

CD8+ T-cell Interleukin-7 Receptor as a Novel Marker of Disease Status in HIV-infected Children

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Abstract

Background: There is a need for better immune markers to guide clinical decisions in managing HIV-infected children. Interleukin (IL)-7 is vital for differentiation and maintenance of memory CD8+ T cells, which in turn are critical for controlling HIV. We hypothesized that CD8+ T cell expression of IL-7 receptor (CD127) is lower in children with more advanced HIV disease. This has been suggested by preliminary findings in adults with HIV infection. Our aim was to determine if CD127 expression on CD8+ T cells could be used as a marker of HIV disease status and virologic control in infected children.

Methods: In a cross-sectional evaluation, we used flow cytometry to measure CD127 expression on CD8+ T cells of whole blood from HIV-infected children with varying immunologic CD4+ T cell frequencies and varying degrees of virologic control.

Results: 31 HIV-infected children were enrolled; 29 were on antiretroviral therapy. CD127 expression was highest in children with a CD4+ T cell frequency in the normal range ($\geq 25\%$, n=23): a median 59% (47-68, 25th-75th percentile) of CD8+ T cells expressed the marker. This contrasted with 28% (21-37) and 22% (1-45) expression when the CD4+ T cell frequency was 15-24% (n=5) and $<15\%$ (n=3), respectively ($p=0.002$). There was a striking correlation between CD8+ T cell CD127 expression and CD4+ T cell absolute counts ($r^2=0.63$, $p<0.001$). In children with good virologic control (HIV RNA $<10,000$ copies/mL, n=22) the median CD127 expression was 59% (44-69), compared with 29% (19-46) when virologic control was poor (HIV RNA $\geq 10,000$ copies/mL, n=9, $p=0.005$).

Conclusions: CD8+ T cell CD127 expression is significantly higher in children with immunologic and virologic control of their HIV disease, and appears to be a sensitive immunologic surrogate of disease status. To assess utility of this marker in guiding clinical patient management, we will now determine changes in CD127 expression longitudinally, in HIV-infected children.

Introduction

- Virus-specific CD8+ cytotoxic T lymphocytes (CTL) are essential for protective immunity against HIV infection
- IL-7 has been shown to enhance CD8+ T cell proliferation and cytolytic activity
- Expression of the IL-7 receptor alpha (characterized by the surface marker CD127) on the CD8+ T cell is a marker for long-lived memory cells
- CD127 may therefore be important in modulating the HIV immune response
- Decreased production of CD127 may correlate with poor HIV-specific immunity and poor memory T cell production
- Our aim is to determine if the percentage of CD127 expression on CD8+ T cells correlates with disease severity in HIV-infected children

Methods

- Cross-sectional evaluation
- HIV-infected children enrolled from University of Miami Special Immunology Clinic during routine clinic visit
- Inclusion criteria: any infected child from birth to 18 years of age
- Exclusion criteria: any child with acute illness or anemia (Stage II Common Toxicity Criteria, hemoglobin <10 g/dL)
- Informed consent obtained
- 2mL whole blood collected, red cells lysed with FACS lysing solution
- Lysed blood washed and stained the following morning
- Flow cytometry done to quantitate percentage of CD8+CD127+ T cells



Phlebotomy lab at University of Miami Special Immunology Clinic

Results

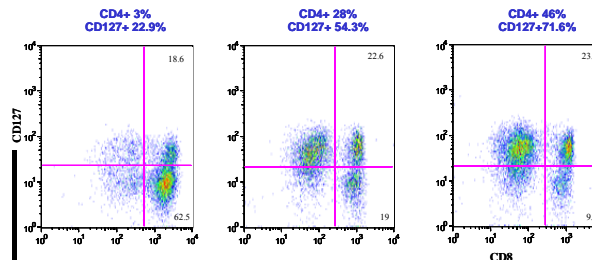
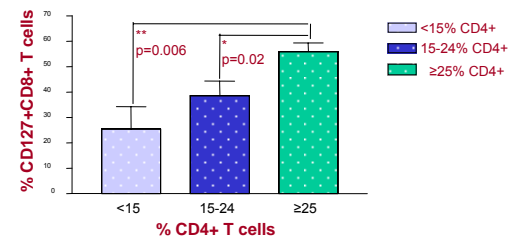


Figure 1: Flow cytometry data for 3 patients with varying CD4+ T cell frequencies. Percent expression of CD127+CD8+ T cells was calculated using the percentage of cells in the right upper quadrant (RUQ) over the total percentage of CD8+ T cells (RUQ + RLQ).

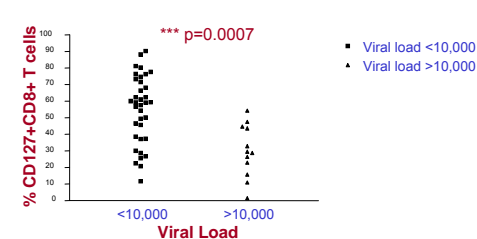
Description of Cohort

- 31 children with perinatally-acquired HIV infection were enrolled
- 14 males, 17 females
- Age range: 3.3 – 18 years
- CDC classification: 13%N, 26%A, 35%B, 26%C
- Immunologic classification: 35% category 1, 23% category 2, 42% category 3
- Median current CD4%: 31.5%
- 29 children receiving antiretroviral therapy, 2 children receiving no therapy

CD127+CD8+ T cell Expression Correlates with CD4 Frequency



CD127+CD8+ T cell Expression Correlates with Viral Load



Conclusions

- Improved immune function in patients who are virologically well-controlled on effective antiretroviral therapy is associated with increased IL-7 receptor (CD127) expression
- Restoration of CD127 expression with decreased HIV RNA levels implies that cytokine signaling may be improved in patients with adequate viral suppression
- CD127 may serve as an effective, novel immunologic surrogate to measure HIV disease progression and recovery.