Reduced Peripheral α4β7^{+} CD4^{+} T Cells Correlate with Mucosal CD4^{+} T Cell Loss in Acute HIV Infection (AHI)

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ABSTRACT

Intestinal CD4^{+}CCR5^{+} T cells are rapidly and profoundly depleted early during acute HIV infection (AHI) contributing to persistent systemic immune activation. The integrin homing receptor α4β7 is thought to play a major role in the propagation and dissemination of HIV-1. CD4^{+} T cells expressing high levels of α4β7 (α4β7^{hi}) are CD45RO^{+} and also express high levels of CCR5 and activation markers. Due to the difficulty monitoring intestinal CD4^{+} T cells we evaluated α4β7 as a predictive marker for the loss of intestinal CD4^{+}CCR5^{+} T cells during early AHI.

Thirty-three subjects underwent phlebotomy and sigmoid biopsy at the time of AHI diagnosis. AHI was grouped using the fourth generation (4thG) immunoassay (IA) staging, with all stages being HIV RNA+ (Stage I: 4thGIA^{-}/3rdGIA^{-}; II: 4thGIA^{+}/3rdG^{-}; III: 4thGIA^{+}/3rdGIA^{+}). Of the 33 subjects 14 were 4thGI and 19 4thGIII. Multiparameter flow-cytometry was performed to determine the frequency of mucosal CD4^{+}CCR5^{+} T cells and the frequency of peripheral β7^{high} CD4^{+} T cell subsets at the time of AHI diagnosis.

During 4thGI the frequency of mucosal CD4^{+}CCR5^{+} T cells and peripheral β7^{high} CD4^{+} T cells remained comparable to HIV-uninfected subjects, however with progression of 4thG stage a significant decrease in frequency was observed (Table 1). The frequency of peripheral β7^{high} CD4^{+} T cells correlated inversely with plasma (r=-0.52, p<0.001) and sigmoid (r=-0.36, p=0.03) HIV RNA and directly with the loss of mucosal CD4^{+}CCR5^{+} T cells (r=0.36, p=0.02). Additionally, we observed a loss of peripheral central memory (CM; CD27^{+}CD45RO^{+}) CD4^{+} T cells expressing CCR5 and β7^{high} during progression of AHI (Table 1). The frequency of CCR5^{+} β7^{high} CM CD4^{+} T cells showed a strong direct correlation with the loss of mucosal CD4^{+}CCR5^{+} T cells (r=0.35, p=0.02) and correlated inversely with plasma HIV RNA (r=-0.31, p=0.04).

The loss of peripheral β7^{high} CD4^{+} and CCR5^{+} β7^{high} CM CD4+ T cell subsets closely paralleled the loss of mucosal CD4^{+}CCR5^{+} T cells during early AHI. This is consistent with the hypothesis that α4β7 has a role in the selective depletion of mucosal CD4^{+} T cells, and indicates that monitoring β7^{high} expression on peripheral blood CD4^{+} T cells could be a useful surrogate marker to estimate mucosal CD4^{+} CCR5^{+} T cell loss.

BACKGROUND

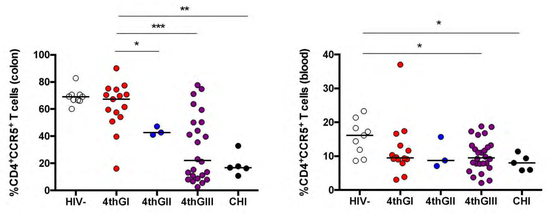
- During acute HIV infection mucosal CD4^{+}CCR5^{+} T cells are rapidly depleted contributing to the disruption of the mucosal barrier and subsequently to the persistent systemic immune activation
- α4β7 Integrin is induced on T cells after priming by mucosa-derived DC
- α4β7 Integrin mediates T cell trafficking via receptor interactions on mucosal endothelial cells that include the addressin MAdCAM
- α4β7 Integrin can serve as a receptor and signaling molecule for HIV/SIV and thus enhance virus infection, cell-cell spread and trafficking of virus infected cells from the periphery and lymphoid organs to mucosal sites
- α4β7^{+} CD4^{+} T cells appear to be preferentially depleted during HIV/SIV infection
- Administration of anti-α4β7 monoclonal antibody reduces plasma and tissue VL in the SIV model

HYPOTHESIS

We hypothesis, that α4β7 expressed on peripheral CD4^{+} T cells could serve as a predictive marker for the loss of mucosal CD4^{+}CCR5^{+} T cells during early AHI.

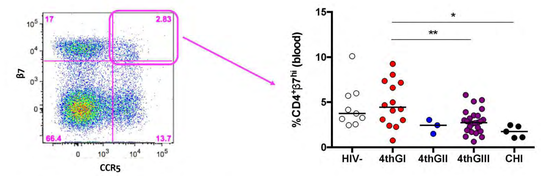
RESULTS

Significant Decrease in the Frequency of Mucosal CD4^{+}CCR5^{+} T Cells with the Progression of AHI (4thGI to 4thGIII)



1

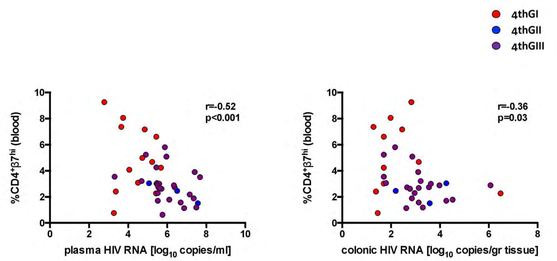
Significant Decrease in the Frequency of peripheral CD4^{+}β7^{hi} T Cells with the Progression of AHI (4thGI to 4thGIII)



Gating of CCR5^{+}β7^{high} expressing CD4 T cells
(Wang et al. showed that the majority of cells expressing β7 also express α4)

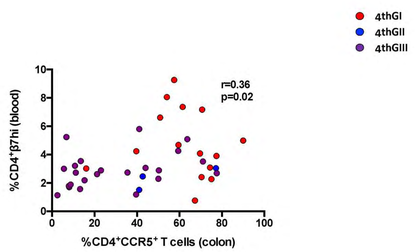
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Frequency of peripheral CD4^{+}β7^{hi} T Cells Correlates Inversely with the Plasma and Colonic HIV RNA during AHI



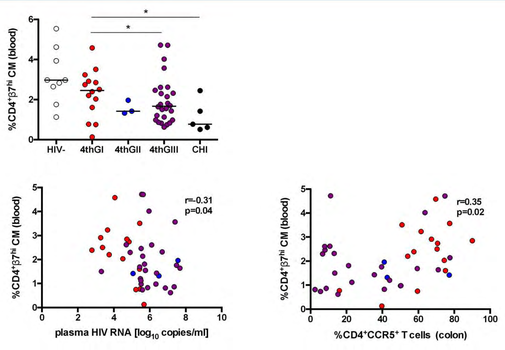
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Frequency of peripheral CD4^{+}β7^{hi} T Cells Correlates Directly with the Frequency of Mucosal CD4^{+}CCR5^{+} T Cells



4

Decrease of peripheral CD4^{+}β7^{hi} T Cells Mainly Occurs in the Central Memory (CM) Subset, also Correlating with the Loss of Mucosal CD4^{+}CCR5^{+} T cells



5

QUESTION

Does the expression of α4β7 on peripheral CD4^{+} T cells predict the loss of mucosal CD4^{+}CCR5^{+} T cells during early AHI?

CONCLUSION

- There is a significant loss of mucosal CD4^{+}CCR5^{+} T cells observed during AHI from 4thGI to 4thGIII
- The loss of mucosal CD4^{+}CCR5^{+} T cells closely parallels the loss of CD4^{+}β7^{hi} as well as CD4^{+}β7^{hi} CM T cells
- **Those results indicate that monitoring the expression of α4β7 on peripheral CD4^{+} T cells could be a useful surrogate marker to estimate CD4^{+}CCR5^{+} T cell loss in the mucosa**

The views expressed are those of the authors and should not be construed to represent the positions of the U.S. Army or the Department of Defense.