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Enhanced induction of HIV-specific CTL by dendritic cell-targeted delivery of SOCS-1 siRNA

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Background

Dendritic cells (DC) are potent antigen-presenting cells that play a critical role in the activation of T cells. Antigen-loaded dendritic cell-based vaccines have been used for immunotherapy of human cancers and chronic infections, but only with limited success. RNAi-mediated silencing of negative immunoregulatory molecules expressed by DCs may provide a strategy to enhance the potency of DC-based vaccines and immunotherapy.

Methods

We have used a novel human HLA-A2 transgenic NOD/SCID-iL2rg chain -/- mice reconstituted with CD34+ HSC from A2 donors as a preclinical model to induce a robust CD8+ T cell-mediated protective immune response to HIV infection.

Results

SOCS-1 knockdown in human DCs a) enhanced their cytokine responses to LPS, and stimulated a strong mixed lymphocyte reaction in vitro, b) elicited a strong primary in vitro response to HLA-A2-restricted Melan-A/MART-1 and HIV Gag epitopes in naïve CD8+ T cells from healthy donors and c) increased the HIV gag-specific proliferation and polyfunctional cytokine response in CD8 T cells from seropositive subjects. More importantly, injection of gag peptide-pulsed, SOCS-1 silenced, but not just peptide pulsed HLA-A2 DCs, in the novel HLA-A2 humanized mice, gave rise to a robust multi-epitope-HIV specific CD8 T cells that could dramatically reduce the replication of a HIV-Gag-vaccinia recombinant challenge virus infection.

Discussion

These results demonstrate the feasibility of using manipulated DC as a prophylactic vaccine strategy for HIV infection in a humanized mouse model.

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