Immune Reconstitution: Quantitative and Qualitative aspects

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The 3 phases of the ART-induced immune reconstitution: the 1997-2000 years

1. Early Memory CD4 T cell Redistribution: « Fake » quantitative restoration of CD4 counts but no functionnal restoration

2. Decreased activation with virus control: allows functional restoration

3. Late Naive T cell regeneration > long term CD4 T cell quantitative expansion and Restoration of defenses against OI

(Autran 97, Pakker 98, Li 98, Lederman 98, Bucy 98, Gorochov 98….)
Quantitative and functional CD4 cell reconstitution with HAART

Rapid CD4 counts restoration in end stage disease with high risk of CMV retinitis

300 patients treated with HAART, viral loads <200 copies/ml

Restoration of proliferative CD4 responses to CMV in end stage disease

(Autran 97, Li 98, Lederman 98, Rinaldo 99,
Similar prognostic significance of CD4 counts during disease and immune reconstitution

Immunological recovery and antiretroviral therapy in HIV-1 infection

Manuel Battegay, Reto Nüesch, Bernard Hirschel, Gilbert R Kaufmann

Figure 1: Kaplan-Meier plots of the probability of progression to AIDS or death
Schematic prediction of Time to restore normal CD4 counts according to CD4 cell depletion at time of ART initiation

(B Autran et al. 1998)

Factors influencing quantitative CD4 T cell reconstitution:

- **Positively:**
  - amplitude of HIV control at initiation of ART
  - rapid CD4 decrease before ART initiation (Renaud et al, 1999)

- **Negatively:**
  - outbreaks of virus replication (blips, STI) (Bategay, 2006)
  - HCV co-infections (Koziel 2007)
  - X4 virus tropism for naive CD4 T cells (Delobel, 2006)
Schematic prediction of Time to restore normal CD4 counts according to CD4 cell depletion at time of ART initiation:

Where are we today?

Do drugs influence the quantitative CD4 T cell reconstitution:

- Similar Immune restoration with PI sparing and PI containing regimens (INITIO) (Samri et al. Antiviral Ther. 2007)
- Do new drugs generate a distinct profile of immune restoration???
  - entry inhibitors?
  - integrase inhibitors?
Restoration of Immune Defenses against pathogens with ART

- Restore defenses to all pathogens (Autran97; Li98, Lederman 98, Rinaldo 99, Garcia 99, Pontesili99….)
- Allow arrest of prophylaxis against Opport. Inf (Furrer,99 Reiss 99, Ledereberger 01, Jouan 01..)

B.A. Jni07
Recovery of Memory CD4+ T cell reactivity to CMV allows control of CMV viremia with HAART

Li et al. AIDS Res. Retrov., 99
Restoration of a CMV-specific T cell reactivity with HAART allows to withdraw prophylaxis against CMV retinitis in advanced disease.

47 patients:
With prior CMV retinitis, 2 relapses after arrest of anti-CMV therapy,

Jouan et al, AIDS, 2001
Restoration of T cell-mediated immune protection against CMV disease

- Benefits from HAART:
  
  => Restoration of CD8 T cell-mediated immune protection against CMV retinitis:

=> Comparison of the CMV-specific CD8 T cell magnitude, repertoire breadth and differentiation in:

  HN: Healthy HIV- (n=11)

  LTNP: HIV+HCMV+ Long Term Non Progressors (n=10), med CD4: 733/mm3

  HIV+ Recovering from CMV retinitis on ART, after stopping GCV:
    - Short Term Recovery (18 months, n=8): CD4: 357/mm3
    - Long Term Recovery (>50 months, n=6): med CD4: 345/mm3

  Acute CMV retinitis: (n=8): med CD4: 50/mm3

Short Term Recovery of strong responses against the CMV early IE1 antigens after CMV retinitis

Restoration of Immune Protection against CMV retinitis in HAART treated patients

Sacre et al., JEM 2005

- **CD4 counts**
- **CMV Replication** (detection threshold)
- **Repertoire & diversity of CMV-specific CD8 T cells** against pp-65 and IE1
- **Magnitude of HCMV-specific CD8 T cells** per target antigen
- **Differentiation of HCMV-specific CD8 T cells**
  - % CD27-28-
  - % CD27-/+28+
  - % CD27+28+
  - Naive

<table>
<thead>
<tr>
<th>HIV infection</th>
<th>Healthy CMV+ HIV-negative</th>
<th>Healthy CMV+</th>
<th>CMV retinitis</th>
<th>Recovery from CMV retinitis</th>
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<td>EARLY</td>
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<td>LATE</td>
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HAART
Sequential Restoration of Immune protection against opportunistic pathogens

• CMV retinitis:
  – Loss of CD4 responses to HIV => Limited repertoire & diversity of short-lived anti-CMV CD8 T cells => Loss of CMV control
  – Gancyclovir: control of CMV replication
    BUT no restoration of immunity to CMV

• HAART:
  – Controls HIV =>Restores CD4 counts
    • Restores protective Immunity against CMV:
      – CD4 responses to CMV
      – CD8 cells to CMV –IE1 antigens
        » Large breadth and diversity
        » long-lived memory CD8 T cells

=> Restores Long Term control of CMV without gancyclovir
Rapid restoration of protective memory responses against opportunistic pathogens with HAART

- Reduction in morbidity / mortality (Hogg, 97, Pallella, 98…)
  - Discontinuation of prophylaxis against Opportunistic Infections: PCC. Pneumoniae, CMV retinitis (Furrer, 99, Jouan 2001…)
  - at all stages of the disease: illustrating the lack of definitive immune alterations

- BUT Induces the Immune Restoration Syndrome (IRS,)
  
  M French, 98, 2006, Monsuez 99, Breton 2005………..

  - during opportunistic infections concomitantly treated with HAART
  - reactivation of pathogen-associated symptoms +/- systemic inflammatory syndrome without microbiological relapse, or of auto-immune diseases
  - particularly frequent during mycobacterial infections (MAI, TB: 40%)
TB and VIH

- Diminution Nb activated macrophages
- Diminution of intra-cellular BK lysis

Consequences of CD4 defects in HIV infection:
- Disparition of Ag-specific responses, = Anergy to TB antigens
- Poor Granuloma, without caseum, poorly functionals
- Disseminated pauci-symptomatic Tuberculosis

A. Bourgarit 05
IRS: Hypothesis

Rapid Restoration of CD4 counts and function with HAART
=> Amplification +++ of the specific CD4 Th1 cells to Mtb
=> inflammatory Syndrome « cytokine Storm »

A. Bourgarit 05
ANRS EP-21: PARADOX-TB:
A prospective analysis of the Immunological characteristics of the TB-associated IRS

Bourgarit et al. AIDS, 2006

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<tr>
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<th>IRS+</th>
<th>IRS-</th>
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<tr>
<td>n</td>
<td>11</td>
<td>13</td>
<td>NS</td>
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<tr>
<td>M/F</td>
<td>6/5</td>
<td>9/2</td>
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<td>Age</td>
<td>38 (30-56)</td>
<td>36 (26-63)</td>
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<td>Pulmonary TB</td>
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<td>4/13</td>
<td>NS</td>
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<tr>
<td>Disseminated TB</td>
<td>9/11</td>
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<td>BAAR+</td>
<td>3/8</td>
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<tr>
<td>HIV Infection</td>
<td>CD4 (/mm3)</td>
<td>26 (6-145)</td>
<td>54 (15-267)</td>
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<td>CV (Log)</td>
<td>6 (4.8-6.5)</td>
<td>5.2 (4.3-8)</td>
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<td>M0HAART</td>
<td>Délai /TBK (j)</td>
<td>36 (7-77)</td>
<td>50 (14-111)</td>
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<td>IRS</td>
<td>Délai / M0 (j)</td>
<td>23 (7-85)</td>
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<tr>
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<td>CD4</td>
<td>108 (59-430)</td>
<td>163 (9-580)(M1)</td>
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<td>ΔCD4 /M0 (/mm3)</td>
<td>+54 (-1;+393)</td>
<td>+77 (-50;+250)</td>
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<tr>
<td>M3</td>
<td>CD4</td>
<td>117 (58-399)</td>
<td>132 (49-410)</td>
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<td>ΔCD4 /M0 (/mm3)</td>
<td>+86 (-74;+367)</td>
<td>+73 (-88;+354)</td>
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<td></td>
<td>CV &lt;200</td>
<td>7/10</td>
<td>8/11</td>
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Bourgarit et al. AIDS, 2006
TB-IRS: Acute Exacerbation of a Th1 response to tuberculin but not to live TB (ELISpot IFN-γ) (Bourgarit, AIDS 2006)

- N IFN-g producing T cells to PPD significantly stronger in IRS +
- No or weak response to live TB-associated antigens: ESAT-6, CFP-10, 85B
- Mediated by CD4 T cells: up to 35% of circulating CD4 T cells
Multiplex Detection of cytokines – Chemokines in culture supernatants (Chimioluminescence)

=> Intense inflammatory response both Ag-specific (PPD) and non-specific: cytokines: TNF-a, IL-6, IL-10
chemokines: RANTES, MCP1..

• A frequent syndrome:
  - in 40% (9/22) TB-HIV co-infected patients with severe CD4 defects and rapid CD4 restoration within 3 months after treatment initiation

• A brutal explosion of tuberculin-specific T cells
  - Poorly or undetectable at baseline,
  - Rapidly restored and exacerbated, within a month
  - Mediated by activated CD4 Th1 cells + γδ T cells
    - with specific release of Th1 cytokines and pro-Th1 chemokines
      - but without deregulated Th2 response
  - Directed against Antigens present in tuberculin
  - Associated to an acute non-specific inflammatory response

Bourgarit et al. AIDS, 2006
Immune Restoration Syndrome associated with TB in HIV infection

- **Paradox-TB**: Pending Questions > BK-VIR-IS
  - Clonality of the response?
  - Antigens involved? And role of γ-δ T cells?
  - Role of regulatory T cells?
  - Individual susceptibility?

- Why only 40% IRs if this corresponds to a physiological restoration of tuberculin specific T cells?
  - Strains?
  - Host Genetic Predisposition?
    » HLA
    » Other Genes: Th1 pathways…,

_Bourgarit et al. AIDS, 2006_
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