The Iddm14 gene is Tcrbv-13S1A1: Prevention of Autoimmune Diabetes in the Rat with an Allele-Specific Depleting Antibody That Recognizes the Vβ13a T Cell Receptor Beta Chain

Michael Habib
University of Massachusetts Medical School

Ryan Eberwine
Drexel University College of Medicine

Zhijun Liu
University of Massachusetts Medical School

See next page for additional authors
THE \textit{Iddm14} GENE IS \textit{Tcrbv-13S1A1}: PREVENTION OF AUTOIMMUNE DIABETES IN THE RAT WITH AN ALLELE-SPECIFIC DEPLETING ANTIBODY THAT RECOGNIZES THE V\textit{\beta}13a T CELL RECEPTOR BETA CHAIN

Michael Habib, Ryan Eberwine, Zhijun Liu, Thomas Herrmann, Dale Greiner, Laura Cort, Elizabeth Blankenhorn and John P. Mordes

Worcester, MA, Würzburg, Germany, and Philadelphia, PA

Contact: Michael.habib@umassmed.edu

To identify new intervention strategies for autoimmune type 1 diabetes (T1D), we investigated several rat models of the disorder. We dissected the powerful \textit{Iddm14} diabetes susceptibility locus in eight T1D susceptible vs. resistant rat strains by single nucleotide polymorphism (SNP) haplotyping. We identified an allele of a T cell receptor (TCR) beta chain gene, \textit{Tcrb-V13S1A1} (encoding V13\textit{\beta}a) as a candidate gene. In three separate trials, treating LEW.1WR1 rats, which are susceptible to T1D, with a depleting anti-V\textit{\beta}13 monoclonal antibody reduced diabetes frequency from 75\% (N=50) to 17\% (N=30, p<0.001. Anti-V\textit{\beta}13 monoclonal antibody also prevented T1D in spontaneously diabetic BBDP rats. We then analyzed the phenotype of infiltrating T cells recovered from the cultured islets of LEW.1WR1 rats exposed to a diabetogenic trigger. Within 5 days, up to 22\% of CD4+ T cells recovered from islets were V13\textit{\beta}+, most of these CD25+FoxP3-. We also recovered V\textit{\beta}13 transcripts from pre-diabetic islets and observed a limited number of J\textit{\beta} variant transcripts, indicating an oligoclonal TCR response to pancreatic beta cells. These data indicate that, in susceptible rats, V13\textit{\beta}a on diabetogenic T cells is required to recognize a critical T1D autoantigen. Interestingly, the diabetogenic and non-diabetogenic alleles of V\textit{\beta}13 have non-conservative sequence differences in both CRR1 and CDR2. The data suggest that it is possible to prevent T1D in the rat with a very narrowly targeted deletional therapy. Preliminary data suggest that a specific alpha chain may preferentially pair with V\textit{\beta}13a. We are currently generating rat T cell hybridoma clones with which to analyze the interaction of putative autoantigens with a diabetogenic TCR.