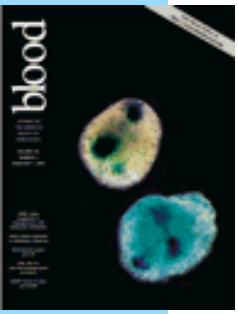

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Skewed representation of functionally distinct populations of virus-specific CD4 T cells in HIV-1 infected subjects with progressive disease: changes after antiretroviral therapy

Alexandre Harari, Stéphanie Petitpierre, Florence Vallelian, and Giuseppe Pantaleo

Laboratory of AIDS Immunopathogenesis, Division of Immunology and Allergy, Department of Medicine, Centre Hospitalier Universitaire Vaudois, University of Lausanne, Switzerland

ABSTRACT

HIV-1- and cytomegalovirus (CMV)-specific CD4 T-cell-mediated antiviral immunity was evaluated by assessing the frequency of interleukin 2 (IL-2)- and interferon γ (IFN-γ)-secreting cells following antigen-specific stimulation in blood and lymph node. HIV-1-infected subjects with progressive disease at early stage of infection with no previous history of antiretroviral therapy (ART), subjects with nonprogressive disease, and HIV-negative subjects were studied. On the basis of the ability to secrete IL-2 and IFN-γ, 3 functionally distinct populations of CD4 T cells were identified: (1) IL-2-secreting cells; (2) IL-2/IFN-γ-secreting cells; and (3) IFN-γ-secreting cells. CMV-specific CD4 T cells were almost equally distributed within the 3 functionally distinct cell populations in the 3 study groups as well as HIV-1-specific CD4 T cells in subjects with nonprogressive disease. However, a skewing toward IFN-γ-secreting cells (70% of HIV-1-specific CD4 T cells) was observed in subjects with progressive disease, and IL-2- and IL-2/IFN-γ-secreting cells were almost absent. The frequencies of IL-2- and of IL-2/IFN-γ-secreting HIV-1-specific CD4 T cells were negatively correlated with the levels of viremia. Interestingly, prolonged ART was able to correct the skewed representation of different populations of HIV-1-specific CD4 T cells but was associated with only a partial recovery of IL-2-secreting cells. These results indicate that the composition of the pool of functionally distinct virus-specific CD4 T cells is important for virus control.

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Phenotypic heterogeneity of antigen-specific CD4 T cells under different conditions of antigen persistence and antigen load

Alexandre Harari, Florence Vallelian, and Giuseppe Pantaleo

Laboratory of AIDS Immunopathogenesis, Division of Immunology and Allergy, Department of Medicine, Centre Hospitalier Universitaire Vaudois, University of Lausanne, Switzerland

ABSTRACT

The factors responsible for the phenotypic heterogeneity of memory CD4 T cells are unclear. In the present study, we have identified a third population of memory CD4 T cells characterized as CD45RA(+)CCR7(-) that, based on its replication history and the homeostatic proliferative capacity, was at an advanced stage of differentiation. Three different phenotypic patterns of memory CD4 T cell responses were delineated under different conditions of antigen (Ag) persistence and load using CD45RA and CCR7 as markers of memory T cells. Mono-phenotypic CD45RA(-)CCR7(+) or CD45RA(-)CCR7(-) CD4 T cell responses were associated with conditions of Ag clearance (tetanus toxoid-specific CD4 T cell response) or Ag persistence and high load (chronic HIV-1 and primary CMV infections), respectively. Multi-phenotypic CD45RA(-)CCR7(+), CD45RA(-)CCR7(-) and CD45RA(+)CCR7(-) CD4 T cell responses were associated with protracted Ag exposure and low load (chronic CMV, EBV and HSV infections and HIV-1 infection in long-term nonprogressors). The mono-phenotypic CD45RA(-)CCR7(+) response was typical of central memory (T(CM)) IL-2-secreting CD4 T cells, the mono-phenotypic CD45RA(-)CCR7(-) response of effector memory (T(EM)) IFN-gamma-secreting CD4 T cells and the multi-phenotypic response of both IL-2- and IFN-gamma-secreting cells. The present results indicate that the heterogeneity of different Ag-specific CD4 T cell responses is regulated by Ag exposure and Ag load.