Effects of Aging on HIV-1 Pathogenesis

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Abstract
Background: Human Immunodeficiency Virus (HIV-1) is associated with loss of CD4+ T cells from the peripheral blood, over the course of infection. Gut associated lymphoid tissue (GALT) harbors the majority of CD4+ T lymphocytes in the body and is an important target for HIV. Severe depletion of intestinal CD4+ T cells occurs during primary HIV-1 infection and persists through the course of infection in the absence of antiretroviral therapy. Inflammation and immune activation continue to be up regulated during Highly Active Anti-Retroviral Therapy (HAART) and are associated with lower levels of CD4+ T cell restoration. Studies suggest that younger HIV-1 infected patients have immune systems similar to uninfected older individuals, characterized by a loss of regenerative capacity and an accumulation of aging T cells.

However, the effects of aging itself on HIV-1 pathogenesis are poorly understood. A growing proportion of HIV-1 infected individuals are now over 50 yrs old. In a chronic inflammatory setting, such as HIV infection, the pathogenic effects of HIV may be exacerbated by the altered hormonal levels during menopause.

Methods: Patient groups were analyzed in context of age (men) and hormonal status (women). We evaluated mucosal T lymphocyte subsets and activation using flow cytometry and immunohistochemistry. Gene expression profiles and viral loads in adult HIV-1 positive patients of all age groups were analyzed using DNA microarray technology and real-time PCR.

Results: Immune activation was up regulated during HIV-1 infection and is associated with lower levels of CD4+ T cell restoration in all patient groups during HAART. Alter T cell subsets including central memory T cells and effector memory T cells were observed in post menopausal women. Increased levels of T cell activation were observed in post menopausal women and age matched men in both HIV positive and HIV-1 negative groups. Higher expression of pro-inflammatory factors was observed in CD4+ T cells from older negative controls. Similar results were observed in both HIV-1 positive men and women in the older age group prior to and following the use of HAART.

Conclusions: Aging results in increased levels of inflammation as well as T cell activation in HIV-1 negative controls and these effects are exacerbated in the presence of HIV infection. The results of this pilot study will be extremely valuable in management of HIV disease worldwide.

Study Subjects

HIV Status Age Group Age Range (in yrs) n # of Subjects PBMC CD4+ T cell % of CD3 Gated CD4+ T cells

HIV Negative Male < 45yrs 23-49 5 471-740 1.19E+04
HIV Negative Male > 45 yrs 45-57 3 380-1271 N/A
HIV Negative Female Pre Menopausal 23-43 5 584-1507 N/A
HIV Negative Female Post Menopausal 50-57 3 1.00E+04

Increased T Cell Activation In Chronic HIV Infection

High levels of T cell activation is the hallmark of HIV infection. T cell activation is analyzed using the surface markers CD38 and HLA-DR which are expressed on activated T cells. Significantly higher levels of CD4+ T cell activation are observed in older men with HIV infection.

Long term HAART can Lead to CD4+ T cell Restoration in GALT of HIV Infected Patients

Long-term therapy could reduce, but not fully suppress, HIV RNA levels in the gut mucosa, though higher levels of T cell activation in peripheral blood as well as in GALT persisted. Compared to men, women have higher levels of CD4+ T cell restoration in peripheral blood as well as in GALT.

Image 1: Long-term therapy could reduce, but not fully suppress, HIV RNA levels in the gut mucosa, though higher levels of T cell activation in peripheral blood as well as in GALT persisted. Compared to men, women have higher levels of CD4+ T cell restoration in peripheral blood as well as in GALT.

Conclusions
HIV infection results in CD4+ T cell depletion in GALT
Progression is associated with T cell activation and tissue inflammation
Partial cell restoration occurs with HAART
A threshold of CD4+ T cell restoration correlates with:
    Reduced immune activation in GALT
    Reduced inflammation in GALT
    Suppression of viral replication

Persistence of the immune activation despite the viral suppression
Aging is associated with higher levels of T cell activation in women
Effects of menopause on inflammation and immune activation plays an important role in HIV pathogenesis.

Acknowledgements
We thank UCIGM GI and J. St Clinic staff, CARES... California HIV AIDS Research Program CHS-0-696, Dr Jerome Breen for statistical advice, patients for their participation and Hickle Santos and Lylel Clancy for assistance with patients... Study support was provided by the National Institute of Health (ROI HD024297 and California HIV AIDS research program CHS-0-696). We also thank the Lucy Whittier Molecular Core and the School of Medicine Microscopy Core for technical support.