Humanized Mice for Studying HIV Persistence in Long-Lived Tissue-Resident Macrophages

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The contribution of myeloid cells to HIV reservoir persistence during antiretroviral therapy (ART) remains controversial. Recent advances revealed the existence of two pools of tissue resident-macrophages (TRM):

- **long-lived (LL-TRM):**
  - self-renewal capacity
  - derived from embryonic stem cells of the yolk sac and the fetal liver

- **short-lived (SL-TRM):**
  - derived from bone-marrow monocytes

Although the presence of LL-TRM in the brain, liver, lungs and dermis is well-established, recent studies demonstrated the existence of LL-TRM in multiple other tissues including blood vessels and heart. In contrast, gut-associated lymphoid tissues are mainly infiltrated by monocyte-derived SL-TRM.

Our previous studies demonstrated that **blood monocytes and colon SL-TRM rarely carry HIV-DNA reservoirs in ART-treated people living with HIV.** Our capacity to investigate HIV persistence in myeloid cells is limited by difficulties in accessing deep tissues from PLWH. Humanized mice (hu-mice) represent appropriate models for HIV reservoir studies.
RESULTS

1. Engraftment of human cells in processed hu-BLT samples

- Liver
- Lungs
- Spleen

2. Gating strategy: representative strategy on liver cells

- Vivid-
- CD45-
- Lin-

4 populations sorted:
  - Mouse CD45+ cells
  - CD4+ T cells
  - CCR2- MF
  - CCR2+ MF
3. Integrated HIV-DNA in liver and lung-infiltrating cells

**RESULTS**

Human myeloid cells were identified as cells expressing a mCD45-CD3-CD4lowCD33+HLADR+CCR2+/CCR2- phenotype.

In HIV+ untreated mice:
→ integrated HIV-DNA was detected in both CCR2+/CCR2-myeloid cells and CD4+ T-cells from the liver and lungs.

In HIV+ ART-treated mice:
→ integrated HIV-DNA was detected in CD4+ T-cells from the liver and lungs and in CCR2- myeloid cells from the lungs.
→ It was not detected in both CCR2+/CCR2- from the liver and CCR2+ myeloid cells from the lungs.

**CONCLUSION**

These results provide preliminary evidences on the contribution of LL-TRM vs SL-TRM to HIV reservoir persistence during ART in the lungs.