AUTOIMMUNE DISEASE

Targeting IL-7 reverses type 1 diabetes

Two recent studies published in *PNAS* suggest that blocking the function of interleukin-7 (IL-7) using monoclonal antibodies could provide a disease-modifying approach in type 1 diabetes. The papers also show that modulation of effector T cells — T cells that can migrate to peripheral sites of inflammation — underlies the therapeutic effects of targeting IL-7.

Type 1 diabetes is an autoimmune disease in which effector T cells infiltrate pancreatic islets and cause destruction of insulin-producing β-cells. How these T cells overcome the various inhibitory and tolerance mechanisms that should protect against autoimmune disease is not fully understood, but IL-7 is believed to be involved.

So, to investigate the role of IL-7 — and the effect of blocking the activity of this cytokine — in the pathogenesis of type 1 diabetes, the authors of both studies used IL-7 receptor (IL-7R)-blocking antibodies in the non-obese diabetic (NOD) mouse model of type 1 diabetes.

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Administration of the antibodies (given by once- or twice-weekly injection) to pre-diabetic mice prevented onset of the disease and resulted in less infiltration of effector T cells into pancreatic islets. When IL-7R antibodies were administered to mice with new-onset type 1 diabetes, blood glucose levels were normalized in ~50–85% of treated animals, demonstrating that blockade of IL-7R could reverse established diabetes. Moreover, this effect persisted even after treatment was stopped.

Because IL-7 is known to be involved in T cell survival and homeostasis, the authors were surprised to find that depletion of islet-reactive effector T cells did not appear to be the mechanism behind the efficacy of IL-7R blockade. So they next investigated the effects of IL-7 and IL-7R-targeted antibodies in T cells isolated from NOD mice.

These studies suggested that two mechanisms are likely to mediate the effects of IL-7R blockade. First, IL-7 was shown to increase the number of interferon-γ-producing effector T cells, which are known to be involved in the pathogenesis of type 1 diabetes, and this effect was reversed by IL-7R-targeted antibodies.

Second, IL-7R-targeted antibodies increased the expression of programmed cell death protein 1 (PD1), a negative regulator of T cell activity expressed on the surface of effector T cells that is involved in immune tolerance (the process by which the immune system ignores self-antigens). Furthermore, in previously diabetic mice in which hyperglycaemia was normalized using IL-7R antibodies, treatment with an antibody against PD1 led to disease relapse, adding weight to the idea that the increase in PD1 mediated the beneficial effect of IL-7R-targeted antibodies.

In addition, adoptive transfer of effector T cells from IL-7R antibody-treated mice to recipient mice failed to establish diabetes. Together, this second set of studies suggested that the IL-7R antibody-mediated upregulation of PD1 induces cell-intrinsic immune tolerance.

Although further work is needed before this research can be translated into humans, these two studies suggest that IL-7R-targeted antibodies could provide a new therapeutic approach for the treatment of type 1 diabetes.

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ORIGINAL RESEARCH PAPERS Penaranda, C. *et al.* IL-7 receptor blockade reverses autoimmune diabetes by promoting inhibition of effector/memory T cells. *Proc. Natl Acad. Sci. USA* 25 Jun 2012 (doi: 10.1073/pnas.1203692109) | Lee, L.- F. *et al.* Anti-IL-7 receptor-α reverses established type 1 diabetes in nonobese diabetic mice by modulating effector T-cell function. *Proc. Natl Acad. Sci. USA* 25 Jun 2012 (10.1073/pnas.1203795109)