Next, the authors investigated the impact of calcineurin on negative selection. Negative selection of H-Y TCR-transgenic, Cnb1-deficient thymocytes was shown to occur normally in male mice, which express the male-specific H-Y antigen. This lack of requirement for calcineurin was confirmed using several *in vitro* assays. When Cnb1-deficient thymocytes were co-cultured with control thymocytes (from wild-type littermates) in the presence of antibodies specific for both CD3 and CD28, both cell populations displayed similar levels of DP cell death. Similar results were obtained (using a more physiological model) when moth cytochrome c peptide–I-E^k complexes were added to co-cultures of Cnb1-deficient and control thymocytes transgenic for the cognate TCR, 5C.C7. Moreover, Cnb1-deficient thymocytes had the same threshold for negative selection as wild-type thymocytes and expressed similar levels of the pro-apoptotic protein Bim (which is required for negative selection) and the anti-apoptotic protein Bcl-X_L.

Calcineurin and another signal transducer, extracellular-signal-regulated kinase (Erk), are known to be activated by both positively and negatively selecting signals, although neither of these is required for negative selection. So the authors suggest that the lowest molecule which is common to the signalling pathways of both positive and negative selection must be upstream of calcineurin and Erk (and also Bim) and downstream of TCR-proximal signalling molecules, which are clearly required for TCR signalling. They propose a model whereby both low- and high-intensity signals activate the calcineurin and Erk pathways, but high-intensity signals cause negative selection by activating a dominant pathway, which induces apoptosis through Bcl-2 family members (including Bim).

Davina Dadley-Moore

References and links

ORIGINAL RESEARCH PAPER Neilson, J. R. *et al.* Calcineurin B1 is essential for positive but not negative selection during thymic development. *Immunity* **20**, 255–266 (2004)

FURTHER READING Palmer, E. Negative selection — clearing out the bad apples from the T-cell repertoire. *Nature Rev. Immunol.* **3**, 383–391 (2003)

WEB SITE

Jerry Crabtree's lab:
http://crablab.stanford.edu/

So, the authors suggest that activation of APCs through receptors of the innate immune system can tip the balance between peripheral tolerance and autoimmunity in favour of autoimmune disease.

Lucy Bird

References and links

ORIGINAL RESEARCH PAPER Waldner, H., Collins, M. & Kuchroo, V. K. Activation of antigen-presenting cells by microbial products breaks self tolerance and induces autoimmune disease. *J. Clin. Invest.* **113**, 990–997 (2004)

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autoimmune disease: aetiology and pathogenesis

IN BRIEF

AUTOIMMUNITY

Human lupus T cells resist inactivation and escape death by upregulating COX-2.

Zu, L. *et al. Nature Med.* **10**, 411–415 (2004)

This study used microarray analysis to look at why $CD4^+$ T helper (T_H) cells from patients with systemic lupus erythematosus (SLE) are resistant to anergy and activation-induced cell death (AICD). They show that the *PTGS2* gene, which encodes COX2, is upregulated in T_H cells from patients with SLE. COX2 expression protects T_H cells from death by upregulating expression of the anti-apoptotic protein c-FLIP and decreasing signalling through the FAS (CD95) apoptotic pathway. COX2 overexpression did not result in prostaglandin E_2 production by the T_H cells, which indicates that COX2 has a role in transcriptional regulation that does not depend on its enzymatic activity. This could lead to the development of selective inhibitors of the COX2 anti-apoptotic pathway.

LYMPHOPOIESIS

Development of a human adaptive immune system in cord blood cell-transplanted mice.

Traggiai, E. *et al. Science* **304**, 104–107 (2004)

To overcome the limitations of studying development of the human immune system *in vitro*, researchers have long sought to develop an *in vivo* model involving transplantation of human cells into immunodeficient mice. A new system reported in this paper has for the first time led to the formation of a functional adaptive immune response. The authors transplanted $CD34^+$ human cord-blood precursors into the liver of newborn *Rag2*$^{-/-}\gamma c^{-/-}$ mice and analysed them up to 6 months of age. They showed that the development of human T cells, B cells and dendritic cells occurred normally in the xenotransplanted mice and resulted in the formation of organized lymphoid structures. Furthermore, the mice mounted a good immune response to vaccination with tetanus toxoid or infection with Epstein–Barr virus.

AUTOIMMUNITY

Coxsackieviral-mediated diabetes: induction requires antigen-presenting cells and is accompanied by phagocytosis of β cells.

Horwitz, M. S. *et al. Clin. Immunol.* **110**, 134–144 (2004)

This study indicates a crucial role for antigen-presenting cells in initiating the destruction of pancreatic β-cells induced by viral infection. Epidemiological studies have shown a link between infection with coxsackie B virus (CBV) and type 1 diabetes. To investigate the pathogenic process, Sarvetnick and colleagues used a diabetes model involving infection of islet-specific T-cell receptor (TCR)-transgenic mice with CBV strain 4 (CB4). They show that CB4 infects insulin-producing β-cells without causing necrosis. Instead, the stressed islet cells are phagocytosed by resident macrophages, which present islet epitopes to autoreactive T cells. These macrophages could induce diabetes after adoptive transfer to uninfected TCR-transgenic mice. Therefore, viral infection could be the last initiating step in multi-step diabetes development, requiring the pre-existence of autoreactive T cells.