IN BRIEF

ANTIBODY FUNCTION

Antibody catalysis of the oxidation of water.

Wentworth, P. Jr *et al. Science* **293**, 1806–1811 (2001)

It was recently shown that antibodies can generate hydrogen peroxide from singlet oxygen. The authors now show that the oxidation of water serves as the electron source for this catalytic process. They also identified a highly conserved oxygen-binding domain within the immunological fold in which this unusual chemistry might take place. Whether this reaction allows antibodies to detoxify singlet oxygen, or aids in cell killing through the production of hydrogen peroxide, remains to be determined.

REGULATORY T CELLS

Cell contact-dependent immunosuppression by $CD4^+CD25^+$ regulatory T cells is mediated by cell surface-bound transforming growth factor β.

Nakamura, K., Kitani, A. & Strober, W. *J. Exp. Med.* **194**, 629–644 (2001)

$CD4^+CD25^+$ regulatory T cells mediate suppression of $CD4^+CD25^-$ T cells in a cell-contact-dependent manner, and in the absence of secreted cytokines. Nakamura and colleagues show that these cells do, in fact, produce the suppressive cytokines transforming growth factor-β (TGFβ) and interleukin-10, and that suppression is dependent on presentation of TGFβ at the cell surface.

HAEMATOPOIESIS

The Notch ligand, Delta-1, inhibits the differentiation of monocytes into macrophages but permits their differentiation into dendritic cells.

Ohishi, K. *et al. Blood* **98**, 1402–1407 (2001)

Notch signalling pathways regulate cell-fate decisions in many developmental systems. The authors studied the role of the Notch ligand, Delta-1, in monocyte differentiation. Monocytes cultured in the presence of the immobilized extracellular domain of Delta 1 ($Delta^{ext\text{-}myc}$) and appropriate cytokines can differentiate into mature dendritic cells (DCs) but not into macrophages. The results indicate a role for Notch signalling in the regulation of cell-fate decisions by bipotent macrophage/DC precursors.

T-CELL DEVELOPMENT

Early thymocyte development is regulated by modulation of E2A protein activity

Engel, I. *et al. J. Exp. Med.* **194**, 733–746 (2001)

The products of the *E2A* gene (the E47 and E12 basic HLH transcription factors) are important in T-cell development. Here, the authors show that the block in T-cell development seen in $Rag^{-/-}$ and *scid* mutant mice can be rescued by a deficiency in E2A. In addition, mimicking pre-TCR signals in $Rag^{-/-}$ thymocytes resulted in decreased E47 DNA-binding and increased expression of the E-protein antagonist Id3. They conclude that E2A acts to ensure the developmental arrest of thymocytes with defects in TCRβ expression.

NATURAL KILLER T CELLS

Tipping the balance

Natural killer T (NKT) cells are a subset of T cells that express both T-cell and NK-cell markers. In contrast to conventional T cells, NKT cells express semi-invariant, self-reactive antigen receptors, and they recognize glycolipid antigen in the context of the major histocompatibility complex (MHC)-like molecule CD1d. Previous studies have indicated an association between reduced numbers of NKT cells and the development of autoimmune diseases. Two groups now report in *Nature Medicine* that stimulation of NKT cells in non-obese diabetic (NOD) mice with α-galactosylceramide (αGC) — a glycolipid isolated from marine sponges, which is a potent stimulator of NKT cells — can prevent the development of type 1 diabetes (T1D).

T1D is, like other autoimmune diseases, thought to be mediated by pathogenic T-helper type 1 (T_H1) cells, and is associated with a defect in regulatory T cells. NOD mice, which spontaneously develop diabetes, and patients with T1D have reduced numbers of NKT cells and defects in interleukin-4 (IL-4) production (a cytokine that is necessary for the development of T_H2 responses). Previous work had shown that αGC stimulation of NKT cells leads to the development of T_H2 responses. Furthermore, increasing the number of NKT cells prevented diabetes in NOD mice. On the basis of this previous work, the two groups decided to investigate the effect of αGC on the development of diabetes in NOD mice.

Both groups showed that administration of αGC to NOD mice inhibited the development of diabetes in a dose-dependent manner, particularly when treatment was initiated at an early age. So, how does αGC inhibit the development of diabetes? The precise mechanism of action of αGC has been an issue of some debate, but in these two studies, αGC seems to stimulate NKT cells to tip the balance away from a pathogenic T_H1 response towards the development of protective T_H2 cells. Disease prevention was associated with reduced interferon-γ production and elevated serum immunoglobulin E levels. When NOD mice were crossed with CD1d-deficient mice, αGC could not prevent the development of diabetes, indicating that αGC modulates diabetes by activating NKT cells in a CD1d-dependent manner.

Sharif *et al.* also showed that αGC treatment prolonged the survival of islet transplants in newly diabetic NOD mice. In addition, they showed that, under conditions in which αGC alone could not prevent diabetes, IL-7 could act synergistically with αGC to prevent the onset of diabetes. The researchers suggest that IL-7 acts by restoring normal NKT cell maturation and function in NOD mice, so that αGC treatment is more effective.

Although αGC is hepatotoxic in mice, the toxicity in humans is not so severe, and it might be possible to develop αGC analogues with reduced toxicity. Furthermore, as the NKT cell response to αGC is conserved in mice and humans, these results indicate that αGC might be a useful therapy for the treatment of T1D and other T_H1-mediated autoimmune diseases.

Elaine Bell

References and links

ORIGINAL RESEARCH PAPERS Hong, S. *et al.* The natural killer T-cell ligand α-galactosylceramide prevents autoimmune diabetes in non-obese diabetic mice. *Nature Med.* **7**, 1052–1056 (2001) | Sharif, S. *et al.* Activation of natural killer T cells by α-galactosylceramide treatment prevents the onset and recurrence of autoimmune Type 1 diabetes. *Nature Med.* **7**, 1057–1062 (2001)

FURTHER READING Godfrey D.I. *et al.* NKT cells: facts, functions and fallacies. *Immunol. Today* **21**, 573–583 (2000)

WEB SITES

Luc van Kaer's lab:
http://www.mc.vanderbilt.edu/microbio/vankaer/index.html

Terry Delovitch's lab:
http://www.rri.on.ca/research/scientists/delovitch.html