Chronic Exposure to Type-I IFN under Lymphopenic Conditions Alters CD4 T Cell Homeostasis

Cecile Le Saou1, Rebecca B. Hasley1, Hiromi Imamichi1, Zonghui Hu2, Megan A.Luckey3, Junq-Hyun Park3, Adam Rupert4, Michael Sneller1, H. Clifford Lane1 and Marta Catalfamo1

1NIH/NIAID, Laboratory of Immunoregulation, Bethesda, MD, 2NIH/NIAID, Biostatistics Research Branch, Bethesda, MD, 3NCI/NIAID, Experimental Immunology Branch, Bethesda, MD, 4Leidos Biomedical Research, AIDS Monitoring Labs, Bethesda, MD

ABSTRACT

Background: HIV infection and the associated chronic immune activation alter T cell homeostasis leading to CD4 T cell depletion and CD8 T cell expansion. While the acute CD4 depletion observed in the initial phase of HIV infection is likely due to direct cytolytic effects of the virus, the mechanisms underlying the steady decline of the CD4 T cell pool during the chronic phase of infection are not totally understood. We hypothesized that the homeostatic response to HIV-induced CD4 T cell depletion occurs in an inflammatory environment rich in Type-I IFNs and driven by HIV replication and that combination of these two distinct forces lead to a form of immune T cell activation that results in a decline in the CD4 T cell pool and an increase in the CD8 T cells.

Methodology: We analyzed the in vitro effects of IL-7 and IFN-α to increase the total expression levels of the Signal Transducer and Activator of Transcription (1STATs) in CD4 and CD8 T cells from healthy controls (n=12). We also analyzed the relationships between CD4 T cell counts and total levels of STAT-1 (1STAT1) in HIV infected patients (n=53). To examine the combined effects of lymphopenia and IFN-α in vivo we developed an animal model in which lymphocytes were adoptively transferred into lymphopenic mice that were receiving chronically administered IFN-α.

Results: IL-7 in vitro upregulated the expression levels of 1STAT-1, -2, -3 and enhanced T cell responsiveness to IFN-α as measured by phosphorylation of STAT-1. In patients with HIV infection and suppressed viremia <50 copies/ml, levels 1STAT1 were inversely correlated with the degree of lymphopenia (R=-0.52, p<0.01 and R=-0.34, p<0.01) in CD4 and CD8 T cells respectively. In addition, a positive correlation between STAT-1 and IL-7 serum levels was observed in CD4 (R=0.38, p=0.01) but not in CD8 T cells. In a murine model, lymphopenia and chronic IFN-α exposure to diminished survival of CD4 T cells and an expansion of CD8 T cells, thus recapitulating the alterations of the homeostasis of these cells observed in patients with HIV infection.

Conclusions: IL-7 in vitro and lymphopenia in vivo can modulate T cell responsiveness to Type-I IFNs, suggesting a synergistic interaction of these cytokines. Therefore, the persistent stimulation of this pathway in the setting of a lymphopenic host, such as chronic untreated HIV infected patients could be deleterious for CD4 T cell homeostasis and may contribute to the aberrant immune activation and eventual depletion of the CD4 T cells. The analysis of these pathways may contribute to the development of new strategies to reverse the dysregulation of the T cell pools seen in patients with HIV infection.

RESULTS

Figure 2. In vitro culture with IL-7 increases IFN-α-induced STAT1 activation.

Figure 3. Levels of STAT1 in HIV-infected patients undergoing CART are associated with CD4 lymphopenia and IL-7 serum levels.

RESULTS

Figure 5. In vivo lymphopenia-induced upregulation in T cells is partially dependent on IL-7.

CONCLUSIONS

- Naive and Memory CD4 T cells and Naive CD8 T cells from viremic HIV-infected individuals expressed high level of 1STAT1 that decreased after treatment.
- In vitro culture with IL-7 and IFN-α induced high expression of 1STAT1 in Naive and Memory CD4 T cells and Naive CD8 T cells from healthy donors.
- T cells cultured with IL-7 became more responsive to IFN-α and showed increased phosphorylation of STAT1.
- In vivo exposure to lymphopenic conditions enhances 1STAT1 expression and IFN-α responsiveness in T cells.
- Continuous exposure to Type-I IFN under lymphopenic conditions led to enhanced CD4 donor T cell expansion, and decreased CD8 donor T cell counts in the spleen.

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