Depletion of pDC abolishes IFN-1 induction during acute HIV-1 infection in DKO-hu mice. Humanized Mice were treated with either B6DC2 specific (15B) or isotype control (iso) antibody. After pDC depletion, mice were adoptively transferred with HIV-1 RA3 and terminated at 8dpi. (A) Precentage of pDC (CD45+CD123+) in total blood leukocytes (B) Plasma IFN2u of uninfected, HIV-1 infected and 15B treated mice were quantified. (C and D) The mRNA levels of IFN1 and interferon stimulated genes in purified human cells from spleens. All bars in dot graphs indicate median value. Error bars indicate standard deviations (SD). * and ** indicate p<0.05 and p<0.01, respectively.

Pre-depletion of pDC reduced HIV-1 pathogenesis in acute infection. Humanized mice were infected with HIV-1 three days after pDC depletion and terminated at 8dpi. (A, B and C) Cell counts of human T cells, total leukocytes in peripheral blood and spleen. (A) CD4 T cell (CD3+CD4+) counts. (B) CD8 T cell (CD3+CD8+) counts. (C) huCD4+ leukocyte counts. (D and E) Representative histograms and summarized data show percentages of dead CD4 T cell, CD8 T cell and hucD4+ cell in spleen in RA3A infection at 8dpi. All bars in dot graphs indicate median value. * and ** indicate p<0.05 and p<0.01, respectively.

Depletion of pDC increases HIV-1 replication in chronic infection. HIV-1 infected humanized mice were start treatment with 15B at 11wpi and terminated at 21wpi. (A-C) Cell counts of human T cells or total leukocytes in peripheral blood and spleen. (A) CD4 T cell (CD3+CD4+) counts. (B) CD8 T cell (CD3+CD8+) counts. (C) huCD45+ leukocyte counts. (D) Immunohistochemistry staining for human CD4+ cells in spleen. (E and F) Representative histograms and summarized data show percentages of dead CD4 T cell, CD8 T cell and hucD45+ cell in spleen. All bars in dot graphs indicate median value. * indicate p<0.05.

Depletion of pDC decreases HIV-1 pathogenesis in chronic infection. HIV-1 infected humanized mice were start treatment with 15B at 11wpi and terminated at 21wpi. (A-C) Cell counts of human T cells or total leukocytes in peripheral blood and spleen. (A) CD4 T cell (CD3+CD4+) counts. (B) CD8 T cell (CD3+CD8+) counts. (C) huCD45+ leukocyte counts. (D) Immunohistochemistry staining for human CD4+ cells in spleen. (E and F) Representative histograms and summarized data show percentages of dead CD4 T cell, CD8 T cell and hucD45+ cell in spleen. All bars in dot graphs indicate median value. * indicate p<0.05.

CONCLUSIONS

• pDCs suppress HIV-1 replication in vivo.
• pDCs contribute to HIV-1 infection induced cell death in vivo.
• Depletion of pDCs decrease human cell death.
• Blocking of pDCs function or depletion of pDCs may be a novel treatment for HIV infection.

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Dual roles of plasmacytoid dendritic cells in HIV-1 infection and pathogenesis
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ABSTRACT

The role of plasmacytoid dendritic cells (pDCs) in human immunodeficiency virus type 1 (HIV-1) infection and pathogenesis is likely important but remains unclear. We have developed a monoclonal antibody that specifically depletes human pDC in humanized mice. The expression of type I interferons (IFN-I) and interferon-stimulated genes (ISGs) are severely impaired by pDC ablation either before or during chronic HIV-1 infection. HIV-1 replication was significantly up-regulated in pDC-depleted mice. Surprisingly, HIV-1 induced depletion of human immune cells including T cells and total human leukocytes was reduced in spite of the increased viral replication. We conclude that pDCs play a role not only in suppressing HIV-1 infection but also in promoting HIV-1 induced pathogenesis. These findings suggest that pDC-depletion or suppression of pDC function will provide a novel approach for HIV-1 therapy.

RESULTS

HIV viremia and pathogenesis in RS/UK dual tropic HIV-1 infected DKO-hu mice terminated at 3wpi. (A) Viral copy numbers in plasma from mice intravenously inoculated with 1ng p24/mouse of RA3 [n = 10]. (B) Summary data for the percentages of HLA-DR+CD38+ CD8 T cells (CD3+CD4-CD8+) in peripheral blood and spleen. (C) Summary data for the percentages of CD3+CD8+CD4- T cell in CD3+ cells. (D) The production of IFN-α in plasma from uninfected and infected DKO-hu mice. (E) The relative level of Mx1 and TRIM22 gene expression in hucD45+ cell in spleen. (F) Comparison of absolute CD4 T-cell, CD8 T-cell and hucD45+ cell numbers in spleen from uninfected control mice and RA3A infected mice. All bars in dot graphs indicate median value. Error bars indicate standard deviations (SD). * and ** indicate p<0.05 and p<0.01, respectively.

Pre-depletion of pDC increase HIV-1 replication. Humanized mice were infected with HIV-1 three days after pDC depletion and terminated at 8dpi (RA3, A and B) or three weeks (JR-CSF, C, D and E) post infection. (A) Plasma HIV-1 RNA levels at 8dpi. (B) Immunohistochemistry staining for p24 positive cells in spleen. (C) Plasma HIV-1 RNA levels at 2wpi. (D) Representative FACS plots for p24 positive CD4 T cells in spleen at 3wpi. (E) Summarized data of Figure 3d. Bars in dot graphs indicate median value. * indicate p<0.05.