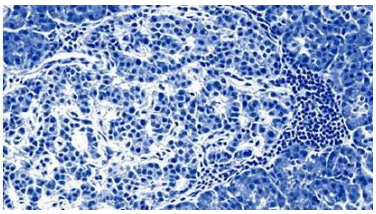
nPOD
Network for Pancreatic Organ Donors with Diabetes



D-peptides as a novel targeted immunotherapy for Type 1 Diabetes

AUTHORS

***Angela Lombardi*[1], *Erlinda Concepcion*[1], *Hanxi Hou*[1], *Hanane Arib,*[2] *Mihaly Mezei*[3], *Roman Osman*[3], *Yaron Tomer*[1]**

[1]Department of Medicine, Division of Endocrinology; Department of Microbiology and Immunology; The Fleischer Institute for Diabetes and Metabolism, Albert Einstein College of Medicine, Bronx, NY, USA; [2]Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [3]Department of Pharmacological Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA.

PURPOSE

HLA-DQ8 has been shown to present antigenic islet peptides driving the activation of CD4+ T-cells in Type 1 Diabetes (T1D) patients. Specifically, the insulin peptide InsB:9-23 activates self-reactive CD4+ T-cells, causing pancreatic beta cell destruction. The aim of the current study was to identify D-amino acid based peptides (D-peptides) that can block T-cell activation by antagonizing the presentation of InsB:9-23 peptide within the HLA-DQ8 pocket.

METHODS

To achieve our aim we used the following tools: human B cells homozygous for HLA-DQ8, transgenic mice expressing human HLA-DQ8, and peripheral blood mononuclear cells (PBMCs) from new onset HLA-DQ8 T1D patients.

SUMMARY OF RESULTS

We identified one D-peptide (RI-EXT) that inhibited InsB:9-23 binding to recombinant HLA-DQ8 molecule, as well as its binding to HLA-DQ8 expressed on a human B-cell line. Specifically, RI-EXT averted T-cell activation in a mixed lymphocyte reaction containing human DQ8 cells loaded with InsB:9-23 peptide and murine T-cells expressing a human TCR specific for the InsB:9-23–DQ8 complex. These results were confirmed in transgenic DQ8 mice both *ex vivo* and *in vivo,* as shown by decreased production of IL-2 and IFN-γ and reduced lymphocyte proliferation. Importantly, RI-EXT inhibited InsB:9-23-mediated lymphocyte activation in peripheral blood mononuclear cells isolated from new onset DQ8-T1D patients.

CONCLUSIONS

In summary, we discovered a D-peptide that blocks InsB:9-23 binding to HLA-DQ8 and its presentation to T-cells in T1D. These data set the stage for using our approach of blocking antigen presentation by D-peptides as a novel therapeutic approach for autoimmune diseases.