AUTOIMMUNITY

Homing in on the target

Although multiple pancreatic islet-cell molecules are targets of autoimmune responses in human type 1 diabetes and in mouse models, conclusive evidence of the autoantigens that are important for initiation of the disease has been difficult to obtain. Now, two articles in *Nature* show that insulin is likely to be a crucial autoantigen in the development of type 1 diabetes in both the mouse model and human patients.

Previously, it has been shown that most $CD4^+$ T cells infiltrating the pancreas in non-obese diabetic (NOD) mice recognize insulin, in particular peptide 9–23 of the insulin B chain. So, to test the role of this response in the development of disease, Nakayama *et al*. generated NOD mice in which both insulin genes (*Ins1* and *Ins2*) were deleted and replaced with a transgene encoding mutant pro-insulin. The mutant pro-insulin contained a single amino-acid change at position 16 of the insulin B chain, which preserves the metabolic activity of insulin but prevents recognition by the infiltrating T cells. None of the $Ins1^{-/-}Ins2^{-/-}$ NOD mice expressing the modified insulin showed signs of an immune response to the islet cells, and they did not develop diabetes (although autoimmune reactions were still evident in the salivary glands). By contrast, the presence of either insulin gene in these mice was sufficient to restore diabetes, confirming a crucial role for both insulin genes as targets of organ-specific autoimmunity.

Unlike mouse studies, the study of human autoimmune diseases is often hindered by the scarcity and lability of the relevant target tissues or draining lymph nodes. But in the second study, Kent *et al*. obtained viable pancreatic draining lymph nodes from three individuals with type 1 diabetes (two with long-term disease and one with recent-onset disease) and three control individuals. From these lymph-node samples, the authors generated single T-cell clones in a non-biased manner and analysed their T-cell receptor (TCR) repertoire and their antigen specificity. T-cell clones isolated from pancreatic lymph nodes of control individuals expressed heterogeneous TCR repertoires, indicative of polyclonal expansion. By contrast, more than half of the T-cell clones from the long-term diabetic individuals expressed identical Vβ chains, and of these clones, half had the same TCR α-chain, implying antigen-driven expansion of a common progenitor cell. The clones from the long-term diabetic individuals, but not those from control individuals, proliferated specifically in response to peptide 1–15 of insulin A in a dose-dependent manner. This response was restricted by the MHC class II allele HLA-DRB1*0401, which is known to confer genetic susceptibility to diabetes.

To rule out the possibility that the insulin-specific T-cell responses could have arisen from long-term use of daily insulin injections (to control blood glucose levels), Kent *et al*. showed that insulin-reactive T cells were not found in the spleen of one of the long-term diabetic individuals, and $CD4^+$ T-cell clones from pancreatic draining lymph nodes of an individual with type 2 diabetes did not recognize any pro-insulin peptide.

Knowing which autoantigens trigger autoimmunity is still out of reach for many researchers studying autoimmune disease, but the evidence from both of these papers that insulin has a crucial role will no doubt increase our chances of developing antigen-specific tolerization therapy for diabetic patients.

Lucy Bird

References and links

ORIGINAL RESEARCH PAPERS Nakayama, M. *et al*. Prime role for an insulin epitope in the development of type 1 diabetes in NOD mice. *Nature* **435**, 220–223 (2005) | Kent, S. C. *et al*. Expanded T cells from pancreatic lymph nodes of type 1 diabetic subjects recognize an insulin epitope. *Nature* **435**, 224–228 (2005)