Innate Immune Effector Mechanism in SIV/HIV Infection
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• Epidemiological figure of HIV and AIDS in Thailand
• Mucosal Immunity
• Approach to study innate immunity
  – Functional activity of NK cells
  – Role of KIRs
• Non-human primate model for SIV/HIV studies

Global distribution of HIV-1 infection, December 2007

Situation of AIDS in Thailand as of 2011

Estimated total population, 2011 66,720,153
Estimated number of people living with HIV, end of 2009 530,000
Adults (15+)
  = 520,000
Women (15+)
  = 210,000
Children (0-15)
  = 13,000
Estimated adult HIV prevalence 1.3%
Estimated number of AIDS deaths in 2009 28,000


Current number of HIV-infected individuals with access to NHSO ART program
≈ 158,500 cases out of 300,000
(≈ 300,000 to 350,000 CD4 testings/year)

The New England Journal of Medicine

RESULTS: In the intention-to-treat analysis involving 16,402 subjects, there was a trend toward the prevention of HIV-1 infection among the vaccine recipients, with a vaccine efficacy of 26.4% (95% confidence interval [CI], -4.0 to 47.9; P=0.08). In the per-protocol analysis involving 12,542 subjects, the vaccine efficacy was 26.2% (95% CI, -13.3 to 51.9; P=0.16). In the modified intention-to-treat analysis involving 16,395 subjects (with the exclusion of 7 subjects who were found to have had HIV-1 infection at baseline), the vaccine efficacy was 31.2% (95% CI, 1.1 to 52.1; P=0.04). Vaccination did not affect the degree of viremia or the CD4+ T-cell count in subjects in whom HIV-1 infection was subsequently diagnosed.
Natural history of HIV infection

The Profiles

Highest research priorities identified at the NIAID HIV Vaccine Summit, March 2008

A jigsaw to understand the mechanisms of HIV/SIV infection

Why innate immunity is important?

- During the period of acute infection, the rate of viremia appears to dictate the rate of disease progression.
- Gut associated lymphoid tissues are the major target of SIV and HIV infection during acute phase.
Why understanding of mucosal innate immunity is important?

- Mucosal transmission is the principal route of acquisition.
- Only 1/3 of infants born to infected mothers acquire infection.
- Sexual transmission occurs between 1/100 to 1/1000 exposures.
- Exposure to infected blood products does not absolutely lead to infection.
- Some CSWs remain uninfected despite repeated exposure.
- Most infections from the mucosal transmission are initiated by single virus.

Mucosal epithelium act as immunity’s front line

- As the physical barrier against invasion.
- Mucosal cells mediate innate defense against microbes under hormonal control.
- Signalling system thru TLRs that recognize and respond to pathogen-associated molecular patterns by secreting:
  - Defensins
  - Protease inhibitor
  - Lactoferrin and lysozyme
  - Protein A
  - Complement
- Signalling thru chemokines and cytokines to recruit pDCs thus initiate link between innate and adaptive immunity.

Inflammation, innate immunity, mucosal epithelial signalling and target cell availability at mucosal front lines.

Time frame, sites and major events in vaginal transmission and the fast phase of lentivirus infection.

Ill effects of systemic infection and too little too late immune response.

Targeting on the early infection is critical

- Viral vulnerabilities due to the small “founder population”.
- Early intervention that reduces viral growth rate to < 1 will have the desired outcome.
- Preventing local expansion so that insufficient virus and infected cells could not establish systemic infection.
- Virus specific CD8 T-cell response is “too little and too late” to prevent gut CD4 T-cell depletion.
### What are the questions?

- What do we know about the role of innate immunity in humans and NHPs during acute infection.
- How do these effector mechanisms execute their function within the GI tissue.
- How can this knowledge be exploited for the formulation of an effective vaccine against HIV-1?

### Is AIDS Vaccine possible?

- Natural hosts infected with SIV do not get sick
- Vaccine-mediated protection against SIV is possible in non-human primates
- There are “elite controllers” with viral loads at or below detectable limits without treatment
- Some people remain virus negative despite of repeated exposures

### Evidences that Vaccine may work

- Phase III vaccine trial combining an HIV envelope protein with canarypox-HIV vector showed 30% reduction in acquisition.
- Induction of virus-specific CD8 T-cell responses, though does not prevent infection in monkeys, it can curtail SIV replication if strong and broad enough.
- Use of simian CMV to continuously deliver SIV antigens limit systemic infection in some monkeys after intrarectal challenge with SIV.

### Components of innate immunity

**Components of innate immunity**

- Phagocytes
- NK cells
- γδ T cells
- Monocyte/macrophage
- Dendritic cells

### Major cell lineages of the Innate Immune System

One of the major subset of hematopoietic cells Thought to be involved in inducing innate immunity During acute viral infections are cells of the NK Cell subsets

- NK cells – KIRs, NKCR, CD94/NKG2a, homing molecules (integrins)
- NK T cells
- γδ T cells
- Monocyte/macrophage
- Dendritic cells

### Flow Based Identification of NK Cell Subsets

1. Set up generous gates for FSC and SSC since NK cells include LGL’s.
2. First gate out CD14+ and CD20+ cells
3. Gate out CD3+ cells but select CD3- CD8+ cells
4. Gate on CD3-, CD8+, NKG2a+ cells and determine the frequency that express:
   - A. CD16+, CD56+
   - B. CD16+, CD56-
   - C. CD16-, CD56+
   - D. CD16-, CD56-
Effect of SIV Infection on the Frequency of NK Cell Subsets from RM

Effect of SIV Infection on NK Cell Subsets

Effect of SIV Infection on the Frequency of NK Cell Subsets from RM

Effect of SIV Infection on NK Cell Subsets

Effects of HIV/SIV on NK cell functions
NK cell function in SIV-infected RM

- 51Cr Release assay
- 3H reduction
- Cytokine assay
- CD107a assay

PBMCs from 12 Mamu-A01+ long term non-progressors (LTNP) RM, 15 normal progressors (NP) RM and 6 sooty mangabeys infected with the same aliquot of SIVmac251 were assayed for absolute #s of NKG2a+ cells prior to and following infection. The #s reflect the mean values with S.D. of <20%.

Killer immunoglobulin-like receptors


Previous studies on rhesus KIRs

- RM PBMC samples were identified for KIR types based on their structure and homology to human KIRs (J Immunol. 2001;166(7):4380-90)
  - RM-KIR1D; one KIR1D and 11 splice variants (n = 1 from 5 RM)
  - RM-KIR2DL4; one KIR2DL4 and 2 allelic (n = 1 from 5 RM)
  - RM-KIR2DL5; 2 allelic (n = 2 from 5 RM)
  - RM-KIR3DL; 11 allelic and multiple splice variants (n = 5 from 5 RM)
  - RM-KIR3DH; 4 allelic and multiple splice variants (n = 1 from 5 RM)

- Bostik P, Kolkkila-Roos J, Tang W, et al., investigated RM-KIR3DL allelic and their variants using NK cells. Results showed that the higher frequency of inheritance of KIR3DL allele 13 and 14 characterized by a SNP at 159 H/Q was associated with plasma viral load and fast progressive SIV-infected RM (J Immunol 2009;182(6):3638-49)

- Chaichompoo P, et al., found three more KIR loci (KIR1D, KIR2DL4 and KIR3DH) and showed that selected KIR3DH alleles appear to be more strongly associated with high plasma viral loads than KIR3DL alleles 13 and 14. (Cell Immunol 2010;23:176-87)
Why use non-human primate model for HIV/SIV infection

• 1. NHP not only provide the most optimal model to study the virological and immunological aspects during acute infection but they also permit the relative specific manipulation of the virus and the host or both with the potential of identifying strategies that would lead to enhanced control of viremia, decrease and/or elimination of viral reservoirs and potentially preservation or reconstitution of the immune capabilities of the host.

• 2. In addition, the natural hosts of SIV provide a valuable model to examine similar issues and attempt to identify those events that are similar to LTNP or “elite” controllers which can be potentially harnessed for vaccine design.

Models to study innate immunity

Pathogenic SIV
Apathogenic SIV
Low dose repeated intravaginal/intrarectal infection with pathogenic SIV
Low dose repeated intravaginal/intrarectal infection with apathogenic SIV

A) Mamu A01, B08, B17
B) Non Mamu A01, B08, B17

Models to study innate immunity

Infection with Pathogenic SIV
Infection with Pathogenic SIV
MCT
MCT

Modified from Ansari AA.

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