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P19-43. Regulatory T Cell Epitopes in a Dendritic Cell-Targeted HIV Vaccine Delivery Platform

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Poster presentation

P19-43. Regulatory T cell epitopes in a dendritic cell-targeted HIV vaccine delivery platform

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Background

Dendritic cell-targeting antibodies (e.g. anti-DEC-205) are used to deliver HIV vaccine immunogens for antigen presentation. As antibodies contain sequences that contribute to immunosuppression induced via regulatory T cells, we are modifying the anti-DEC-205 sequence to reduce its tolerogenicity to make it an effective HIV vaccine delivery vehicle.

Methods

IgG sequences were computationally screened for T-cell epitopes using EpiMatrix. Class II HLA competition binding assays were performed to validate predicted epitope peptides. T cell functional and immunophenotyping assays were performed using peptide-stimulated PBMCs provided by healthy human donors.

Results

Six highly promiscuous HLA class II T-cell epitopes in both the heavy and light chain constant domains of IgG were identified computationally. Epitopes were synthesized and shown to bind multiple HLA class II molecules with high affinity. These sequences specifically upregulate FoxP3 expression of CD4+CD25high T cells from healthy human donors. Co-incubation of these epitopes with various self and foreign antigens leads to antigen-specific suppression of effector T cell proliferation and cytokine secretion and an increase in IL-10 and CTLA-4 expression suggesting conversion of Teff to adaptive Tregs. The anti-DEC-205 sequence was computationally screened for putative HLA DR4-restricted, regulatory T-cell epitopes using EpiMatrix. Epitopes were analyzed using OptiMatrix to select mutations that will reduce epitope binding affinity for HLA. Five regulatory T-cell epitopes were computationally identified. Per epitope, three modified sequences were selected and synthesized.

Conclusion

These studies suggest that Treg epitopes in IgG may be responsible for antigen-specific tolerance observed for vaccine antigens targeted to dendritic cells via anti-DEC-205. Modification of regulatory T-cell epitopes may significantly diminish tolerogenicity, enabling the use of modified anti-DEC-205 as a HIV antigen-delivery system that obviates the dangers associated with non-specific activation of the immune system.