HIV-1 infection: When the virus and the host play hide and seek

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HIV-1 infection starts with transmission of limited number of founder viruses

Several factors determine the selection of the founder viruses:
- Sensitivity to autologous antibodies
- Sensitivity to IFN
- Level of glycosylation
- Fitness to infect target cells
HIV-1 replication cycle: multiple targets for antiretroviral therapy

However antiretroviral therapy does not target the integrated provirus

Adapted from A Fauci
HIV persists in cellular reservoirs despite durable antiretroviral treatment

Time on treatment: 65.7 year

Chomont et al unpublished
Establishment of HIV reservoir is a multifaceted process

Cell susceptibility to infection

Balance between restriction and dependency factors

Restriction factors
- APOBEC3 proteins
- TRIM5α proteins
- BST-2/Tetherin
- MX2
- SAMHD1

Dependency factors


Late RT

HIV gp120
CD4
CCR-5
CD4
MACROPHAGE

Copies per 100 ng DNA

0 500 1000 1500 2000 2500 3000

0 4 24 48 96

Hours p.i.
Establishment of HIV reservoir is a multifaceted process

Cell susceptibility to infection

Survival to HIV infection

Resistance to HIV induced apoptosis

Escape immune surveillance

FDC cytokines ➔ enhance HIV replication in TFH cells and increase proliferative rate of infected TFH cells viral persistence, since germinal centers are relatively devoid of cytolytic CD8+ T cells.
Establishment of HIV reservoir is a multifaceted process

Cell susceptibility to infection

Survival to HIV infection

Cell Persistence

Half life

Turnover

Finzi et al. Cells 1997
Two models to explain persistence on cART

Low level HIV replication

Survival and cell proliferation

Viral particles are released by infected cells that persist by homeostatic proliferation

cART does not completely block viral replication (and in particular cell-to-cell transmission)

Adapted from Shen and Siliciano. JACI 2008
HIV infects cells from the immune system that contribute to spread and persistence

- **Dendritic cells**
- **CD4+ T lymphocytes** (including HIV-specific cells)
- **Monocytes/macrophages**
- **Microglial cells**
- **Follicular DCs**
- **T Follicular Helper**
- **T cells**
- **T cells (α4β7, CCR6+)**
- **Macrophages**
- **Hematopoietic progenitor cells**

HIV replication is compartmentalized

Santangelo et al Nat Methods 2015

Adapted from A. Fauci
Spread and establishment of reservoirs is a fast process

SIV reservoir established within 3 days?

Log RNA in plasma

Whitney et al. Nature 2014

cART day 3 p.i.

Log DNA copies per $10^6$ cells

PBMCs

LNMCs
Development of Immune responses during acute HIV-1 infection

Concomitant establishment of viral reservoirs and development of immune responses

Adapted from McMichael et al Nat Rev Immunol 2010
Innate immunity constitutes a first barrier of defense against HIV infection:

- NK cells have direct antiviral activity and promote adaptive immunity
- Type I IFN production by pDCs
- Early and strong cytokine response may contribute to viral dissemination, establishment of reservoir and may decide the fate of immune responses
The CD8+ T cell response contributes to partially control HIV infection

CD8+ T cells produce soluble anti-HIV factors (β-chemokines, CAF(?)) and eliminate infected cells through cytotoxic mechanisms.

- Coincidence between the appearance of HIV specific CD8+ T cells and control of primary infection.
- Depletion of CD8+ T cells during SIV infection leads to increased viral load.
- Association between Class I HLAs and level of viremia

Antibodies against HIV: multiple ways to tackle the infection

Cell-free viral neutralization

Inhibition of cell-to-cell viral spread

Fc-dependent antiviral activity

Inhibition of viral transcytosis

1 Intracellular viral neutralization

H Mouquet Trends Immunol 2014
Ultimately these defenses are inefficient to control the virus.

Virus evolves to escape immune responses

1% of variability/year in each infected individual

Global flu

HIV

HIV in Congo

Viral diversity 1996

Adapted from R Weiss Nature 2003 and B Korber Br Med Bull 2001

Inefficient control of infection leads to exhaustion of immune responses and damage of lymphoid structures

Freeman et al. *JEM*, 2006, 203, 2223-2227

Disruption of reticulin network in T cell zone


Loss of organized B cell follicles

Kök et al. *Mucosal Immunol* 2015, 8, 127-40
HIV associated chronic inflammation

HIV-associated fat
Metabolic syndrome

CMV
Excess pathogens

HIV production
HIV replication

Loss of regulatory cells

Inflammation
↑ Monocyte activation
↑ T cell activation
Dyslipidemia
Hypercoagulation

Co-morbidities
Aging

Steven Deeks, IAS 2013, KL
Immune activation and HIV pathogenesis

Immune Activation

HIV Replication

Immune Cell Depletion

Immune Cell Dysfunction

Aberrant Lymphocyte Turnover

Organ System Dysfunction, e.g. Cardiovascular Disease

A Fauci. 30 years of HIV infection. 2013
All the same, but all different in response to HIV

Extensive interindividual variability in response to HIV (susceptibility to virus, transmission and disease progression…)

Differences in viral set points, rates of CD4 T cells decline, levels of viremia, inflammation/immune activation, emergence of CTL escape mutants or development of opportunistic infections

A small proportion of HIV-1 infected people show « natural resistance » to infection (HESN) or to disease progression (HIC, LTNP)

F Barré-Sinoussi
Distinct HIV/SIV infection outcomes

Adapted from G. Silvestri

Noel et al AIDS 2014
Three steps to control HIV-1 infection

1- Limit viral reservoirs
2- Develop efficient mechanisms to control viral rebound
3- Restrain immune activation/inflammation
HIV/AIDS: an outstanding global health problem

~ 36.9 million people living with HIV
cART introduction changed the face of the epidemic, however:
- 2.0 million new infections/year
- 1.2 million deaths/year
- 60% of patients still in need of life-long cART

Patients request alternative strategies