Heterogeneity in the Recovery of Polyfunctional HIV-1-Specific CD8 but not CD4 T-Cell Responses Following ART

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ABSTRACT

Background: High levels of HIV replication are characterized by the lack of IL-2 secreting and proliferating HIV-1-specific CD4 and CD8 T cells and by the dominance of IFN-γ T cell responses. Little is known regarding the recovery of these responses following ART-mediated control of HIV replication.

Methods: Functional characterization (secretion of IFN-γ and IL-2 and proliferation) of HIV-1-specific CD4 and CD8 T cells was performed in peripheral blood of 99 subjects following 1 year of ART using 464 peptides (15-mers overlapping by 11 amino acids) encompassing gag, pol, nef and env. Four peptide pools were used separately, i.e. GAG, POL, Nef and EnV, for the assessment of both, the cytokine secretion and the proliferation. Furthermore, HIV-1-specific proliferative responses were evaluated using the CFSE dilution assay.

RESULTS

Using pools of overlapping peptides, we have confirmed that HIV-1-specific CD4 T-cell responses were consistently polyfunctional after suppression of HIV-1 replication by ART (Fig. 2) while in contrast, two distinct patterns of HIV-1-specific CD8 T-cell responses were observed. One group (named "IL-2 group", n=32) had HIV-1-specific IL-2 secreting CD8 T cell responses while the other group (named "No IL-2 group", n=67) did not (Fig. 3).

CONCLUSIONS

In conclusion, in contrast to HIV-1-specific CD4 T-cell responses, polyfunctional CD8 T-cell responses are not homogeneously recovered after ART. The recovery of polyfunctional HIV-1-specific CD8 T cell responses was associated with a more rapid control of virus replication and a greater increase in CD4 T cells. Therefore, polyfunctional CD8 rather than CD4 T cell responses are better immune correlates of protective antiviral immunity.

METHODS AND STUDY DESIGN

Functional characterization (secretion of IFN-γ and IL-2 and proliferation) of HIV-1-specific CD4 and CD8 T cells was performed in peripheral blood of 99 subjects following 1 year of ART using 464 peptides (15-mers overlapping by 11 amino acids) encompassing gag, pol, nef and env. Four peptide pools were used separately, i.e. GAG, POL, Nef and EnV, for the assessment of both, the cytokine secretion and the proliferation. Furthermore, HIV-1-specific proliferative responses were evaluated using the CFSE dilution assay.

Figure 1

Figure 2

Figure 3

Figure 4

Figure 5

Therefore, the goal of this study was to determine whether polyfunctional CD8 T-cell responses are found after suppression of HIV-1 replication by ART, as it is the case for CD4 T cells.

Furthermore, we have also recently shown that HIV-1-specific CD8 T cells in untreated progressors are mostly composed of single IFN-γ secreting cells while HIV-1-(gag) protein-specific CD4 T cells are polyfunctional (presence of IL-2 and IFN-γ secreting cells) in nonprogressive infection (long-term nonprogressors). In addition, HIV-1-specific proliferating CD4 T cells were detected in progressive but not in progressive HIV-1 infection.

Therefore, the goal of this study was to determine whether polyfunctional CD8 T-cell responses are found after suppression of HIV-1 replication by ART, as it is the case for CD4 T cells.

Furthermore, the analysis of 49 HLA-matched most frequently recognized gag peptides (from Los Alamos database, see Fig. 4) revealed that the "IL-2 group" response was broader (0.3 vs 1.7 gag epitope/patient, P<0.02, Fig. 4).