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

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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.

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

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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.