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Non-classical regulatory HIV-1-specific CD8 T cells in HIV-1 disease progression

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Background

Regulatory T cells may influence HIV-1 disease progression by suppressing immune activation or inhibiting antiviral T cell immune responses. Recently, a distinct population of non-classical regulatory T cells expressing HLA-G was identified. However, the role of HLA-G-expressing T cells specific for HIV-1 is unknown.

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

Methods

36 HIV-1-specific and 25 CMV/EBV-specific CD8 T cell responses were analyzed in 47 HIV-1 infected patients. 27 patients were chronic progressors with median HIV-1 viral loads of 50,300 copies/ml and median CD4 T cell counts of 456 cells/ul. 20 patients were controllers with viremia below 1000 copies/ml and CD4 T cell counts above 600 cells/ul. HLA-G expression on HIV-1 specific CD8 T cells was assessed by multimer staining and flow cytometry. Cytokine production of sorted HLA-G$^+$ and non-regulatory CD8 T cells was assessed in 12 HIV-1 negative individuals following CD3/CD28 stimulation by Luminex.

Results

61 HIV-1, CMV- and EBV-specific CD8 T cell responses were analyzed in 47 HIV-1 infected patients. The frequency of HLA-G$^+$ HIV-1 specific (P=0.0002), 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), while 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

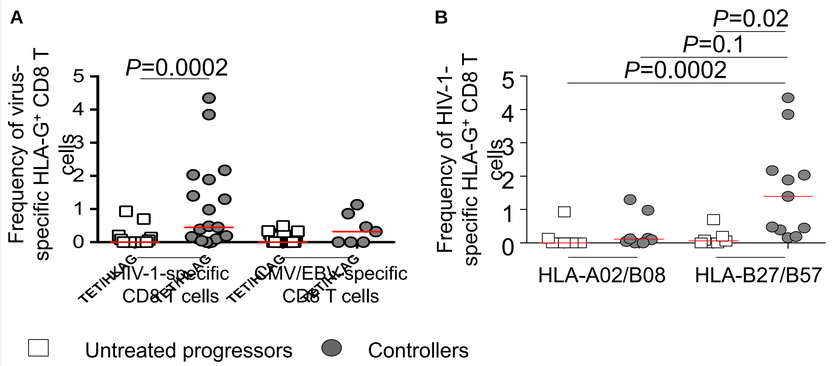


Figure 1. (A) Frequency of HLA-G$^+$ virus-specific CD8 T cells in elite controllers and in chronic progressive HIV-1 infected patients. **(B)** Frequency of HLA-G$^+$ HIV-1-specific CD8 T cells restricted to protective or non-protective HLA-class I alleles in elite controllers and in chronic progressive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

The proportion of HLA-G$^+$ HIV-1-specific CD8 T cells was directly associated with CD4 T cell counts (P=0.0002, r=0.57) and inversely with viral loads (P<0.0001, r=-0.66), while total HIV-1-specific CD8 T cells were not (Figure 2 and data not shown).

Figure 2

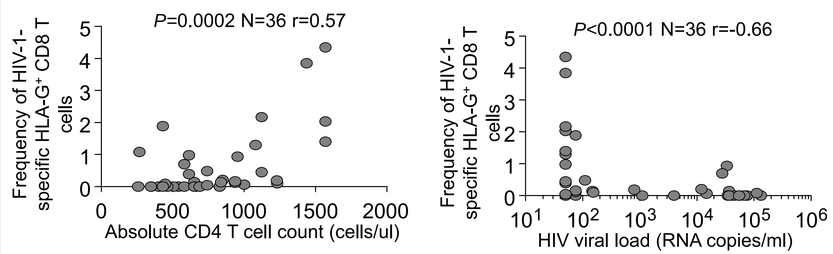


Figure 2. Association between the proportion of HLA-G$^+$ HIV-1-specific CD8 T cells and CD4 T cell count or viral load.

Of interest, HLA-G$^+$ CD8 T cells produced higher amount of IL-10, IL-2, MIP-1α, MIP-1β and RANTES than HLA-G-negative CD8 T cells after anti-CD3/anti-CD28 stimulation (Figure 3).

Figure 3

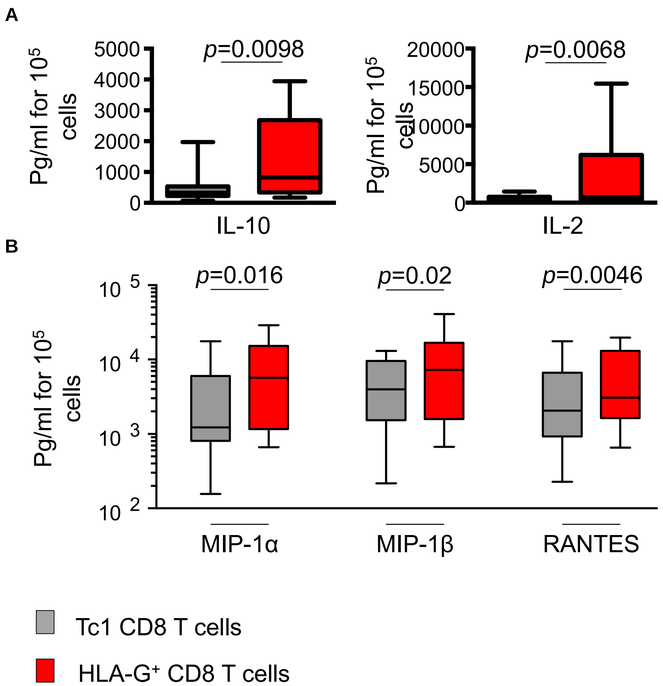


Figure 3. Luminex quantification (Pg/ml for 10^5 cells) of **(A)** IL-10, IL-2 and **(B)** MIP-1α, MIP-1β and RANTES produced by HLA-G$^+$ CD8 T cells after anti-CD3/anti-CD28 stimulation.

Conclusions

These data indicate a potentially protective role of HIV-1-specific HLA-G+ regulatory CD8 T cells on HIV-1 disease progression. The production of MIP-1 α, MIP-1 β and RANTES may be pivotal in controlling HIV-1 replication. Further investigations of functional properties of these non-classical regulatory CD8 T cells are necessary in order to better elucidate their role in HIV immunopathogenesis.