HIV disease progression is associated with exhaustion of lymphopoiesis driven by immune activation.
Immune activation and progression towards AIDS

**Causes**

- HIV infection and replication
  - Main target: activated CCR5+ CD4+ T lymphocytes
- Massive depletion of CD4+ T cells particularly in mucosa
- Immune response against HIV cellular and humoral
- Bacterial translocation TLR ligands
- Viral reactivation in particular CMV
- Production of HIV proteins gp120, nef

**Consequences**

- Systemic immune activation
  - Adaptive and Innate

- Immunosenescence?

Persistence of this process participates to Collapse of the immune system / AIDS

*Appay and Sauce, J Pathol, 2008*
Immunosenescence:
Deterioration of the immune system with time / age

=> Increased susceptibility and severity of old people to infectious, auto-immune and cancerous diseases

=> Alterations of phenotype and function of cells and organs of the immune system associated to advanced age (in particular adaptive immunity)
Immunosenescence in HIV-1 infection?

=> Comparative study of immunological parameters: HIV infection versus old age

Treatment naïve HIV-1 infected patients
H: above 500 CD4⁺ T cells/µl
I: between 200 and 500 CD4⁺ T cells/µl
L: below 200 CD4⁺ T cells/µl

Healthy donors
M: middle aged
O: old
Accumulation of end stage memory T lymphocytes with age or HIV infection

Memory T cell subsets

<table>
<thead>
<tr>
<th>Telomere length</th>
<th>Proliferative capacity</th>
<th>TCR repertoire diversity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCR7+ CD28+ CD27+ CD57-</td>
<td>6.8kb</td>
<td>71%</td>
</tr>
<tr>
<td>CCR7- CD28+ CD27+ CD57-</td>
<td>6.3kb</td>
<td>34%</td>
</tr>
<tr>
<td>CCR7- CD28- CD27+ CD57-</td>
<td>5.9kb</td>
<td>23%</td>
</tr>
<tr>
<td>CCR7- CD28- CD27- CD57+</td>
<td>5.2kb</td>
<td>12%</td>
</tr>
</tbody>
</table>

Membrane T cell differentiation

Central memory

Effector memory

Late Intermediate Early
Accumulation of end stage memory T lymphocytes with age or HIV infection

Memory T cell subsets

<table>
<thead>
<tr>
<th>Central memory</th>
<th>Telomere length</th>
<th>Proliferative capacity</th>
<th>TCR repertoire diversity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCR7+ CD28+ CD27+ CD57-</td>
<td>6.8kb</td>
<td>71%</td>
<td>38.3</td>
</tr>
<tr>
<td>CCR7- CD28+ CD27+ CD57-</td>
<td>6.3kb</td>
<td>34%</td>
<td>38.5</td>
</tr>
<tr>
<td>CCR7- CD28- CD27+ CD57-</td>
<td>5.9kb</td>
<td>23%</td>
<td>53.3</td>
</tr>
<tr>
<td>CCR7- CD28- CD27- CD57+</td>
<td>5.2kb</td>
<td>12%</td>
<td>64.3</td>
</tr>
</tbody>
</table>

Memory T cell differentiation

- Early
- Late
- Intermediate
- Effector

- Telomere length
- Proliferative capacity
- TCR repertoire diversity
- CFSE fluo
- CDR3 length

with age and HIV-1 infection
Collapse of naive T cell frequencies with HIV disease progression and aging
HIV infection and premature immune aging

$=> 40\text{y old AIDS patient} = 80\text{y old uninfected donor}$

(criteria = naive T cell frequency)
Accumulation of end stage lymphocytes with age or HIV infection


Healthy donor

Naive / new Lymphocytes (T, B & NK) → Mature / old Lymphocytes (T, B & NK)

HIV infected Non progressor

HIV infected Progressor

Elderly

Shorter Telomere length

Reduced proliferative capacity

Restricted repertoire

=> Reduced capacity to produce all lymphocyte subpopulations with age or HIV disease progression
Development of lymphocytes: Hematopoietic progenitors

Hematopoietic progenitors

Lymphoid HPC

Myeloid HPC

Primitive HPC

Stromal cells

Bone marrow

-Thymus

CD4

CD8

CD4 T cell

CD8 T cell

Secondary lymphoid organs

B cell

NK cell

SCF

IL3

IL7

FLT3-L

CFU-LT

CFU-LB

CFU-NK

CD4

CD8

B

NK

Blood
Hematopoietic progenitors and HIV infection...
Impaired HPC function: Yes! (reviewed in Moses et al, Blood, 1998)
But relevance in HIV pathogenesis?
Study of circulating hematopoietic progenitors CD34+ cells: quantitative aspects

Analyse HPC in the blood to generate large data set

1. Numbers of circulating CD34+ (lin-) cells

=> Diminution of CD34+ cell number with HIV disease progression or age
Study of circulating hematopoietic progenitors
CD34+ cells: qualitative aspects

2. Clonogenic potential (CFU assay)

3. Lymphoid vs myeloid potential (phenotype)

=> Alteration of both quantitative and qualitative attributes
**Cause of impaired lymphopoiesis?**

I. **Infection of CD34+ cells by HIV?**

- No correlation HIV load vs CD34+ cells
- => No direct effect of HIV on CD34+ cell compartment

II. **Effect of immune activation?**

- VIH- vs VIH+
- Cause of impaired lymphopoiesis?
- sCD14
- CD38
- Ki67
I. Infection of CD34+ cells by HIV?

No correlation HIV load vs CD34+ cells

=> No direct effect of HIV on CD34+ cell compartment

II. Effect of immune activation?

=> Inverse correlation between CD34+ cell frequency and immune activation
Immune activation and hematopoietic factors

SDF-1$\alpha$
(Aiuti et al, JEM, 1997)

IP-10
(Sarris et al, JEM, 1993)

MIG
(Schwartz et al, JI, 1997)

=> Mobilisation of Hematopoietic progenitors (migration & proliferation)

=> Alteration of hematopoietic system in HIV infection related to immune activation
Decrease of immune activation with ART: longitudinal study of treated patients
Immune activation drives premature immune aging in HIV infection

**HIV Pathogenesis**

*HIV disease progression* => exhaustion of lymphopoiesis

Central role of Immune activation

New understanding and clinical relevance...

1. ART and Immunological Failure?
   => ART treated HIV-1 infected patients with distinct reconstitution

2. HIV elite control vs disease progression?
   => Elite controllers with evidence of disease progression
1. ART and Immunological Failure

Cross sectional study of treated patients
ART and lymphocyte reconstitution

=> It is all linked
Lymphopoiesis attributes

=> Association reconstitution of CD4 compartment and lymphopoiesis normalization

[Graphs showing data on CD34+ cells, CFU, and Phenotype with associated statistical significance symbols.]
Lymphopoiesis attributes

=> Association reconstitution of CD4 compartment and lymphopoiesis normalization

=> Immunologic failure = persistent damage to hematopoietic system
2. Elite control of HIV replication and ... disease progression

Elevated immune activation

Hunt et al, JID 2008

Cnp = HIV elite Controller non progressors

Cp = HIV elite Controller progressors
Disease progression despite elite control of HIV replication…

… is associated with exhausted lymphopoiesis
Exhaustion of lymphopoiesis with HIV disease progression

Activation/Mobilization
- Antigenic
- Indirect
- Sys IA

Healthy donor
- Hematopoietic progenitors
- Thymocytes
- Naive T cells

Advanced age
- Early differentiated memory T cells
- Highly differentiated memory T cells

HIV infection
- Chronic infection
- Progression
- ART & CD4 recovery
- ART & Immunologic failure or Cp

Bone Marrow
- Thymus
- Periphery
I. Immune parallel between aging and HIV disease progression
   => exhausted lymphopoiesis ( ! cumulative effect of age and HIV ! )

I. Persistent immune activation / inflammation likely drives exhausted lymphopoiesis

I. CD4 reconstitution with ART is associated with re-established lymphopoiesis

I. But persistent damage to hematopoietic system overtime
   => Immunologic failure & Cp (… implication for therapy)
St Vincent’s Hospital, Sydney
John Zaunders
Anthony D. Kelleher

INSERM U945, Paris
Delphine Sauce
Solène Fastenackels
Martin Larsen
Amélie Guihot
Guy Gorochov
Guislaine Carcelain
Brigitte Autran

AIDS research program, San Francisco
Peter Hunt
Steven Deeks

Hôpital Pitié Salpêtrière, Paris
Christine Katlama
Dominique Costagliola
Michèle Pauchard
Hocine Ait-Mohand
Luminita Schneider
Anne Simon

Hôpital Kremlin Bicêtre, Bicêtre
Olivier Lambotte
Laurence Meyer
Faroudi Boufassa

Institute for Biomedical Aging Research, Innsbruck
Beatrix Grubeck-Loebenstein
Michael Keller