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 $^2$H$_2$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 naïve-phenotype T-cells was also elevated in untreated HIV-infected subjects. To confirm variable kinetic rates of newly-divided T-cells, pulse labeling of T-cell DNA with $^3$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., naïve 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 naïve and memory T cells (McCune, 2001).