HIV-1 Immunopathogenesis: Innate Immunity

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Lecture acknowledgements

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Lecture outline

• Section I:
  – Introduction to HIV-1 disease

• Section II:
  – Innate effectors (DC, NK, macrophage)
  – Innate response in HIV-1 infection:
    immune activation hypothesis
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Section I

• Viral life cycle
• Acute infection
• Stages of immunopathogenesis

Global review: viral life cycle

1. Target cells:
   - CD4 T cells, monocytes/macrophages
   - DC subsets
2. Molecules needed for infection:
   - CD4, CCR5/CXCR4
   - Annexin II/CD63 (monocytes)
3. Post-fusion: determinants for infection
   - Intrinsic factors of resistance (e.g., APOBEC)
   - Intracellular host factors needed for infection (e.g., emerin, transcriptional factors)

Global review: acute infection (1)

Viral transmission: favors high viral load, viral "dose", and results in preferential selection for CCR5 HIV-1
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**Global review: acute infection (2)**

SIV- 1 dpi

SIV- 2h pi

Source: A. Hesse

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**Global review: acute infection (3)**

SIV- 4 dpi

SIV- 21 dpi

Source: A. Hesse

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**Global review: acute infection (4)**

Mechanism create generally favorable environment for expansion of small founder populations of infected cells

- pDCs
- chemokines
- CCR5+ “fuel”

Expand small founder populations

Establish systemic infection

Source: A. Hesse

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Global review: acute infection (5)

Simian Immunodeficiency virus

Source: J. Hoxie

Day 4

Global review: acute infection (6)

CD4+/m3

Weeks

0 3 6 9 12

HIV+ HIV+

GALT CD4(+) T cell depletion during acute pathogenic HIV and SIV infections of humans and Rh is necessary but neither sufficient nor predictive of disease progression, with levels of immune activation, proliferation and apoptosis being key factors involved in determining progression to AIDS

Recent advance: acute infection

How important is the GALT depletion to disease outcome?

GALT CD4(+) T cell depletion during acute pathogenic HIV and SIV infections of humans and Rh is necessary but neither sufficient nor predictive of disease progression, with levels of immune activation, proliferation and apoptosis being key factors involved in determining progression to AIDS
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Global review: acute infection (7)

Why a drop?

Global review: acute infection (8)

Source: J. Hoxie

Global review: acute infection (9)

Viral "set point" as a predictor of disease

% of patients with AIDS
at 5 years

85
62
49
26
8

Time

CD4+/mm^3

Gut CD4%

0 3 6 9 12 1

0 200 400 600 800 1000

0 100 200 300 400 500 600 700
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Primary infection
Acute HIV syndrome
Wide dissemination of virus
Seeding of lymphoid organs

Weeks

600
700
800
900
1000
1100

D4+/mm³

Clinical latency
Opportunistic infections

Ad/ viral titer

Immunosuppression

Immunosuppression

Opportunistic infections

Death

Monocyte/macrophage

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Macrophages & HIV-1 infection
- Cellular targets of HIV-1
- Reservoirs of HIV-1
- HIV-1 impair monocyte/macrophage functions
  - Phagocytosis, chemotaxis, intracellular killing, inflammatory responses and antigen presentation are impaired

<table>
<thead>
<tr>
<th>HIV accessory protein</th>
<th>Some macrophage functions modulated</th>
</tr>
</thead>
<tbody>
<tr>
<td>tat</td>
<td>Upregulates chemokines, CCR5, CXC/CR, TRAIL, downregulates MHC, induces TNF, IL-1, IL-6</td>
</tr>
<tr>
<td>vpr</td>
<td>Downregulates IL-10, inducers IL-1, IL-8, interacts with NFκB, p53 and GR pathway</td>
</tr>
<tr>
<td>vif</td>
<td>Inhibits Src kinase, hck, promotes virus integration</td>
</tr>
<tr>
<td>vpu</td>
<td>Promotes CD4 degradation and virus release</td>
</tr>
<tr>
<td>nef</td>
<td>Activates NFκB, Stat1, AP-1, induces chemokines, promotes CD4 degradation</td>
</tr>
</tbody>
</table>

HIV-1 and monocyte apoptosis
- Resist cytopathic effects of prolonged HIV infection in vitro
- Viral accessory proteins upregulate anti-apoptotic pathways
  - Nef upregulates Bcl-2 in TF macrophage cell line
    (J Biol Chem. 2004 Dec 3; 279(49): 51688-96. Epub 2004 Sep 30)
  - Tat upregulates Bcl-2
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Human DC subsets

Model of DC migration and maturation

MHC I antigen presentation
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Antigen presentation

Proposed pathways of human DC development

Characteristics of human DC

Circulating precursor DC in human peripheral blood
Immunopathogenesis of HIV-1 disease (2)

**Immunopathogenesis of HIV-1 disease**

- **Weeks**
  - 0
  - 2
  - 4
  - 6
  - 8
  - 10
  - 12
- **Primary infection**
- **Acute HIV syndrome**
  - With dissemination of virus
  - Seeding of lymphoid organs
- **Clinical latency**
- **Lymphoid organs**
- **Opportunistic infections**
- **Death**

**CD4** (cells)

0 100 200 300 400 500 600 700 800 900 1000

**AIDS**

**Immunosuppression**

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**Dendritic cell subsets**

**Myeloid dendritic cell (MDC)**
- HLA-DR++
- CD11c+
- CD123-
- FCR (R1, CD32, CD64)
- CD45RA-
- BDCA2+/4
- DC-SIGN+
- IL-12 ++

**Plasmacytoid dendritic cell (PDC)**
- HLA-DR++
- CD123+
- CD45RA+
- CD4+-
- BDCA2+/4
- DC-SIGN+
- IFN-α+++  

**Human DC subsets**

A. **Myeloid DC** = Lin- CD11c+ CD123- MHC II+
B. **Plasmacytoid DC** = Lin- CD11c- CD123+ MHC II+
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Human DC: C-type lectins

2 types of C-type lectins expressed on DC

Pathogens that bind DC-SIGN

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Natural killer cells

CD8+ (cytotoxic) T cell recognition of target cells

Fas-FasL
Perforin/granzyme

Natural killer cell recognition of target cells (1)
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Natural killer cell recognition of target cells (2)

- Fas-FasL
- MHC-I
- KIR
- NCR
- MICA
- Perforin/granzyme
- IL-2
- IL-12
- IL-18
- INF-α

Natural killer cell recognition of target cells (3)

- MHC class-I locus

<table>
<thead>
<tr>
<th>HLA-A</th>
<th>HLA-B</th>
<th>HLA-C</th>
<th>HLA-E</th>
<th>HLA-G</th>
<th>MICA, B</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIR3DL2</td>
<td>KIR3DL1</td>
<td>KIR2DL1/2</td>
<td>LIR1/ILT2</td>
<td>LIR1/ILT2</td>
<td>NK02A</td>
</tr>
<tr>
<td>LIR1/ILT2</td>
<td>KIR3DS2</td>
<td>CD160</td>
<td>NKG2A</td>
<td>MICA, B</td>
<td></td>
</tr>
</tbody>
</table>

- NKp30: HCMV pp65, heparin sulfate
- NKp44: Viral haemagglutinin, HIV-1 gp41
- NKp46: Viral haemagglutinin, Heparin Sulfate

Immunopathogenesis of HIV-1 disease (3)

- Primary infections
- Acute HIV syndrome
- AIDS
- Opportunistic infections
- Death
- Clinical latency
- Lymphoid organs
- Peripheral blood
- CD4+ T cells

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### HIV-1 Immunopathogenesis:
#### Innate Immunity

#### Role of HLA and KIR alleles in rate of progression to AIDS
- HLA B*5701 is highly associated with restriction of virus replication in a subgroup of HIV-infected long term nonprogressors
  - *PNAS* 2003, 100:2709-14
- Progression of HIV to AIDS: a protective role for HLA-B27
- Epistatic interaction between KIR3DS1 and HLA-B delays the progression to AIDS
  - *Nature Genetics* 2002, 31:429
- Increased proportion of KIR3DS1 homozygotes in HIV-exposed uninfected individuals
  - *AIDS* 2006, 20:593-9
- Increased NK activity in HIV-1 exposed but uninfected Vietnamese intravenous drug users
  - *Journal of Immunology* 2003, 171: 5663

### NK cells & HIV-1 infection
**Impaired NK cell function in HIV-infected patients**
- Impairment appears in early stages, before the onset of CD4+ T cell depletion
- Characterized by loss of:
  - Cytotoxicity
  - Production of IFN-γ
  - Response to IFN-α (progression indicator)
  - Decrease in mature NK subsets
- Progressive reduction of NK cell number (in association with generalized hematopoietic failure) at late stage disease (AIDS)
- The pathogenic mechanisms of NK cell inactivation is unknown
- Limited reports postulate mature NK cells are infected by HIV-1

### To kill or not to kill?
**NK balancing act:**
+/- NK cell differentiation state
+/- Killing activating interactions (ex., NCR, Ab)
+/- Killing inhibitory interactions (ex., MHC-I)
+/- Dendritic cell help (ex., type-1 IFN)
+/- T-cell activation state (ex., IL-2)
+/- NK functional/activation state
  
  + Kill
  - Not Kill
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Measuring recovery following immune reconstitution and HIV-1 therapy

ART & innate reconstitution

Understand the impact of steady-state HIV-1 replication on the innate effector compartment based on the study of HIV-1 infected persons off antiretroviral therapy

Determine the degree of immune reconstitution of innate effector cell function following antiretroviral therapy

AIDS; 2007 Jan 30; 21(3): 293-303

RO1 AI51225 - prospective study: Philadelphia FIGHT cohort
- ART-naive HIV-infected patients initiating ART (NRTI backbone + NNRTI or PI)
- Controls: non HIV-infected donors
- Both genders, >18 y.o

Variable time, visits every 4 weeks
Baseline
HIV RNA
Suppression = 0 wks
4 wks
8 wks
16 wks
32 wks
52 wks
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**Reconstitution of PDC & NK cytotoxicity**

NK antiviral function directly related to level of plasmacytoid dendritic cell recovery of function

**Summary model of immune reconstitution time-line**

Suppressive antiretroviral therapy
Conclusion

- Innate compartment is recovered after a period >32 weeks of viral suppression; Evidence for a negative effect of HIV-1 on PDC frequency and function
- Not all immune reconstitution is the same after a year of HIV-1 suppression is achieved
- Evidence for a predetermined potential for innate recovery leading to heterogeneity in immune reconstitution

Section II

Does the innate immune activation response determine HIV-1 disease?

Recent paradigm shift: viral load & CD4 loss

Only a small proportion of CD4 cell loss variability (4%-6%) could be explained by presenting plasma HIV RNA level

Rodriguez et al., Predictive value of plasma HIV RNA level on rate of CD4 T-cell decline in untreated HIV infection; JAMA 2006 Sep 27; 296(12): 1498-506
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**Immune activation & disease progression**

Evidence #1:

Immune activation (though related to VL) predicts HIV disease progression risk independently

- CD38 expression a better predictor of disease progression than VL  
  (Liu *JAIDS* '98, Giorgi *JID* '99, Deeks '04, Wilson '04)

- Pre-seroconversion, CD70 expression predicts disease progression risk  
  (Hazenberg *ACS* '04)

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**Natural SIV hosts are the origin of HIV-1, HIV-2, and SIVmac**

Evidence #2

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**Natural host (SIV smm)**

- High level viremia
- CD4 depletion extremely rare
- No OIs
- Low level immune activation

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**HIV-1 model (if given SIV smm)**

- High level viremia
- Circulating CD4 depletion
- OI risk and death
- High level immune activation
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Key reference: evidence for TLR activation and immunopathogenesis (1)

Mandl et al., Divergent TLR7 and TLR9 signaling and type I interferon production distinguish pathogenic and non-pathogenic AIDS virus infections; Nat Med. 2008 Oct; 14(10):1077-87

HIV-1 Nef associated with HIV-1 activation events

Evidence #3

Schindler et al. Nef-Mediated suppression of T cell activation was lost in a lentiviral lineage that gave rise to HIV-1. Cell, 125: 1055-1067, 2006

Evidence # 4: plasma LPS levels are increased in chronic HIV infection

Brenchley et al., Nat Med 06

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Evidence #5: HIV RNAs can activate T cells indirectly via TLR 7, 8

Evidence #6: CD4 T cells activated to enter cell cycle by microbial TLR ligands do not complete division but instead die by apoptosis

Data and slide courtesy of M. Lederman
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Key reference: evidence for TLR activation and immunopathogenesis (2)


Recent advance: immune activation hypothesis

Evidence #7:

- Loss of CD4 in natural SIV host with virus yet without activation does not lead to disease
  Milush et al., Virally induced CD4+ T cell depletion is not sufficient to induce AIDS in a natural host. J Immunol. 2007 Sep 1; 179: 3047-56

- Viral replication without CD4 activation or loss of function associates with slow disease progression
  Choudhary et al., Low immune activation despite high levels of pathogenic human immunodeficiency virus type 1 results in long-term asymptomatic disease; J Virol. 2007 Aug; 81: 8838-42

Disease model: it's the interaction!

J Exp Med. 2007 Sep 3; 204(9): 2171-85
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Major hypothesis

Innate cell function is a dominant feature of immune health, disease progression, and adaptive immune control in chronic HIV-1 infection and AIDS pathogenesis.

Thank you!