Retrovirology

Poster presentation

P19-56 LB. Priming with SOCS-1 silenced Dendritic cells induces robust HIV-specific CTL response in a novel HLA-A2 transgenic humanized mouse model

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Background

Cytotoxic T lymphocytes (CTL) are thought to play a central role in protection against HIV infection. This has been a major impetus for the design and testing of vaccines capable of eliciting a broad and vigorous CTL response to prevent or as a lesser goal, to ameliorate the disease course and viral transmission.

Methods

A chimeric peptide containing a 12-mer DC binding moiety fused to nonamer D-arginine residues (9dR) was developed for potential DC-specific siRNA delivery in vivo.

Results

Targeted silencing of SOCS-1 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 SL9 epitope in naïve CD8+ T cells from healthy donors and c) increased the HIV gag-specific cytokine response in CD8 T cells from seropositive subjects. More importantly, in HLA-A2 transgenic NOD/SCID-iL2rγ-/- mice reconstituted with CD34 HSC from HLA-A2 donors, injection of SOCS-1 silenced DCs pulsed with HIV A2-restricted gag peptides, but not the irrelevant flu peptide, gave rise to a robust HIV specific CD8 T cell response which protected effectively against lethal challenge with recombinant HIV Gag-vaccinia.

Conclusion

These results demonstrate the feasibility of using targeted RNAi to manipulate DC as a strategy to boost the immunogenicity of CTL epitope vaccines for HIV and attest to the value of the novel HLA-transgenic humanized mouse model in dissecting the protective role of HIV specific CD8 T cells restricted by specific HLA- alleles.