)

<table>
<thead>
<tr>
<th>CCR5 Genotype</th>
<th>CCR5 genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>++</td>
</tr>
<tr>
<td>HRSN (n = 43)</td>
<td>29</td>
</tr>
<tr>
<td>Seroconverters (n = 28)</td>
<td>15</td>
</tr>
<tr>
<td>NRSN (n = 6)</td>
<td>2</td>
</tr>
<tr>
<td>Healthy controls (n = 24)</td>
<td>23</td>
</tr>
</tbody>
</table>

Salkowitz et al, *Clin Immun* ‘01
High Risk Seronegative Hemophiliacs – what we’ve learned

43 hemophiliacs at 95% risk for HIV infection but who remained uninfected (HRSN)

– 16% were homozygous for CCR5 Δ32

– Among the remainder:
  • No T cell responses to HIV (G. Shearer)
  • No decreased in vitro susceptibility to HIV
  • No increase in beta chemokine (MIP-1α, MIP1β, RANTES) production
  • No decrease in CCR5 density on CD14+ monocytes or CD4+ T cells.
  • No plasma neutralizing antibodies (M. Cho)

(Salkowitz et al Clin Immunol ’01)
Does immune activation predict risk for HIV acquisition?

- Lymphocytes of HRSN were less readily activated to cycle and proliferate than were lymphocytes of healthy controls (unstimulated and in 7 different stimulation conditions). Also significantly lower frequency of alloreactive antibodies in serum (Salkowitz et al Clin Immunol ’01)

- CD4+ cells of at risk seronegative gay men were less frequently in cell cycle, less frequently CD70+ than CD4+ cells of gay men who later acquired HIV infection. (Koning et al J Immunol ’05)
Hypothesis: Does lower level activation state somehow protect persons from HIV acquisition?

• This may predict an intrinsic decreased susceptibility to HIV infection (though we could not show it) or alternatively a diminished ability to mobilize activated target cells into first sites of HIV replication.
Summary

• There are numerous plausible (but few proven) determinants of decreased \textit{in vivo} susceptibility to HIV infection.

• As protection mediated by these factors may be additive, inconsistent and vary according to the route of transmission, sorting this out may be challenging.

• We should be rigorous about the definition of “high risk” for infection.
Thanks to:
The Son of BBC-II

CWRU
Scott Sieg
Benigno Rodriguez
Bob Silverman
Aaron Weinberg
David McDonald
Donald Anthony
Heather Pilch
Clifford Harding
Gareth Hardy
Eric Arts
Michael Cho

EVERYWHERE ELSE:
Jim Goedert
Galitt Alter
Danny Douek
Mary Carrington
David Goldstein
Paul Bienacz
Demetre Daskalakis
Carlton Haywood
Sophie Lanzkron