How HIV infiltrates our immune system
and lessons on how to strike back

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Disclosure of speaker’s interests

No conflict of interest
Sexual transmission of HIV-1

- Sexual intercourse is main route of infection
  Involvement of mucosal tissues and immune cells

- Low number of CD4+ T cells in mucosal tissues

- Dendritic cells as antigen presenting cells are main immune cells in mucosal tissues

Infiltration by HIV-1: Which immune cells are involved?

Fight back: How can we induce efficient immunity to HIV-1?
Dendritic cells mediate HIV-1 transmission

- Antigen presentation
- T cell activation
Dendritic cells efficiently bind HIV-1

Immature dendritic cells

C-type lectin receptor:
- binds carbohydrates (mannose)
- binds viruses (HIV-1, Measles virus, HCV, Ebola virus)
- virus transmission
- induces signaling pathways
- suppresses RNA sensors RIG-I/Mda-5

Geijtenbeek et al. Cell 2000a/b
HIV-1 transmission by dendritic cells

‘infectious synapse’
Dendritic cells mediate HIV-1 transmission

Carla Ribeiro, restriction mechanism
Nienke van Teijlingen, HIV-1 ticking bomb
Maartje Nijmeijer, HCV transmission

Gringhuis et al. Nat Immunol 2010
De Witte et al. Nat Med 2007
HIV-1 sensing by dendritic cells?

DCs sense invading pathogens

- Type I IFN responses
- DC maturation
- Cytokine responses

Induction of adaptive immunity
- CD4 T cell responses
- CD8 T cell responses
Type I IFN induces antiviral immunity response

Antiviral IFN stimulated genes
- Restriction factors (TRIM5α, MxA, APOBEC3G, ISG15)
→ Limit viral replication
→ Causes immune activation (adaptive immunity)
→ Early type I IFN controls SIV infection in Rhesus Macaques
→ Continuous exposure accelerates SIV disease progression (Sandler Nature 2014)
Cytosolic receptors induce type I IFN responses to viruses

HIV-1 sensing by dendritic cells?
Is HIV-1 infection sensed in dendritic cells?

Adapted from Yan & Chen NI 2012

HIV-1 replication cycle
HIV-1 infection does not induce type I Interferon

- Infect monocyte-derived DCs with HIV-1

- robust HIV-1 replication
- no type I IFN response
- no DC activation
- no cytokines

Hertoghs et al J Immunol 2015
Dendritic cells are ‘unresponsive’ to HIV-1

HIV-1 infection of DCs (no sensing or inhibition?)

No type I IFN responses
No DC maturation
No cytokines

No efficient immune response to HIV-1 (detrimental to HIV-1 infected patients)

How does HIV-1 escape immune surveillance?
Sensing of viruses by cytosolic receptors

- HIV-1 binding to DC-SIGN activates Raf-1

- Measles virus binding to DC-SIGN inhibits RIG-I/Mda5

Does HIV-1 target DC-SIGN to block RNA/DNA sensors?

Mesman et al., Cell Host & Microbes 2014
HIV-1 blocks type I IFN responses via Raf-1

Monocyte-derived DC infected with HIV-1

HIV-1 blocks type I IFN responses in primary DC subsets via Raf-1

\[ \rightarrow \text{Independent of HIV-1 strain (X4, R5 and primary isolates)} \]
HIV-1 blocks type I IFN responses via Raf-1

Type I IFN induces expression of antiviral IFN-stimulated genes (ISGs)

HIV-1 infects dendritic cells by suppressing type I IFN responses.

Blocking DC-SIGN signaling enhances type I IFN responses and restricts HIV-1 infection.

Which cytosolic sensor detects HIV-1?
HIV-1 sensor signals via MAVS

Infect DCs with HIV-1

IFNβ

mRNA expression (relative)

Control siRNA

MAVS siRNA

HIV-1 + GW5074

mRNA expression (relative)

Control siRNA
cGAS siRNA

STING siRNA

Cytosol

Nucleus

DNA sensor

cGAS

RNA sensor

MAVS

STING

IRF3

IFNβ

**
HIV-1 sensor is RNA helicase DDX3

- Screening of siRNA library of RNA sensors and related family members (Dead-Box Helicase family)

◊ DDX3 silencing blocks type I IFN responses after HIV-1 infection

Abortive RNA from HIV-1 triggers DDX3

Physiological relevance of the suppression of DDX3 sensing?

DDX3 function: Melissa Stunnenberg
In vivo relevance of the DC-SIGN / DDX3-MAVS pathway

- identified two linked MAVS polymorphisms
- polymorphisms render MAVS insensitive to DC-SIGN inhibition

Type I IFN responses and HIV-1 infection in homozygous MAVS donors?
The dual MAVS mutant is insensitive to HIV-1 suppression.

MAVS polymorphisms similar phenotype as DC-SIGN inhibition with drugs.
Type I IFN response required for DC activation

Immature DC → Activated DC

Co-stimulatory molecules (CD86)

→ DCs with MAVS polymorphisms secrete cytokines upon HIV-1 infection

How does this mechanism affect HIV-1 pathogenesis in HIV-1 infected patients?
Lower HIV-1 replication in MAVS homozygous individuals

Amsterdam cohort studies for HIV-1/AIDS (untreated HIV-1 infected men)

→ low viral load at setpoint (stabilized viral load) indicates better adaptive immunity

→ HIV-1 replication is attenuated in infected men homozygous for MAVS
DDX3 is a novel RNA sensor for HIV-1 in human dendritic cells

Novel RNA sensing system via DDX3-MAVS pathway

A natural SNP in MAVS confers protective immunity in vitro/in vivo

DC-SIGN pathway as target to enhance immunity to HIV-1
Conclusions

Currently investigating the mode of control in chronic phase in patients (CD8 T cell activation, restriction factors)

Inducing HIV-1 sensing during sexual transmission inhibits virus replication in chronic phase!
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Advanced Grant
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