DIABETES

Mobilizing regulatory T cells against type 1 diabetes

Type 1 diabetes (TD1) is characterized by the autoimmune destruction of pancreatic β-cells. Several immunotherapeutic approaches are being investigated that aim to prevent the onset of disease in individuals 'at risk', including vaccination strategies with natural insulin epitopes. However, results from clinical trials have so far been disappointing. Now, reporting in the *Journal of Experimental Medicine*, von Boehmer and colleagues present a new approach using an insulin mimetope that can induce regulatory T (T_{reg}) cell-mediated dominant tolerance in a mouse model of TD1, completely preventing the onset of disease.

The development of TD1 in non-obese diabetic (NOD) mice, is controlled by the same genetic factors (including specific MHC class II genes) as in humans. Mice usually develop symptoms by 12–28 weeks of age, and the onset of disease is preceded by an elevation in insulin autoantibody (IAA) levels. It is thought that TD1 and other autoimmune diseases develop when T cells with specificity for weakly binding autoantigens escape negative selection in the thymus and then mount an autoimmune attack in the periphery. Based on their earlier studies, the authors hypothesized that such poorly agonistic peptides not only fail to induce negative selection, but also fail to induce dominant tolerance, mediated by antigen-specific $FOXP3^+$ T_{reg} cells that control autoimmunity in peripheral tissues.

It was previously shown that naive T cells can be converted into T_{reg} cells when they are exposed to highly agonistic antigens under subimmunogenic conditions. To test whether this strategy can be applied to prevent the development of TD1, the authors designed a strongly agonistic insulin mimetope by changing a single amino acid of a natural insulin epitope. The mimetope was delivered using subimmunogenic vaccination strategies to 4–12-week-old NOD mice and, despite the presence of IAAs before vaccination (except if these were present at exceptionally high levels), the protocol completely prevented the onset of TD1 for up to 70 weeks. By contrast, vaccination with the corresponding insulin epitope only induced a modest delay in disease onset. The conversion of naive transgenic T cells into $FOXP3^+$ T_{reg} cells was demonstrated in T cell transfer experiments, in which vaccination with the mimetope induced conversion rates of 40–50%. Activated monoclonal insulin-specific and polyclonal T cells from newly diabetic mice were suppressed when transferred to mimetope-treated NOD mice, demonstrating that the induced T_{reg} cells act as dominant suppressors of T cell activation. Further experiments showed that co-administration of the rapamycin analogue everolimus enhances the effect of the mimetope strategy, and that the T_{reg} cells suppress the proliferation of interferon-γ and interleukin-17 secreting insulin-specific effector cells, but do not affect interleukin-10 secretion.

Collectively, these experiments indicate that subimmunogenic vaccination with a strongly agonistic insulin mimetope might offer a strategy to convert autoreactive T cells into antigen-specific T_{reg} cells. This requires only a single epitope, as T_{reg} cells suppress immune responses to antigens from the same source through a process known as bystander suppression. The authors argue that the strategy should be readily translatable to the human system, where individuals with IAAs and high-risk MHC alleles present a well-defined population to vaccinate with this method.

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ORIGINAL RESEARCH PAPER Daniel, C. *et al.* Prevention of type 1 diabetes in mice by tolerogenic vaccination with a strong agonist insulin mimetope. *J. Exp. Med.* **208**, 1501–1510 (2011)