

## **CD8<sup>+</sup> T cell tolerance in NOD mice can be restored by *insulin dependent diabetes (Idd)* resistance alleles**

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The development of autoimmune diseases such as T1D is of complex etiology and mediated by multiple genetic and environmental factors. Although candidate genes controlling autoimmune disease can now be identified, a major challenge that remains is defining the resulting cellular events mediated by each locus.

In congenic NOD mice, the genetic regions controlling diabetes, designated as *Insulin dependent diabetes (Idd)* loci, have been replaced by resistant alleles obtained from nondiabetic strains of mice. We hypothesize that critical genetic susceptibility loci regulate the maintenance of self-specific CD8<sup>+</sup> T cells.

We have therefore compared the fate of islet-reactive CD8<sup>+</sup> and CD4<sup>+</sup> T cells in diabetes susceptible NOD mice with that observed in diabetes-resistant NOD congenic mice having protective alleles at *Idd3*, *Idd5.1* and *Idd5.2* (*Idd3/5* strain) or at *Idd9.1*, *Idd9.2* and *Idd9.3* (*Idd9* strain). We demonstrate that protection from diabetes in each case is correlated with functional tolerance of islet specific CD8<sup>+</sup> T cells, however, this is achieved in different ways. In *Idd3/5* mice, tolerance occurs during the initial activation of islet-specific CD8<sup>+</sup> and CD4<sup>+</sup> T cells in the pancreatic lymph nodes where the presence of CD25<sup>+</sup> Tregs prevents their accumulation. In contrast, resistance alleles in *Idd9* mice do not prevent the accumulation of islet-specific CD8<sup>+</sup> and CD4<sup>+</sup> T cells in the pancreatic lymph node, thereby suggesting that tolerance occurs at a later checkpoint. These results underscore the variety of ways that autoimmunity can be prevented and identify the elimination of islet-specific CD8<sup>+</sup> T cells as a common indicator of high-level protection.