

Diabetogenic T cell recognition of an insulin antigen

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Type 1 diabetes (T1D) is one of the most common incurable autoimmune diseases. Insulin is the major target for T1D in humans and rodents. A single polymorphism at β 57 in major histocompatibility complex class II (MHCII) molecules is associated with T1D. This polymorphism causes poor MHCII presentation of critical insulin epitopes to diabetogenic CD4 T cells. Different C terminal modifications dramatically improve both peptide IAg7 binding and recognition by two different types of T cells (A and B). Type A and B CD4+ T cells prefer different insulin modifications at position P8. We solved the crystal structures of these modified peptides bound to IAg7 and of TCRs from a Type A and B CD4+ T cells bound to the appropriate peptide/IAg7 complex. The Type A I29 and Type B 8F10 TCRs dock on their ligands with totally different orientations. But the TCR Va interactions with insulin-IAg7 complexes are conserved despite of different sequences. Apparently, the binding chemistry of p8 amino acid determines Type A vs. Type B recognition of IAg7-insulin complexes. These data explain the different specificities of these two T cell types. It implies that there may be natural modifications of the insulin peptide, creating improved TCR agonists. We suggest that diabetogenic T cells escape elimination during thymic development because they recognize epitopes uniquely generated in the pancreas by modifications to the C-terminus of this insulin peptide. These results open up the possibility of new target to develop diagnostic and therapeutic reagents for human T1D.

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