P16-08. Combined blockade of the PD-1 and IL-10 pathways synergistically enhance HIV-specific CD4 T cell functions

Retrovirology

Poster presentation

P16-08. Combined blockade of the PD-1 and IL-10 pathways synergistically enhance HIV-specific CD4 T cell functions

F Porichis*[1], DS Kwon[1], DP Tighe[1], DF Pavlik[1], DG Kavanagh[1], GJ Freeman[2], BD Walker[1] and DE Kaufmann[1]

Address: [1]Ragon Institue of MGH, MIT and Harvard Medical School, Boston, MA, USA and [2]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

* Corresponding author

from AIDS Vaccine 2009
Paris, France. 19–22 October 2009

Published: 22 October 2009

Retrovirology 2009, **6**(Suppl 3):P237 doi:10.1186/1742-4690-6-S3-P237

This abstract is available from: http://www.retrovirology.com/content/6/S3/P237

Background

HIV-specific T cell dysfunction is a prominent feature of HIV infection. We have reported that the PD-1 and IL-10 pathways mediate a reversible impairment of HIV-specific proliferative T cell responses. However, the responses are frequently modest and not all infected subjects respond to blockade of either pathway. It is therefore crucial to determine whether combined PD-L1 and IL-10Rα blockade can overcome these limitations and synergistically revive HIV-specific T cell responses.

Methods

We investigated 17 persons with HIV infection that were divided into groups according to treatment status. We used Luminex arrays to measure IFN-γ and IL-2 secretion in supernatants of CD8-depleted PBMC stimulated for 48 h with a Gag peptide pool or left unstimulated in the presence of isotype control antibody, anti-PD-L1, anti-IL-10Rα or combined blockade.

Results

In viremic individuals (n = 10), blockade of a single or two inhibitory pathways resulted in a significant increase in IFNγ secretion by HIV-specific CD4 T cells when compared to the isotype control condition ($p < 0.0001$, Friedman test with Dunn's post-test). The median fold-increase in IFN-γ secretion was 1.8 for PD-L1, 5.1 for IL-10Rα and 13.4 for combined blockade. In subjects with higher viral loads, combined PD-L1/IL-10Rα blockade resulted in an occasionally dramatic synergistic effect, even when a limited increase was seen with PD-L1 blockade alone. We also observed a non-significant trend toward increased IL-2 secretion upon inhibitory blockade. In contrast, in aviremic subjects, IL-10Rα blockade was not more effective than PD-L1 blockade, and additive effects of combined blockade were inconstant.

Conclusion

These data indicate that combined blockade of the PD-1 and IL-10 pathways synergize to restore effector functions of HIV specific CD4 T cells and demonstrate the potential of targeting multiple inhibitory pathways to reverse T cell exhaustion in humans. These results may have significant implications for development of novel immunotherapeutic interventions.