Liver Macrophages and HIV-1 Persistence

**Abstract**

Background: Cellular reservoirs of HIV-1 infection that persist despite combination antiretroviral therapy (cART) are a major challenge in the era of treatment as prevention. Liver macrophages (TREM) express factors that may represent an important reservoir of HIV-1. We hypothesized that liver macrophages (LM) harbor immune cells containing proviral HIV-1 at the removal of HIV-1 using cART.

Methods: LM were purified from fresh liver explants from 3 HIV-1 infected subjects with uncontrolled (LT01) and cART-suppressed (LT02) viremia. LM were isolated from liver tissues taken from HIV-1-infected persons with uncontrolled (n=1) and cART-suppressed viremia to determine if purified LM contain infectious HIV-1. LM purity was confirmed using qPCR assays, and when required LM were maintained with a high-affinity T cell immunotoxin (aCET) to prevent the growth of T cells.

Results: LM were purified from liver explants taken from HIV-1 infected persons with uncontrolled (n=1) and cART-suppressed viremia. LM supernatants were tested periodically for the presence of viral RNA. LM supernatants were sufficient to propagate HIV-1 in reporter cells. Infectious virus was detectable in LM supernatant from the individual with uncontrolled viremia after a prolonged duration; therefore, LM may represent an important reservoir after was detectable in LM supernatant from the individual with uncontrolled viremia. Poly(A) HIV-1 RNA >170 days; LM supernatants were sufficient to propagate HIV-1 in reporter cells. Infectious virus was also recovered during and after in vitro exposure to cART for 24 days. Poly(A) HIV-1 RNA was detectable in LM supernatants from the individual with uncontrolled viremia 60 days after cART was stopped. LM supernatants were sufficient to propagate HIV-1 in reporter cells. Infectious virus was detected in LM supernatants from both individuals with uncontrolled viremia after 180 days. LM supernatants from LT01 infected LM were sufficient to propagate HIV-1 in reporter cells. LM supernatants from LT02 infected LM were sufficient to propagate HIV-1 in reporter cells. Supernatants from LT01 and LT02 LM were assessed at day 24 and day 60. LM supernatants were sufficient to propagate HIV-1 in reporter cells at day 24 and day 60. LM supernatants from LT01 infected LM were sufficient to propagate HIV-1 in reporter cells at day 60. LM supernatants were sufficient to propagate HIV-1 in reporter cells. Infectious virus was detectable in LM supernatants from both individuals with uncontrolled viremia after 180 days. LM supernatants from LT01 infected LM were sufficient to propagate HIV-1 in reporter cells. LM supernatants from LT02 infected LM were sufficient to propagate HIV-1 in reporter cells. Supernatants from LT01 and LT02 LM were assessed at day 24 and day 60. LM supernatants were sufficient to propagate HIV-1 in reporter cells at day 24 and day 60. LM supernatants from LT01 infected LM were sufficient to propagate HIV-1 in reporter cells at day 60. LM supernatants were sufficient to propagate HIV-1 in reporter cells. Infectious virus was detectable in LM supernatants from both individuals with uncontrolled viremia after 180 days. LM supernatants from LT01 infected LM were sufficient to propagate HIV-1 in reporter cells. LM supernatants from LT02 infected LM were sufficient to propagate HIV-1 in reporter cells. Supernatants from LT01 and LT02 LM were assessed at day 24 and day 60. LM supernatants were sufficient to propagate HIV-1 in reporter cells at day 24 and day 60. LM supernatants from LT01 infected LM were sufficient to propagate HIV-1 in reporter cells at day 60.

Conclusions:these data provide strong evidence that LM, the largest TRM population, release infectious HIV-1 after a prolonged duration; therefore, LM may represent an important reservoir of HIV infection and potential impediment to cure.

**Fig 2: HIV-1 DNA is detectable in liver tissue from HIV-infected persons**

(A) DNA
(B) RNA

**Fig 3: Liver Macrophages isolated from HIV-infected persons with uncontrolled and with controlled viremia harbor infectious virus**

(A) N1
(B) N2
(C) N3
(D) LT01
(E) LT02

**Results**

Whole liver tissue was obtained from HIV-1-infected individuals at time of death (+) from NDR and during liver transplantation (+). After whole liver tissue was obtained for HIV-1 proviral DNA and RNA. Cell numbers were estimated using ERV3 DNA quantification from the same samples. The table indicates the latest available CD4+ T cell count, cART status, and plasma HIV-1 RNA. N2, N3, LT01 and LT02 were HCV+ while N2 and N3 were HBV+.

**Fig 4: Long-term viral kinetics of HIV-1 infected Liver Macrophages**

(A) LT01
(B) LT02

**Results**

Whole liver tissue was obtained from HIV-1-infected individuals at time of death (+) from NDR and during liver transplantation (+). After whole liver tissue was obtained for HIV-1 proviral DNA and RNA. Cell numbers were estimated using ERV3 DNA quantification from the same samples. The table indicates the latest available CD4+ T cell count, cART status, and plasma HIV-1 RNA. N2, N3, LT01 and LT02 were HCV+ while N2 and N3 were HBV+.

**Fig 5: HIV-1 production of GFP positive Liver Macrophages in culture during treatment with cART**

(A) LT01
(B) LT02

**Results**

Whole liver tissue was obtained from HIV-1-infected individuals at time of death (+) from NDR and during liver transplantation (+). After whole liver tissue was obtained for HIV-1 proviral DNA and RNA. Cell numbers were estimated using ERV3 DNA quantification from the same samples. The table indicates the latest available CD4+ T cell count, cART status, and plasma HIV-1 RNA. N2, N3, LT01 and LT02 were HCV+ while N2 and N3 were HBV+.

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