

### **Mechanisms of CD4+ T-cell depletion in HIV disease**

J. M. McCune. Gladstone Institute of Virology and Immunology, San Francisco General Hospital; Departments of Medicine and of Microbiology and Immunology, University of California at San Francisco.

Antigenic stimulation of T-cells gives rise to short-lived effector cells and long-lived memory cells. To characterize the effect of infection with the human immunodeficiency virus, type I (HIV) on kinetically-distinct subpopulations of T-cells, we followed long-term stable isotope label incorporation and label decay in DNA of human T-cells *in vivo* (Hellerstein et al., 2002). Utilizing a recently-developed, deuterated-water labeling technique, label incorporation during long-term oral  $^2\text{H}_2\text{O}$  administration exhibited two phases: a rapid early incorporation through weeks 3-5 followed by a slower labeling phase through week 9. This biphasic pattern was observed for total and m/e- but not naive-phenotype T-cells. After 9 weeks of labeling, 50-60% of m/e-phenotype CD4+ and CD8+ T-cells had divided in untreated HIV infection compared to only 10-15% in seronegative controls, with intermediate values in antiretroviral (ARV)-treated subjects. The replacement rate of naive-phenotype T-cells was also elevated in untreated HIV-infected subjects. To confirm variable kinetic fates of newly-divided T-cells, pulse labeling of T-cell DNA with  $^2\text{H}$ -glucose was performed (Hellerstein et al., 1999; McCune et al., 2000). Biphasic die-away kinetics, with a rapid turnover and a label-retaining subpopulation, were observed for total and m/e- but not naive-, phenotype CD4+ and CD8+ T-cells. A lower proportion of newly-divided CD4+ and CD8+ T-cells remained after 3 weeks in untreated HIV-infected subjects (46% and 52%, respectively) than in healthy controls (67% and 80%). Effective long-term ARV therapy restored these values to normal.

We conclude that kinetically-distinct subpopulations exist within T-cell pools in humans and that the production of short-lived m/e-phenotype T-cells is well maintained in HIV/AIDS, but that the capacity to produce long-lived (i.e., naive and true memory) CD4+ T-cells and to keep such cells quiescent over time is deficient in HIV/AIDS and restored by ARV therapy. These data are consistent with the hypothesis that CD4+ T-cell depletion in HIV disease is associated with both accelerated destruction of mature effector cells and the inability to regenerate these cells from pools of long-lived naive and memory T cells (McCune, 2001).

1. Hellerstein MK, Hoh RA, Hanley MB, Cesar D, Lee D, Neese RA, McCune JM. Subpopulations of long-lived and short-lived T-cells in humans: effects of infection with the human immunodeficiency virus, type 1. submitted, 2002.
2. Hellerstein M, Hanley MB, Cesar D, Papageorgopoulos C, Wieder E, Schmidt D, Siler S, Hoh R, Neese R, Macallan D, Deeks S, McCune JM. Directly measured kinetics of circulating T lymphocytes in normal and HIV-1-infected humans. *Nature Med*, 5:83-89, 1999.
3. McCune JM, Hanley MB, Cesar D, Halvorsen R, Hoh R, Schmidt D, Wieder E, Deeks S, Siler S, Neese R, Hellerstein M. Factors influencing T-cell turnover in HIV-1-seropositive patients, *J Clin Invest*, 105: R1-R9, 2000.
4. McCune JM. The dynamics of CD4+ T-cell depletion in HIV disease. *Nature* 410:974-979, 2001.