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

Guangming Li[1], Menglan Cheng[2], Jun-ichi Nunoya[1], Liang Cheng[1], Haitao Guo[1], Haisheng Yu[2], Yong-jun Liu[3], Liguo Zhang[2*] and Lishan Su[1,2,4*]

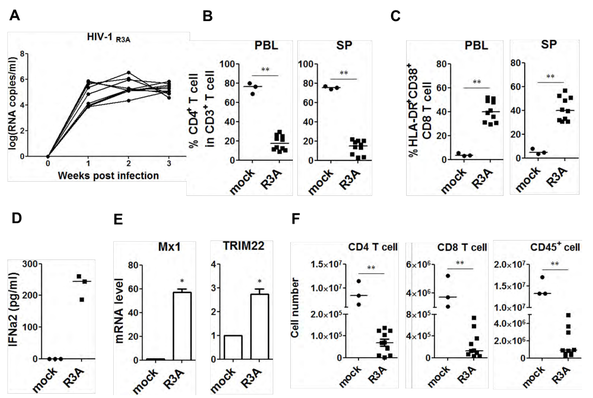
[1]Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA. [2]Key lab of Infection and Immunity, Institute of Biophysics, Chinese Academy of Sciences, Beijing, China. [3]Baylor Institute for Immunology Research, Baylor Research Institute, Dallas, Texas, USA. [4]Department of Microbiology and Immunology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA.

ABSTRACT

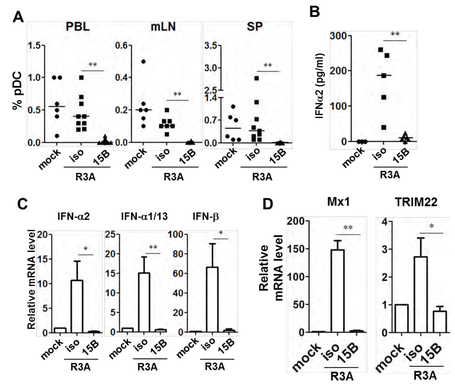
The role of plasmacytoid dendritic cells (pDCs) in human immunodeficiency virus type 1 (HIV-1) infection and pathogenesis is likely important but remains unclear. We have developed a monoclonal antibody that specifically depletes human pDC in humanized mice. The expression of type I interferons (IFN-I) 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

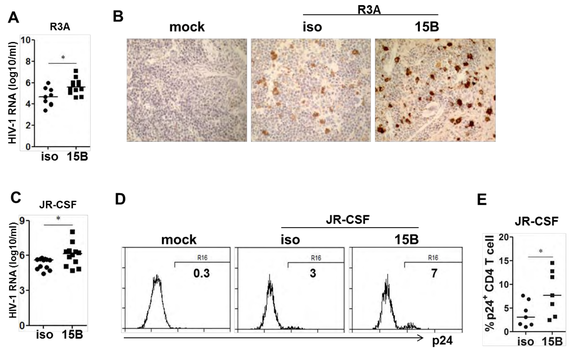
HIV viremia and pathogenesis in R5/X4 dual tropic HIV-1-infected DKO-hu mice terminated at 3wpi. (A) Viral copy numbers in plasma from mice intravenously inoculated with 1ng p24/mouse of R3A (*n* =10). (B) Summary data for the percentages of HLA-DR+CD38+ CD8 T cells (CD3+CD4-CD8+) in peripheral blood and spleen. (C) Summary data for the percentages of CD3+CD8-CD4+ T cell in CD3+ cells. (D) The production of IFN-a2 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 R3A-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.



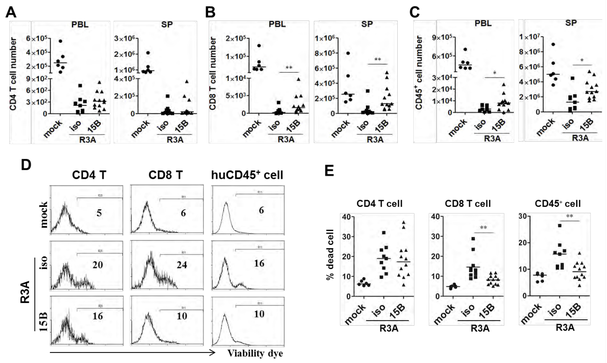
Depletion of pDC abolishes IFN-I induction during acute HIV-1 infection in DKO-hu mice. Humanized Mice were treated with either BDCA2 specific (15B) or isotype control (iso) antibody. After pDC depletion, mice were infected with HIV-R3A and terminated on 8dpi. (A) Percentage of pDC (CD4+CD123+) in total human leukocytes (B) Plasma IFNα2 of uninfected, HIV-1 infected and 15B treated mice were quantified. (C and D) The mRNA levels of IFN-I 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.



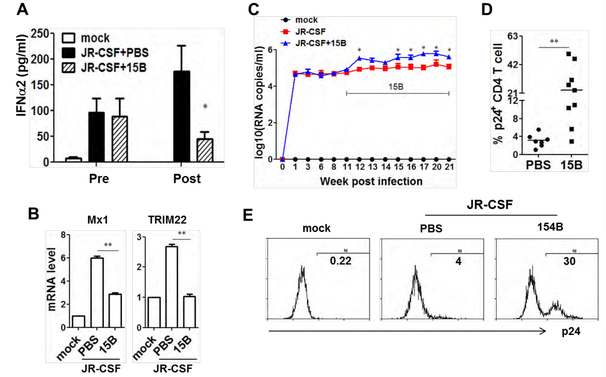
Pre-depletion of pDC increase HIV-1 replication. Humanized mice were infected with HIV-1 three days after pDC depletion and terminated at 8dpi (R3A, A and B) or three weeks (JR-CSF, C , D and E) post infection. (A) Plasma HIV-1 RNA levels at 8dpi. (B) Immunohistochemistry staining for p24 positive cells 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.



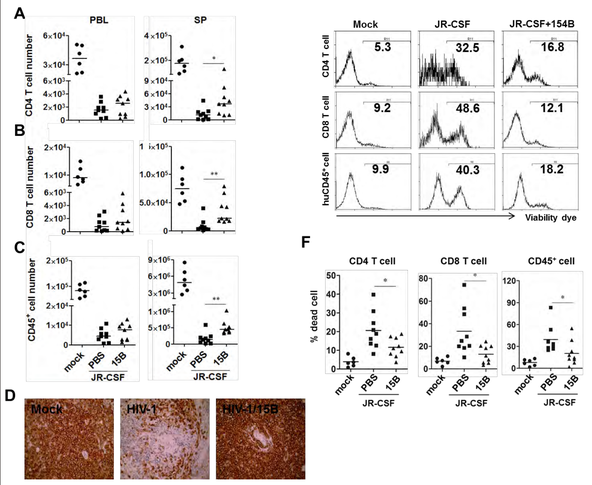
Pre-depletion of pDC reduced HIV-1 pathogenesis in acute infection. Humanized mice were infected with HIV-1 three days after pDC depletion and terminated at 8dpi. (A, B and C) Cell counts of human T cells or total leukocytes in peripheral blood and spleen. (A) CD4 T cell (CD3+CD8-) counts. (B) CD8 T cell (CD3+CD4-CD8+) counts. (C) huCD45+ leukocyte counts. (D and E) Representative histograms and summarized data show percentages of dead CD4 T cell, CD8 T cell and huCD45+ cell in spleen in R3A 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) The production of IFN-a2 in plasma from uninfected, JR-CSF+PBS and JR-CSF+15B at either 11wpi (pre) or 21wpi (post). (B) The mRNA levels of IFN-I and interferon stimulated genes in purified human cells (CD45+) from mouse spleen. (C) Plasma HIV-1 RNA levels. (D and E) Representative histograms and summarized data show percentages of HIV p24 protein positive CD4 T cell (CD3+CD8-) in spleen. Bars in dot graphs indicate median value. * and ** indicate p<0.05 and p<0.01, respectively.



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+CD8-) counts. (B) CD8 T cell (CD3+CD4-CD8+) counts. (C) huCD45+ leukocyte counts. (D) Immunohistochemistry staining for human CD45+ 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.

ACKNOWLEDGEMENTS

University of North Carolina at Chapel Hill
Su lab
Liqun Chi
Anthony Curtis

The University of Texas MD Anderson Cancer Center
Dr Yongjun Liu