Immunology of HIV:
What can we learn from LTNPs / Elite Controllers?

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HIV and Immune Deficiencies:

- Are CD4 defects & AIDS the only complication of the HIV infection?
- The collateral damages of Immune activation…
Chronic Inflammation/activation plays a key role in immunopathology of HIV

**HIV-1 infection and replication**
- main target: CCR5+ activated CD4+ T-cells

**Massive CD4+ T-cell depletion**
- in particular mucosal CD4+ T-cells

**Antibody response**
- cellular and humoral

**Bacterial translocation**
- including TLR-ligands

**Viral reactivation**
- in particular CMV

**Production of HIV proteins**
- tat, gp120, nef

**Systemic immune activation**
- Adaptive and Innate

Appay V et al, J Pathol 08
LTNPs and HIV / Elite Controllers: Models of functional Cure of HIV?

• Who are they ?
  • Definition?
  • Control of CD4 and HIV : is it stable ?
  • Control of Immune Activation ?

• How do they control the virus ? : Is it the Virus or the Host ?
  • Which virus characteristics ?
  • Which Immunity ?

• Are they a model for :
  • Vaccines ???
  • Cure of HIV ?
Which **definition** for LTNP and HIV / Elite Controllers ?

- **LTNPs:**
  - **Immuno/Clinical definition: > 1994:** LTNPs:
    » Seropositivity > 7-8 years
    » No AIDS,
    » Normal CD4 counts : >500, >600/mm3
    » No Treatment
    » (VL not available)

- **HIV / Elite Controllers (Suppressors):**
  - **1st evidences: 2000s:**  
    *Elite Controllers : S Deeks & B Walker 2007*
  - **Virological Definition:**
    ✓ Seropositivity > 8-10 years
    ✓ Plasma Viral Load < 400 or 500 cp / mL over 90% measures +/- undetectability
    ✓ No Treatment
    ✓ (AIDS symptoms or CD4 non necessary)
Which **Epidemiology** for LTNP and HIV / Elite Controllers?

### LTNP:
- **1993: LTS SanFrancisco Cohort:** 7%? *S Buchbinder* (1994, 
  - Others: < 5%, <2%, ....

### HIV / Elite Controllers:
- **late 90s:** *HIV / Elite Controllers:* ??? < 1%

### French Hospital Data Base (FHDH):
- **46,880 HIV+ patients:**
  - **LTNP:** Sero+ >8y, CD4 nadir > 500 = 0.4%
  - **Elite LTNP:** idem + CD4 nadir > 600, CD4 slope+ = 0.05%
  - **HIV Controllers:** >10y, 90% VL<500cp/ml = 0.22%
  - **Elite Controllers:** idem HIC + last VL<50 cp = 0.15%

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• **Recruitment: 1994 – 96:**
  - **Inclusion Criteria:** Seropositivity known > 8 years
    CD4>600/mm³ for > 5 years and + CD4 slope
    Lack of HIV-related symptoms
    Lack of ARV

• N=71: median seropositivity: 9 y

• **Evolution:** very slow decrease in CD4 over an 18 years Follow-up:

<table>
<thead>
<tr>
<th>Years</th>
<th>Number subjects</th>
<th>Nb CD4&gt;600</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>71</td>
<td>46 (65%)</td>
</tr>
<tr>
<td>2</td>
<td>61</td>
<td>28 (46%)</td>
</tr>
<tr>
<td>3</td>
<td>44</td>
<td>17 (27%)</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>12 (40%)</td>
</tr>
<tr>
<td>5</td>
<td>24</td>
<td>8 (33%)</td>
</tr>
<tr>
<td>2001-12</td>
<td>18</td>
<td>9 (44%)</td>
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</tbody>
</table>
HIV – Elite Controllers, LTNPs

• **The Virus** or the Host?
  
  – Deletions ?

  – Evolution and escape ?

  – What is the key parameter ?

• Production or Reservoir ?
ALT-ANRS CO15 cohort: HIV characteristics at entry: It is NOT the Virus!

- Low but Heterogeneous viral production:
  - Median plasma VL =
    - 10,000 cp/mL at entry (20-880,000)
  - Slow increase:
    *Candotti et al. 1999, 2000*

- R5-dependent HIV Type:
  All isolates: NSI (*Candotti J Gen Virology1999*)

- No HIV gene deletion in:
  env, nef, gag, LTR but a Vif signature (*Candotti, Vigne, J Virol 2000*)

- SIMILAR FINDINGS
  in OTHER LTNP COHORTS

- Low Reservoir (cell associated HIV-DNA) correlated to virus production

B.A.EACS 2013
Low HIV Reservoir (HIV-DNA) in PBMC: associated with a low risk of HIV disease progression

S Lewin & C Rouzioux et al. AIDS 2011
HIV / Elite Controllers, LTNPs
Do they control T-cell activation?

Low Immune Activation in Elite Controllers with undetectable pVL:
- CD4 activation as low as in ARV-suppressed patients, CD8 activation higher

Hunt, JID 2008
HIV – Elite Controllers, LTNPs

• The Virus or the Host?

  – Is it all in the Genes?

    • Immune Response genes
      – Adaptive Immunity
      – Innate Immunity

  – Is it the anti-HIV Immunity?
Immune Genetics and control of the HIV Reservoirs: Genome-wide analysis in Elite Controllers and LTNP

- The HLA locus in Chromosome 6 is the strongest genetic marker for:
  - HIV controllers vs Acute infection, (Dalmasso et al.: 2009)
  - Elite Controllers (Pereyra et al. 2010)
  - LTNP (GISHEAL: French & Italian) vs Acute infection (Guergnon et al:2011)

- HLA-B57 (HCP5) is the strongest Marker for low HIV reservoirs (Dalmasso et al.)

Lower Reservoir (HIV-DNA) in B27+/57+ vs negatives

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ANRS-CO15 (ALT) cohort: Immune Genetics of LTNPs: It is the HOST!

- A composite of HLA + chemokine /chemoreceptors gene mutations
  CCR5 Δ32(hzg) + SDF-1 wt + HLA-B27+, DR6-+ 3 of the HLA-A3, B14, B57 + DR7
  Significantly predicts 80% of LTNP vs Progressors (Magierowska et al. Blood, 2000)

- Association HLA-B57 and low pl VL:
  [Graph showing median log10 HIV RNA and DNA levels for different HLA genotypes]
  - Protective HLA enriched during Follow-up: 59% at Year0 vs 75% at year5
  - Distinct influences:
    HLA-B57 and B14 associated to HIV control
    HLA-B27 associated to LTNPs
  [Antoni G, AIDS 2013]

- SIMILAR FINDINGS for HLA-B57 in all LTNP / HIC & EC cohorts
  (M Carrington, 1999, Deeks & Walker, 2007, ...)

- Other genetic parameters???: Mutations of the KIRDL1 gene (M Carrington 2005), CX3CR1 gene (Faure 2001) No gene polymorphisms in TRIM-5, APOBEC3G, FcγR

- Genome Wide Association Studies (GWAS)
HIV – Elite Controllers, LTNPs

• **The Virus or the Host?**
  – Is it Immunity?
    • T cell adaptive Immunity:
      • CD8 T cells?
        Specificity?
        Function?
        Gene associations?
      • CD4 T cells?
        Function?
        Other parameters?

Correlates of protection?
Is it the hen or the egg???
The ANRS Co-18 Cohort of HIV Controllers: CD8 T cells mediate a strong anti-viral activity

CD8 T cells from HIC inhibit HIV production
Saez-Cirion, PNAS 2008

Some correlation between anti-viral functions of CD8 T cells from HIC
HIV inhibition and IFN-g production
Saez-Cirion, JI 2009
LTNP - ANRS-CO15 cohort: Robust HIV-specific CD8 T cells

Strong CD8 T cells against HIV-Gag:

- CD8 T cells anti-Gag but not Nef correlate with low HIV reservoirs

Martinez et al. JID 2005, Jie et al. AIDS 2010
A model for an immune control of the HIV Reservoirs in HLA-B27/57+ LTNPs

**HLA-B27/57 neg**

- **TN**
  - Inflammation ++
  - Activation ++

**HLA-B27/57pos**

- **TN**
  - Antigens

**TEM**

- HIV Transcriptionally active
- HIV Transcriptionally inactive
- Anti gag CD8 T cells
HIV – Elite Controllers, LTNPs

- The Virus or the Host?
  - Is it Immunity?
    - Antibodies?
      - Neutralizing?
      - Others?
ANRS CO-15 ALT and antibodies against HIV Env

• **HIV-specific antibodies**: against HIV-enveloppe:

  • Neutralizing Abs:
    • **Positively** correlated to the VL: \(N'\text{Go et al, AIDS Res Hum Retrov.2003}\)
    • Reactivity against the MPER of gp41 \(\text{Braibant et al. AIDS 2006}\)
    • 2F5-like et 4E10 like Abs in 60% sera \(\text{Braibant et al. Virol. 2011}\)
    • Reactivity against gp120: particular structural characteristics

  ![Diagram of HIV Env and CD4 receptors](image)

  • **Isotype**: IgG2: anti-gp41:
    • Best correlate of protection against disease progression \(N'\text{Go et al., AIDS Res Hum Retrov. 2003}\)
    \(\text{Martinez et al. J Inf Dis. 2005}\)

  • **Inhibition of the NK cell-mediated lysis of CD4 T cells**: **Anti-3S (gp41):**
    • Debré et al. block NK cell lysis and correlate with disease progression \(\text{Vieillard et al. AIDS 2007}\)
LTNP, HIC and EC: Robust HIV-specific CD4 T cells

CD4 responses in HIV Controllers

Cytokine responses to p24 Gag stimulation:

- LTNPs: Gag-specific Th1 CD4 T cells
  - associated with control of HIV & CD4
  - The best marker of protection / progression:

in association with anti-gp41 IgG2 Abs

Martinez et al. JID 2005

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LTNPs, HIC & ECs:
- Strong T cell Immunity to HIV
- Weak Neutralizing Abs but other anti-HIV Abs associated with:
  - low VL (IgG2)
  - stable CD4 (anti-gp41/3S)
Are HIV / Elite Controllers, LTNPs a model for HIV Cure?

Current AntiRetroVirals

Persistence of HIV Reservoirs

NO AIDS

Can we decrease the HIV Reservoirs? and stop ART? Functional Cure?

or eradicate HIV Sterilizing Cure?
Hot Topic in 2013: Models of Cure?

**Sterilizing cure?**
- CCR5 defective stem cell graft (Berlin patient)

**Models of Functional cure**
- **Elite Controllers and Long term non progressors**
  - Infected for 10-30 years
  - Never treated; Genetic Background
  - Strong CD4 and CD8 response/HIV
  - Preserved central-memory CD4 T cells
  - Low immune activation

- **Post-Treatment Controllers (Visconti)**
  - Control HIV without ARV for median 3.5 years
  - After ARV for 5 years started at acute infection
  - No genetic background; Immunity ???
  - Preserved central-memory CD4 T cells
  - Low Immune activation

Hot Topic in Sept 2013:
Potential strategies to reduce HIV reservoirs:
Lessons from LTNPs and HIC / ECs

What can we learn from LTNPs, HIC & ECs for controlling latency??

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