Non-classical Regulatory HIV-1-specific CD8 T Cells in HIV-1 Disease Progression

Viganò S[1], Li C[1], Negrón J[1], Pereyra F[1], Lichterfeld M[1,2], Yu X[1].
[1]Ragon Institute of MGH, MIT and Harvard, Boston, MA; [2]Infectious Disease Division, Massachusetts General Hospital, Boston, MA

Background

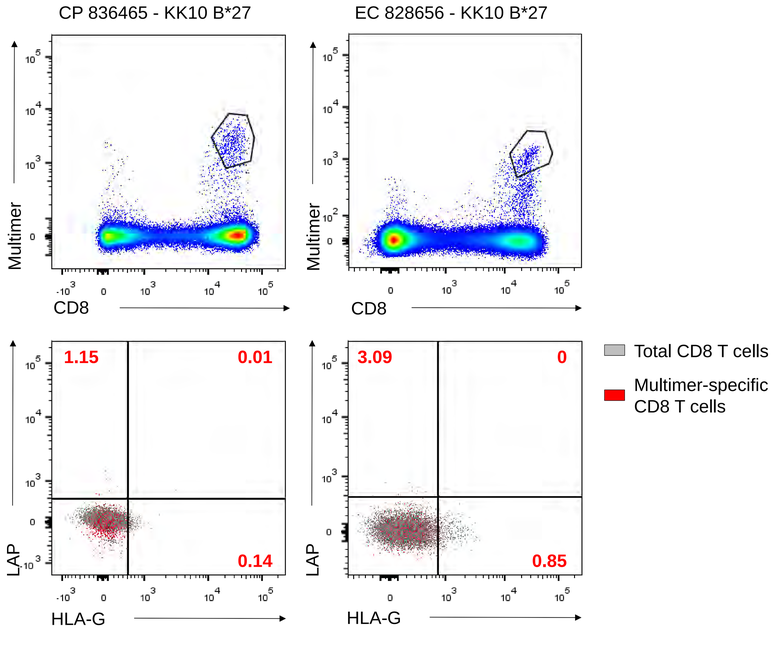
Regulatory T cells may influence HIV-1 disease progression by suppressing immune activation or inhibiting antiviral T cell immune responses. Recent data suggest that the proportion of non-classical regulatory CD4 and CD8 T cells expressing HLA-G was inversely correlated with markers of HIV-1-associated immune activation, as opposed to non-classical regulatory T cells expressing the TGF-β latency-associated peptide (LAP). The role of non-classical regulatory T cell specific for HIV-1 is unknown.

Hypothesis: HLA-G$^+$ HIV-1-specific CD8 T cells are associated with slow disease progression

Methods

31 HIV-1-specific and 19 CMV/EBV-specific CD8 T cell responses were analyzed in 31 HIV-1 infected patients. 17 patients were chronic progressors with a median HIV viral load of 50300 copies/ml and a median CD4 T cell count of 456/ul. The remaining 14 patients were elite controllers with viremia below 1000 copies/ml and CD4 T cell counts above 900/ul. Expression of HLA-G and LAP on HIV-1-specific CD8 T cells was assessed by multimer staining and flow cytometry.

Representative examples:



Results

50 HIV-1, CMV- and EBV-specific CD8 T cell responses were analyzed in 31 HIV-1 infected patients. The frequency of HLA-G$^+$ HIV-1-specific (P=0.015) but not CMV- or EBV-specific (P=n.s) CD8 T cells was increased in elite controllers when compared to chronic progressors (Figure 1A). This increment was mostly driven by CD8 T cells restricted by protective HLA class I alleles (HLA-B27 and HLA-B57). No difference between elite controllers and chronic progressors was observed when CD8 T cells restricted by non-protective alleles (HLA-A02 and HLA-B08) were analyzed (Figure 1B).

Figure 1

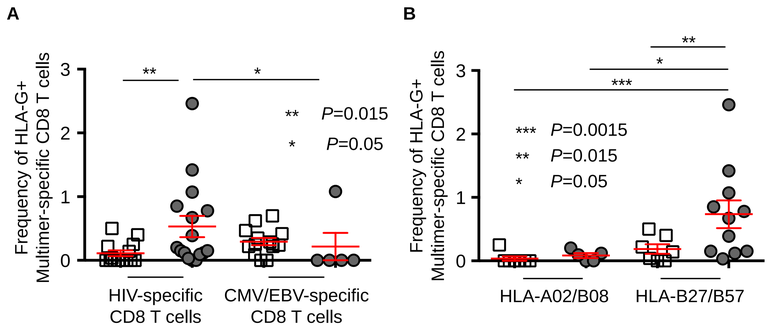


Figure 1. (A) Frequency of HLA-G$^+$ virus-specific CD8 T cells in elite controller (●) and in chronic progressive (□) HIV-1 infected patients. **(B)** Frequency of HLA-G$^+$ HIV-1-specific CD8 T cells restricted to protective or non-protective HLA-class I alleles in elite controller (●) and in chronic progressive (□) HIV-1 infected patients.

The proportion of HLA-G$^+$ HIV-1-specific CD8 T cells was directly associated with CD4 T cell counts (P=0.0083, r=0.48) but not with viral loads (Figure 2).

Figure 2

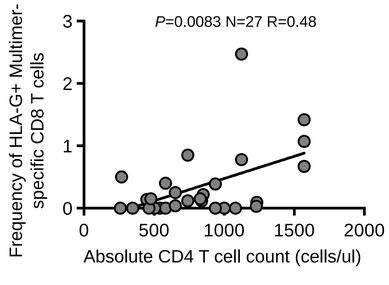


Figure 3. Association between the proportion of HLA-G$^+$ HIV-1-specific CD8 T cells and CD4 T cell count.

In contrast, LAP$^+$ HIV-1-specific CD8 T cells were reduced in frequency in elite controllers in comparison to chronic progressors (Figure 3A). This difference was mostly driven by CD8 T cells restricted by non-protective HLA class I alleles (HLA-A02 and HLA-B08). No difference between elite controllers and chronic progressors was observed when CD8 T cells restricted by non-protective alleles (HLA-B27 and HLA-B57) were analyzed (Figure 3B).

Figure 3

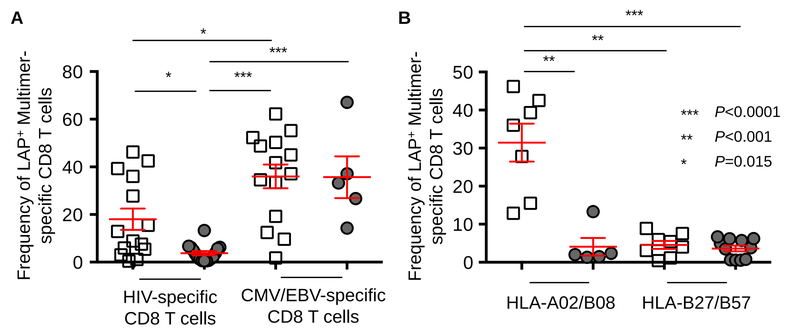


Figure 3. (A) Frequency of LAP$^+$ virus-specific CD8 T cells in elite controller (●) and in chronic progressive (□) HIV-1 infected patients. **(B)** Frequency of LAP$^+$ HIV-1-specific CD8 T cells restricted to protective or non-protective HLA-class I alleles in elite controller (●) and in chronic progressive (□) HIV-1 infected patients.

The frequency of LAP$^+$ HIV-1-specific CD8 T cells was directly associated with viral loads (P=0.0006, r=0.61) and inversely associated with CD4 T cell counts (P=0.024, r=0.4) (Figure 4B).

Figure 4

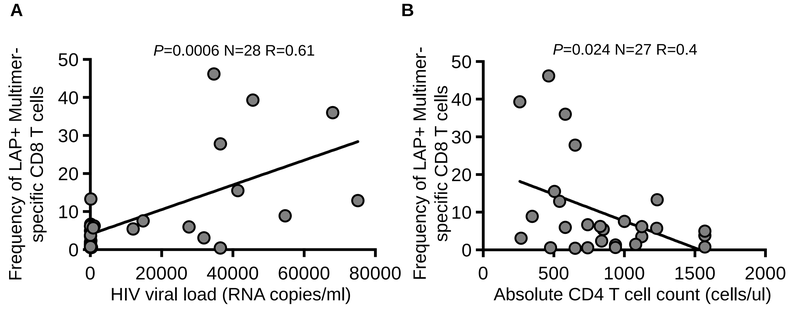


Figure 4. Association between the proportion of LAP$^+$ HIV-1-specific CD8 T cells and **(A)** HIV-1 viral load or **(B)** CD4 T cell count

Conclusions

These data indicate a potentially protective role of HIV-1-specific HLA-G$^+$ regulatory CD8 T cells on HIV-1 disease progression. Further investigation of functional properties of these non-classical regulatory CD8 T cells is necessary in order to better elucidate their role in HIV-1 immune-pathogenesis.

Ragon Institute of MGH, MIT and Harvard

MGH 1811

amfAR MAKING AIDS HISTORY