TOLERANCE

Tim3 – tolerance's little helper!

The immunoglobulin superfamily member Tim3 (T-cell immunoglobulin mucin 3) was first identified as a cell-surface marker preferentially expressed by T helper 1 (T_H1) cells, but the *in vivo* functions of Tim3 have remained unknown. Two papers now published in *Nature Immunology* show that Tim3 regulates T_H1-cell-mediated immune responses and is important for tolerance induction .

To investigate the function of Tim3, Sabatos *et al.* generated soluble fusion proteins in which mouse Tim3 was fused to the Fc portion of human immunoglobulin. Administration of Tim3–immunoglobulin fusion proteins during a T_H1-cell-mediated immune response led to hyperproliferation of T_H1 cells and increased production of T_H1-type cytokines, indicating that Tim3 normally acts to inhibit T_H1-cell effector responses.

Early studies using Tim3-specific monoclonal antibodies indicated that Tim3 acts as a negative regulator of autoimmune responses. To investigate this further, Sánchez-Fueyo *et al.* studied the effects of blocking the Tim3 pathway in NOD mice (which spontaneously develop insulin-dependent diabetes). Treatment with Tim3-specific monoclonal antibodies accelerated the onset of disease in these mice, confirming earlier reports of a role for this protein in inhibiting autoimmune responses.

Both groups investigated the role of Tim3 in the induction of tolerance. Blockade of the Tim3 pathway (either through treatment with Tim3–immunoglobulin fusion proteins or genetic targeting of Tim3) prevented the development of both transplantation tolerance and peripheral tolerance induced with high doses of antigen. Further experiments by Sánchez-Fueyo *et al.* showed that Tim3 normally promotes the induction of tolerance, in part, due to effects on $CD4^+CD25^+$ regulatory T cells.

Jenny Buckland

References and links

ORIGINAL RESEARCH PAPERS Sabatos, C. A. *et al.* Interaction of Tim-3 and Tim-3 ligand regulates T helper type 1 responses and induction of peripheral tolerance. *Nature Immunol.* 12 October 2003 (DOI: 10.1038/ni988) | Sánchez-Fueyo, A. *et al.* Tim-3 inhibits T helper type 1-mediated auto- and alloimmune responses and promotes immunological tolerance. *Nature Immunol.* 12 October 2003 (doi:10.1038/ni987)

FURTHER READING Kuchroo, V. K. *et al.* The *TIM* gene family: emerging roles in immunity and disease. *Nature Rev. Immunol.* **3**, 454–462 (2003)

B-CELL SIGNALLING

It's a knockout!

In a study published in *Current Biology*, Fournier *et al.* now report the first knockout mouse for the B-cell adaptor protein Dapp1 (dual adaptor for phosphotyrosine and 3-phosphoinositides 1). Previous studies have indicated that Dapp1 (otherwise known as Bam32) is crucial for normal B-cell receptor (BCR) signalling, probably functioning to couple downstream signal-transduction molecules to membrane phosphatidylinositol phosphates generated in response to BCR ligation.

Dapp1$^{-/-}$ mice were viable, and had normal B-cell development with no differences in splenic B-cell subsets. However, a mild defect was noted in the proliferation of *Dapp1*$^{-/-}$ B cells in response to BCR crosslinking with mitogens, although not in response to non-BCR mitogens such as lipopolysaccharide. In contrast to earlier studies in cell culture, this B-cell defect could not be explained in terms of specific changes in downstream signalling pathways — activation of mitogen-activated protein kinases and calcium flux, used as a marker of phosphatidylinositol 3-kinase and phospholipase Cγ activity, were normal.

Is Dapp1 required for a normal antibody response? Humoral responses to T-cell-dependent or T-cell-independent type I (TI-I) antigens were normal in the knockout mice, whereas these mice had a marked reduction in the production of IgG3 in response to the TI-II antigen TNP–Ficoll. This marked defect in IgG3 class switching corresponded with the failure to produce γ3 germline transcripts after immunization. The defect is B-cell autonomous, as reconstitution of *Dapp1*$^{-/-}$ mice with wild-type B cells restored the IgG3 response to TNP–Ficoll.

As an IgG3 response to the TI-II capsular polysaccharide antigen of *Streptococcus pneumoniae* has been shown to be required for protection against infection, Fournier *et al.* looked at the susceptibility of *Dapp1*$^{-/-}$ mice to this pathogen. As expected, *Dapp1*$^{-/-}$ mice vaccinated with the *S. pneumoniae* capsule antigen did not produce IgG3 antibodies, and after vaccination, these mice were more susceptible to infection with live bacteria. The authors therefore suggest that mutations of DAPP1 might be responsible for some of the unexplained immunodeficiencies that predispose individuals to infection by bacterial pathogens with a polysaccharide capsule.

Kirsty Minton

References and links

ORIGINAL RESEARCH PAPER Fournier, E. *et al.* The B cell SH2/PH domain-containing adaptor Bam32/DAPP1 is required for T cell-independent II antigen responses. *Curr. Biol.* 25 September 2003 (doi:10.1016/S0960982203007036)

FURTHER READING Kurosaki, T. Regulation of B-cell signal transduction by adaptor proteins. *Nature Rev. Immunol.* **2**, 354–363 (2002)