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S04-04 OA. HIV-specific responses induced by anti-CD40 targeting antibodies

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Background

Antibodies directed against antigen-presenting cell (APC) receptors can deliver antigens very efficiently. This receptor-targeting vaccine system facilitates the uptake, processing and presentation of extracellular antigens. In our approach, an antibody against human CD40 was fused to HIV antigens and these prototype vaccines were tested for their capacity to stimulate the expansion of HIV-specific memory T cells.

Methods

Recombinant anti-CD40 antibodies fused to HIV Gag and/or Nef proteins were tested for their capacity to bind to DCs and to stimulate expansion of HIV-specific T cells. PBMC and dendritic cells (DC) from HIV-infected patients were incubated with Gag-targeting molecules followed by anti-Gag PE secondary antibody. Binding on in CD19+, CD14+ and CD11c+ cells was measured by flow cytometry. Short-term PBMC cultures (10 days) stimulated with DC-targeting vaccines in the presence of IL-2 were re-stimulated with overlapping peptides covering the total sequences of Gag and Nef, followed by multiplex cytokine (Luminex) analysis of supernatants and intracellular staining.

Results

The anti-CD40-HIV-Gag/Nef antibodies bind to B cells, monocytes and DC with a affinity similar to the parental anti-CD40 antibody. The HIV antigen-targeting vaccines displayed a high stimulation capacity *in vitro* compared with isotype control (IgG4) fusion proteins, inducing CD4+ and CD8+ T cell responses against Gag and Nef peptides even at very low concentrations (0.01 nM). Moreover, we observed not only antigen-specific secretion of the Th1/CTL set of cytokines but also of cytokines characteristic of Th2 and IL-21 subsets. The breadth and the quality of the T cell responses observed in PBMC cultures matched responses those observed in DC-T cell co-cultures.

Conclusion

Thus CD40 is an excellent candidate for HIV vaccines based on DC targeting, as it's activation not only causes maturation of APC but permits efficient presentation and cross-presentation of HIV epitopes, thereby stimulating strong recall T cell responses.