IN BRIEF

IMMUNE REGULATION

TIPE2, a negative regulator of innate and adaptive immunity that maintains immune homeostasis.

Sun, H. *et al. Cell* **133**, 415–426 (2008)

A newly discovered member of the tumour-necrosis-factor-α-induced protein 8 (TNFAIP8) family known as TIPE2 has been identified as a crucial regulator of immune responses. This protein was found to negatively regulate T-cell activation, as well as Toll-like receptor signalling in innate immune cells and B cells. Accordingly, TIPE2-deficient mice spontaneously developed fatal autoimmunity and were more susceptible to endotoxin-induced septic shock than wild-type mice. Closer examination of the molecular function of TIPE2 revealed its ability to inhibit the pro-inflammatory activator protein 1 (AP1) and nuclear factor-κB (NF-κB) pathways. Furthermore, TIPE2 promoted activation-induced cell death and FAS-ligand-mediated apoptosis of T cells. The finding that TIPE2 binds caspase-8, an apoptosis initiator and a regulator NF-κB, indicates that TIPE2 might influence immunoreceptor signalling pathways and apoptosis, in part, through this physical interaction.

B-CELL SIGNALLING

Foxo1 directly regulates the transcription of recombination-activating genes during B cell development.

Amin, R. H. & Schlissel, M. S. *Nature Immunol.* 11 May 2008 (doi:10.1038/ni.1612)

The authors sought to determine what factors were involved in the regulation of recombination-activating gene 1 (RAG1) and RAG2 during B-cell development. Using a retroviral cDNA library screen, they found that the stress-regulated protein GADD45a induced *Rag1* transcription through the activation of the kinase p38 and the transcription factor FOXO1, and that FOXO1 could bind directly to the *Rag* locus. Further analysis showed that FOXO1 also regulated *Rag1* transcription in developing primary B cells and 'knockdown' of FOXO1 expression resulted in reduced *Rag1* and *Rag2* transcription in a model of receptor editing. In addition, they found that the suppression of *Rag1* transcription in both pro-B cells and immature B cells, induced by interleukin-7 receptor and B-cell receptor signalling, respectively, was through, in part, the PI3K- and AKT-signalling pathway. Inhibition of AKT increased *Rag1* transcription and decreased FOXO1 phosphorylation.

NKT CELLS

Impact of bacteria on the phenotype, functions, and therapeutic activities of invariant NKT cells in mice.

Kim, S. *et al. J. Clin. Invest.* 1 May 2008 (doi:10.1172/JCI33071)

It is known that repeated stimulation of invariant natural killer T (*i*NKT) cells with the activating ligand α-galactosylceramide (α-GalCer) results in *i*NKT-cell anergy. Microorganisms can also activate *i*NKT cells, so Kim *et al.* examined the effect of prior exposure to bacteria on α-GalCer-mediated activation of *i*NKT cells. They found that *i*NKT cells in mice that were exposed to α-GalCer following bacterial infection were hyporesponsive and could not induce the expression of CD86 or CD69 by B cells and dendritic cells or induce interferon-γ production by NK cells. The therapeutic potential of α-GalCer might be compromised in infected individuals, as α-GalCer was less effective at inhibiting the development of tumour metastases or experimental autoimmune encephalomyelitis in mice pre-treated with bacteria.