Blocking type I interferon signaling enhances T cell recovery and reduces HIV-1 reservoirs

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ABSTRACT

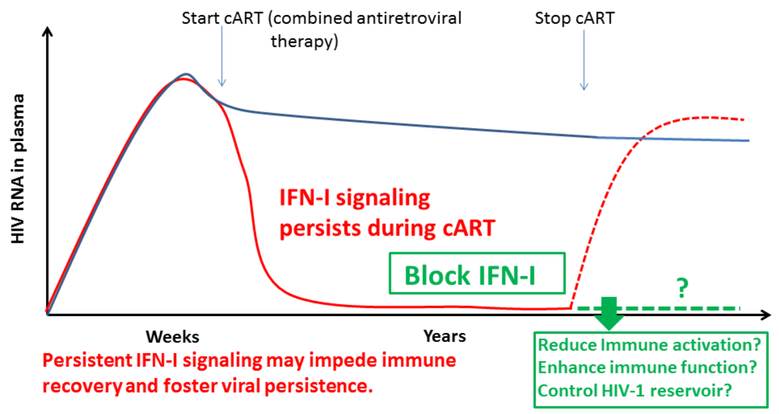
Background: Type I interferons (IFN-I) are critical for controlling virus infections, but their persistent expression also contributes to impaired host immunity and virus persistence. Although IFN-I inhibit HIV-1 replication in vitro and in vivo, persistent IFN-I induction is correlated with immune dysfunction and disease progression in HIV-1 infected patients and in SIV infected monkeys. Moreover, despite efficient suppression of HIV-1 replication with combined antiretroviral therapy (cART), low levels of IFN-I signaling persist in some individuals, which may impede immune recovery and foster viral persistence.

Method: We developed a monoclonal antibody to human IFN-α/β receptor (α-IFNAR) which can block IFN-I signaling in vivo. Humanized mice with persistent HIV-1 infection were treated with cART and IFNAR blockade Ab or isotype control (and human CD8 depleting mAb). At termination, T cell phenotype (expression of activation marker CD38 and HLA-DR, exhaustion marker PD-1, TIM3) was detected by FACS. T cell function was detected by ex vivo HIV-1 Gag peptide pool stimulation followed with IL-2/IFN-γ/TNF-α intracellular staining. Transcriptome analyses by RNA-seq were performed with purified human CD8 T cells to identify pathways and genes contributing to IFN-I-induced T cell dysfunction. To measure HIV-1 reservoir, we detect cell-associated HIV-1 DNA and RNA by PCR, and replication-competent HIV-1 by the quantitative virus outgrowth assay(QVOA). In addition, we measured virus rebound after cART discontinuation.

Results: In HIV-infected humanized mice with cART, IFNAR blockade reduces the level of T cell activation (expression of CD38 and HLA-DR), reverses T cell exhaustion (expression of PD-1 and TIM-3). Transcriptome analysis by RNA-seq with purified CD8 T cells also indicated that IFNAR blockade reduced the expression of ISGs and genes involved in immune activation, exhaustion and cell death. We also found that IFNAR blockade rescued anti–HIV-1 T cells response. Most strikingly, we found that IFNAR blockade in the presence of cART reduced the size of HIV-1reservoirs in lymphoid tissues and delayed HIV-1 rebound after cART cessation in the HIV-1–infected hu-mice. Finally, we found that CD8 T cells rescued by IFNAR blockade were essential for HIV-1 reservoir reduction.

Conclusions: We conclude that low levels of IFN-I signaling contribute to HIV-1–specific CD8 T cell dysfunction and foster HIV-1 persistence in cART treated hosts.

Hypothesis



We hypothesized that IFNAR blockade in the presence of cART would reverse hyper-immune or inflammatory activation and facilitate recovery of functional anti-HIV-1 adaptive immune responses, thereby enabling control of cART-resistant HIV-1 reservoirs.

Results

Figure 1

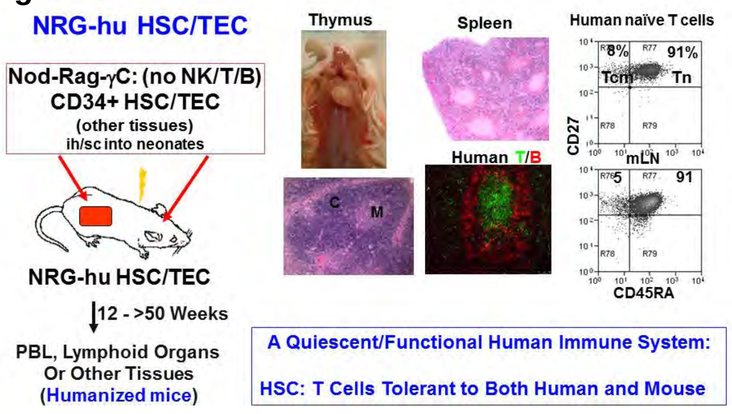


Fig.1. Construction of humanized mouse.

Figure 2

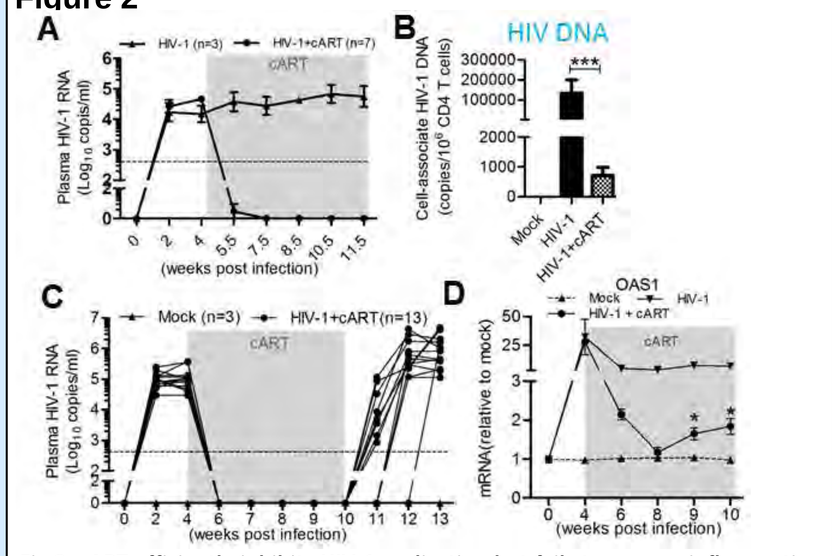


Fig.2. cART efficiently inhibits HIV-1 replication but fails to reverse inflammation and clear HIV-1 reservoirs. Humanized mice infected with HIV-1 were treated with cART as indicated. (A) Plasma HIV genome; (B) Cell associated HIV DNA; (C) Virus rebound after cART discontinuation. (D) OAS1 expression in PBMCs.

Figure 3

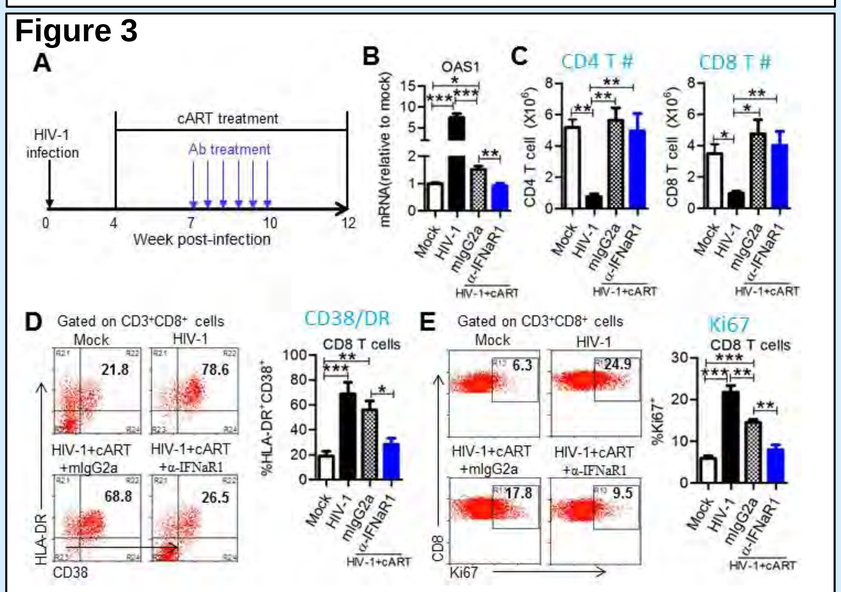


Fig.3. IFNAR blockade during cART-suppressed HIV-1 infection completely reverses aberrant immune activation. (A) Schematic diagram of the experimental design. (B) mRNA levels of OAS1 in PBMCs at 9 wpi. (C) CD4 and CD8 T cells in spleens. (D-E) Percent HLA-DR+CD38+ and Ki67+ of CD8 T cells from spleens.

Figure 4

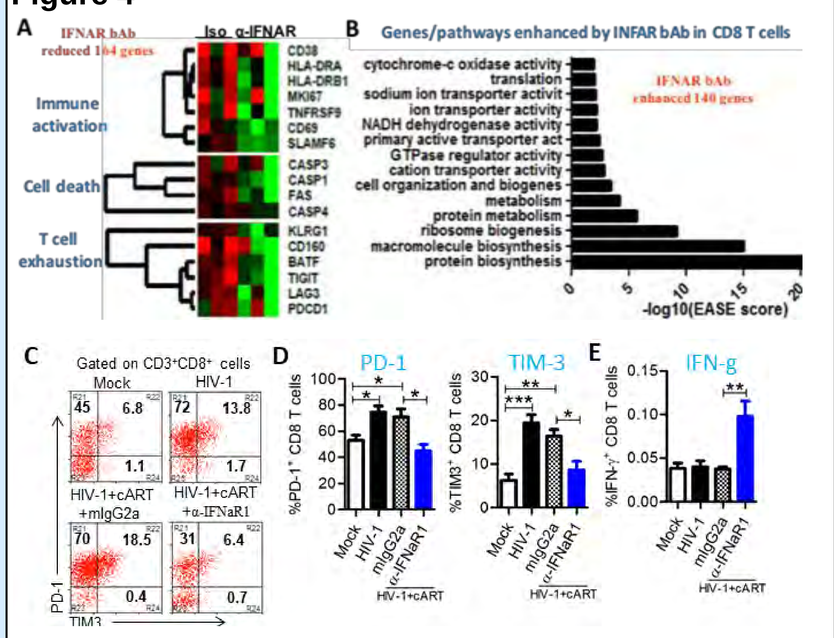


Fig.4. IFNAR blockade during cART-suppressed HIV-1 infection reverses the exhaustion phenotype of CD8 T cells and restores anti-HIV-1 T cell function. Mice were treated as in Fig 3A. (A-B)RNAseq was performed with purified CD8 T cells from spleens at 12 wpi. (A) Summarized data show IFNAR bAb-reduced genes. (B) GO biological process analysis of enhanced genes using DAVID bioinformatics resources. (C-D) PD-1 and TIM-3 expression on CD8 T cells. (E) IFN-g production by CD8 T cells after HIV-Gag peptide pools stimulation.

Figure 5

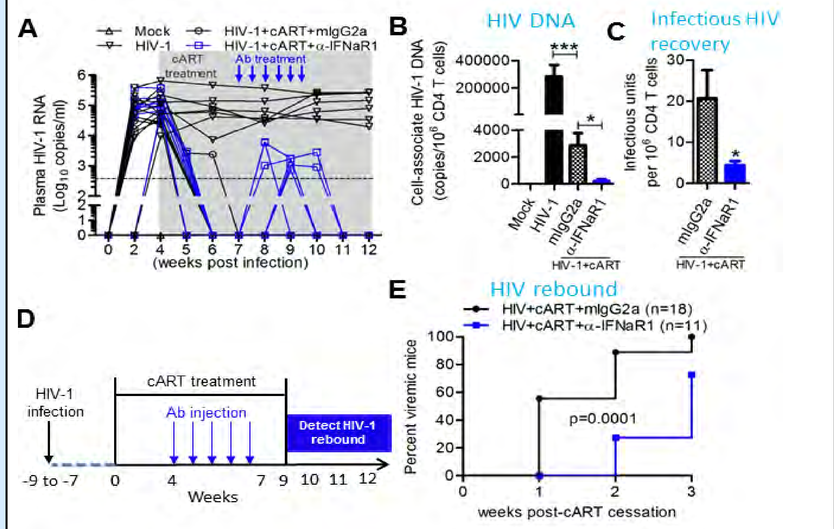


Fig.5. IFNAR blockade during cART reduces cART-resistant HIV-1 reservoirs. Humanized mice infected with HIV-1 were treated as indicated. (A) Plasma HIV genome; (B) Cell-associated HIV-1 DNA; (C) Replication-competent HIV-1 viruses from spleens detected by virus out growth assay; (D-E) Virus rebound after cART discontinuation.

Figure 6

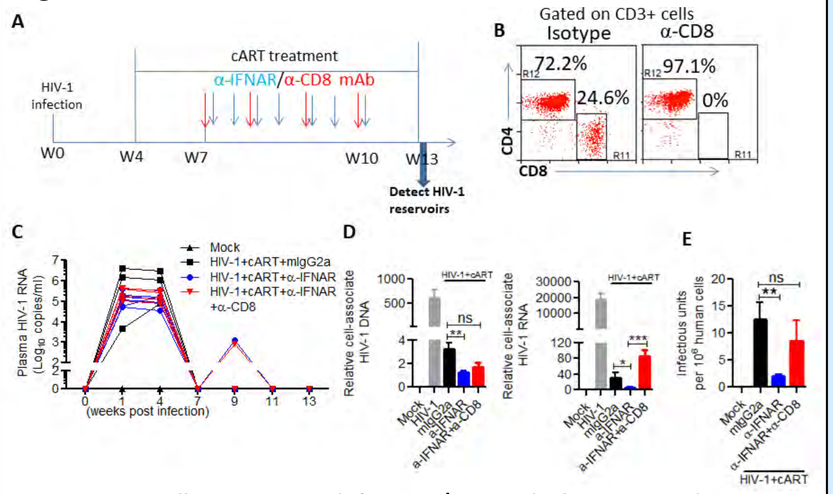


Fig.6. CD8 T cells are required for pDC/IFNAR depletion to reduce HIV-1 reservoir. (A) Schematic diagram of the experimental design. Humanized mice infected with HIV-1 were treated with cART from 4-13 wpi. From 7 to 10 wpi, the cART treated mice were injected with α-IFNaR1 antibody CD8 depletion Ab or isotype control mIgG2a antibody. (B) Specific depletion of CD8 T cells in spleen was detected by FACS.(C) HIV-1 RNA levels in the plasma. (D) Cell-associated HIV-1 DNA and RNA in human cells from spleen was quantified by PCR. (E) Replication-competent HIV-1 viruses from spleens were detected by the quantitative virus outgrowth assay. Shown are combined data from two independent experiments with mean values ± s.e.m. (mock, n=7; HIV-1, n=7; HIV-1+cART+mIgG2a, n=8; HIV-1+cART+α-IFNaR1, n=8). *P < 0.05, **P < 0.01, ***P < 0.001, by One-way ANOVA and Bonferroni's post hoc test.

Conclusion

We conclude that low levels of IFN-I signaling contribute to HIV-1–specific CD8 T cell dysfunction and foster HIV-1 persistence in cART treated hosts.

Significance:

Our results suggest that blocking IFNAR may provide a novel strategy to enhance immune recovery and to reduce HIV-1 reservoirs in those who sustain elevated IFN-I signaling during suppressive cART.

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