AUTOIMMUNITY

TLR signals provide the missing factor

Why is it that normal individuals can harbour autoreactive T cells yet do not develop overt autoimmune disease? A recent report published in *Nature Medicine* provides a potential explanation for this conundrum and indicates that Toll-like receptor (TLR) ligation is required to cause destruction of pancreatic islet β-cells by autoreactive T cells in a mouse model of diabetes.

Zinkernagel and colleagues studied the RIP–GP mouse model of diabetes, in which a lymphocytic choriomeningitis virus (LCMV) glycoprotein (GP) transgene is expressed under the control of the rat insulin promoter (RIP). LCMV infection of these mice induces the clonal expansion of LCMV-GP-specific $CD8^+$ T-cell populations and the development of hyperglycaemia. However, if RIP–GP mice were immunized with an LCMV-GP-derived peptide (gp33) together with CpG-containing oligodeoxynucleotides (to deliver co-stimulation), they did not develop diabetes, despite having large numbers of fully functional gp33-specific $CD8^+$ T cells. The absence of disease was not a consequence of inefficient T-cell migration to the pancreas, as in mice that co-express LCMV-GP and the chemokine CXCL13 in the pancreas, gp33-specific $CD8^+$ T cells infiltrated the pancreatic islets in response to immunization with gp33, yet these mice did not develop diabetes. Next, the authors observed that LCMV infection, but not gp33 immunization, increased the level of serum interferon-α (IFN-α), which upregulated MHC class I expression by β-cells. Pancreatic MHC class I expression could also be induced by administration of the TLR3 ligand polyI:C or the TLR7 ligand R848 to wild-type mice, and when administered to RIP–GP mice that were pre-immunized with gp33, hyperglycaemia developed. The ability of TLR ligands to induce disease was dependent on expression of the type I IFN receptor, indicating that expression of MHC class I in the pancreas in response to TLR-induced IFN-α production renders the pancreas susceptible to attack by autoreactive T cells.

Lucy Bird

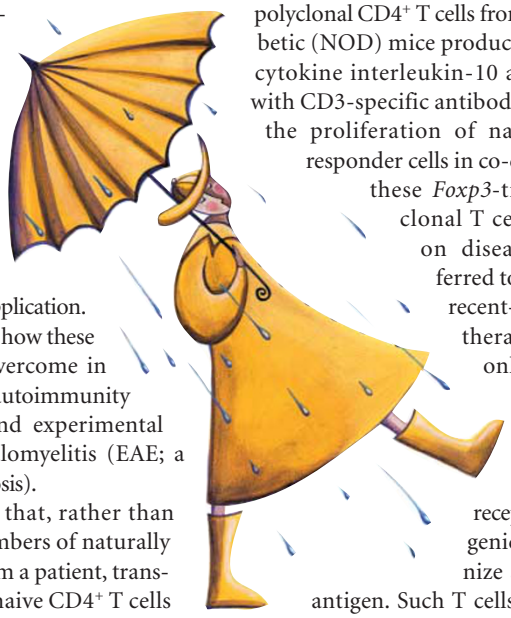
References and links

ORIGINAL RESEARCH PAPER Lang, K. S. *et al.* Toll-like receptor engagement converts T-cell autoreactivity into overt autoimmune disease. *Nature Med.* **11**, 138–145 (2005).

REGULATORY T CELLS

A step closer to the clinic

As the concept of regulatory T (T_{Reg}) cells has become widely accepted during the past ten years, there has been increasing interest in their therapeutic potential to inhibit inappropriate immune responses, such as autoimmune diseases. However, the low frequency and unknown specificity of naturally occurring $CD4^+CD25^+$ T_{Reg} cells limit their immediate application. These two papers show how these problems might be overcome in two animal models of autoimmunity — type 1 diabetes and experimental autoimmune encephalomyelitis (EAE; a model of multiple sclerosis).



Jaeckel *et al.* show that, rather than isolating the small numbers of naturally occurring T_{Reg} cells from a patient, transduction of abundant naive $CD4^+$ T cells with the T_{Reg}-cell-associated transcription factor *FOXP3* (forkhead box P3) can be used to induce a regulatory phenotype. *Foxp3*-transduced polyclonal $CD4^+$ T cells from non-obese diabetic (NOD) mice produced the regulatory cytokine interleukin-10 after stimulation with CD3-specific antibody and suppressed the proliferation of naive $CD4^+CD25^-$ responder cells in co-culture. However, these *Foxp3*-transduced polyclonal T cells had no effect on disease when transferred to NOD mice with recent-onset diabetes. A therapeutic effect was only obtained when the T cells to be transduced with *Foxp3* were isolated from T-cell receptor (TCR)-transgenic mice that recognize a pancreatic-islet antigen. Such T cells showed specific homing to, and activation in, the pancreatic draining lymph nodes, indicating that the antigen specificity of the T_{Reg} cells will be important in determining therapeutic efficacy.

One potential method for redirecting the antigen specificity of polyclonal T_{Reg} cells is described by Mekala and Geiger. They transgenically modified the T_{Reg} cells with a chimeric receptor consisting of a myelin basic protein (MBP) epitope bound to the extracellular and transmembrane domains of MHC linked to the cytoplasmic domain of the TCR ζ-chain. Such receptor-modified T cells specifically recognize, and are activated by, T cells specific for the MBP epitope. Receptor-modified $CD4^+$ $CD25^+$ T cells inhibited both the onset and development of EAE induced with MBP but not with another known EAE autoantigen. The authors suggest that combining this technique with *Foxp3* transduction could be used to generate a population of antigen-specific T_{Reg} cells from the peripheral-blood T cells of a patient.

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References and links

ORIGINAL RESEARCH PAPERS Jaeckel, E., von Boehmer, H. & Manns, M. P. Antigen-specific FoxP3-transduced T-cells can control established type 1 diabetes. *Diabetes* **54**, 306–310 (2005) | Mekala, D. J. & Geiger, T. L. Immunotherapy of autoimmune encephalomyelitis with re-directed $CD4^+CD25^+$ T-lymphocytes. *Blood* 4 Nov 2004 (doi:10.1182/blood-2004-09-3579).