CO-STIMULATION

B7-H1: it's not all negative

Contrary to expectations, the 'co-inhibitory' ligand B7-H1 has been shown to promote autoimmune T-cell responses in a mouse model of diabetes. This study, in *The Journal of Clinical Investigation*, indicates that it might be time for a re-think about the classification of this molecule.

Ligation of cognate receptors (such as PD1) on T cells by B7-H1 results in production of the regulatory cytokine interleukin-10 (IL-10), and many studies have supported the role of B7-H1 as an inhibitor of T-cell responses in *in vivo* tumour, transplant and autoimmune models. Subudhi *et al*. therefore hypothesized that expression of B7-H1 by pancreatic islet β-cells would prevent the T-cell-mediated destruction of these cells that occurs in autoimmune diabetes.

They created transgenic mice in which expression of B7-H1 is under the control of the rat insulin promoter (RIP.B7-H1 mice), and confirmed that B7-H1 is expressed by the same cells that produce insulin without affecting the level of insulin secretion, pancreas morphology or baseline immune-system parameters. Three systems were then used to investigate the effects of B7-H1 expression, with surprising results.

First, B7-H1-expressing pancreatic islets transplanted across minor histocompatibility antigen barriers into mice with chemically induced diabetes were rejected more rapidly than were control islets. This accelerated rejection could be prevented using a blocking monoclonal antibody specific for B7-H1. Second, C57BL/6 mice are normally resistant to the induction of autoimmune diabetes by various means, but 14% of the transgenic mice on this background developed spontaneous diabetes by 6 weeks of age. Third, to study the autoimmune antigen-specific T-cell response more easily, double-transgenic mice were created expressing both B7-H1 and membrane-bound ovalbumin (RIP.B7-H1/mOVA mice). After transfer of OVA-specific $CD8^+$ T cells, the number of dividing T cells recovered from pancreas-draining lymph nodes was significantly greater in RIP.B7-H1/mOVA recipients than in RIP.mOVA recipients. The increased proliferative response in RIP.B7-H1/mOVA mice could be inhibited by an antibody specific for B7-H1, and T-cell proliferation in RIP.mOVA mice could be increased using a B7-H1–immunoglobulin fusion protein. All of these results lead to the conclusion that B7-H1 can co-stimulate T-cell responses *in vivo* and promote the spontaneous development of autoimmune disease. This extends a previous study showing that blockade of B7-H1 can inhibit experimentally induced autoimmunity (see further reading).

How does this study tie in with the previous contradictory findings? The authors suggest that B7-H1 might have different roles depending on the nature and stage of disease pathogenesis — another example of the complexity of immune interactions *in vivo*, which needs to be explored further.

Kirsty Minton

References and links

ORIGINAL RESEARCH PAPER Subudhi, S. K. *et al*. Local expression of B7-H1 promotes organ-specific autoimmunity and transplant rejection. *J. Clin. Invest.* **113**, 694–700 (2004)
FURTHER READING Kanai, T. *et al*. Blockade of B7-H1 suppresses the development of chronic intestinal inflammation. *J. Immunol.* **171**, 4156–4163 (2003)