Human galectin-9 promotes the expansion of HIV reservoirs in vivo in humanized mice

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BACKGROUND

The human endogenous protein Galectin-9 (Gal-9) reactivates latently HIV-infected cells in vitro and ex vivo, which may allow for immune-mediated clearance of these cells. However, Gal-9 also activates several immune cells, which could negatively affect HIV persistence by promoting chronic activation/exhaustion. This potential "double-edged sword" effect of Gal-9 raises the question of the overall impact of Gal-9 on HIV persistence in vivo.

METHODS

We used the BLT (bone marrow, liver, thymus) humanized mouse model to evaluate the impact of Gal-9 on HIV persistence in vivo during antiretroviral therapy (ART). Two independent cohorts of ART-suppressed HIV-infected BLT mice were treated with either recombinant Gal-9 or PBS control. Plasma viral loads and levels of tissue-associated HIV DNA and RNA were measured by qPCR. Immunohistochemistry and HIV RNAscope were used to quantify CD4+ T, myeloid, and HIV RNA+ cells in tissues. T cell activation and exhaustion were measured by flow cytometry, and plasma markers of inflammation were measured by multiplex cytokine arrays.

Human galectin-9 promotes the expansion of HIV reservoirs during the ART while exhibiting little effect on peripheral inflammation and T cell activation.

RESULTS

Gal-9 did not induce plasma markers of inflammation or T cell markers of activation/exhaustion in vivo. However, the treatment significantly increased levels of tissue-associated HIV DNA and RNA compared to controls (P = 0.0007 and P = 0.011, respectively, for cohort I and P = 0.002 and P = 0.005, respectively, for cohort II). RNAscope validated the Gal-9 mediated induction of HIV RNA in tissue-associated myeloid cells, but not T cells.

CONCLUSIONS

Gal-9 treatment is tolerable in vivo but increases levels of tissue-associated HIV DNA and RNA during ART-suppressed HIV infection. Gal-9 treatment does not significantly induce markers of inflammation of T cell activation. Our study highlights the overall adverse effects of Gal-9 on HIV persistence and the potential need to block Gal-9 interactions during ART-suppressed HIV infection.

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Fig. 1

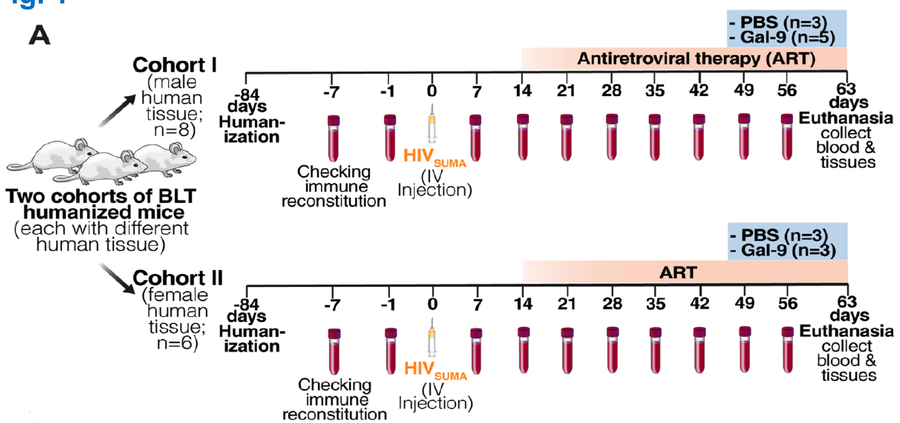

Figure 1. (A) Study design. (B) Reconstitution of BLT (C) Body weight kinetics. (D) Plasma viral load kinetics (E) Tissue-associated HIV DNA and RNA (F) Immunohistochemistry and quantitative image analysis of CD4+ T and myeloid cells in the liver and spleen of both cohorts. (G)Top: representative example of myeloid (blue) and CD4+T (green) cells harboring HIV RNA (red) using RNAscope. Bottom: levels of HIV RNA+ CD4+ T or myeloid cells in the liver and spleen of mice. Unpaired T tests. Mean and SEM are displayed.

Fig. 2

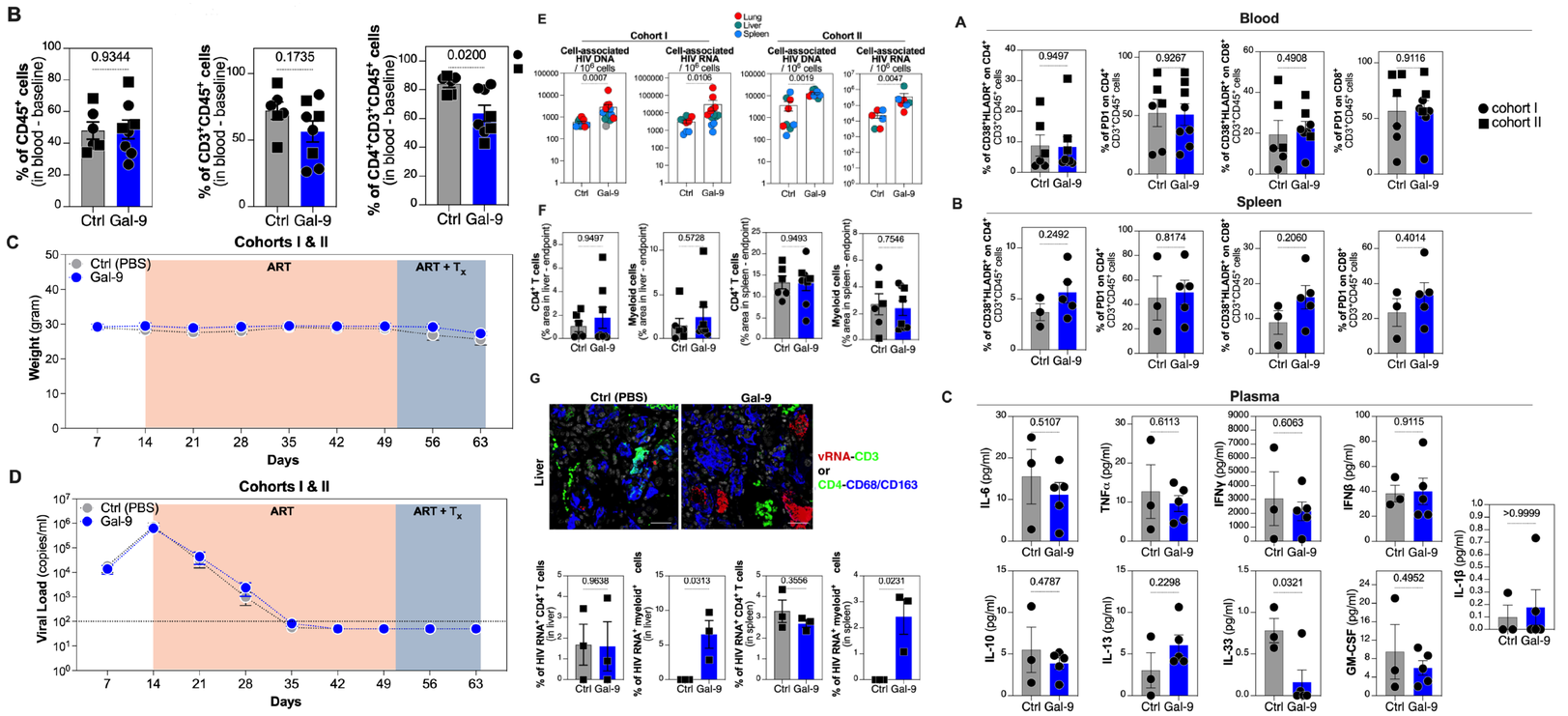

Figure 2. (A-B) impact of Gal-9 treatment on markers of CD4+ and CD8+ T cell activation and exhaustion in the blood (A) and spleen (B). (C) Impact of Gal-9 treatment on plasma levels of markers of systemic inflammation measured by multiplex arrays