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:

![Multimer staining example](image1)

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>0.05) 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

![Frequency of HLA-G* virus-specific CD8 T cells in elite controller and in chronic progressive](image2)

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

![Association between the proportion of HLA-G* HIV-1-specific CD8 T cells and CD4 T cell count](image3)

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

![Association between the proportion of LAP* HIV-1-specific CD8 T cells and (A) HIV-1 viral load or (B) CD4 T cell count](image4)

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.