of the BCR. They also showed that when internalization and phosphorylation are mutually exclusive (as was observed experimentally), responses to low-avidity antigens are enhanced — this could have physiological implications for the initial detection of antigens.

The authors suggest that their model might be helpful in explaining some of the disparate observations in the literature regarding BCR spatial regulation, and say that further studies to identify how receptors are selected for internalization are required. The experimental results presented in this paper have certainly provided a useful platform from which we will hopefully be able to decipher the complex dynamics of BCR signalling and internalization.

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ORIGINAL RESEARCH PAPER Hou, P. *et al.* B cell antigen receptor signaling and internalization are mutually exculsive events. *PLoS Biol.* **4**, e200 (2006)

cultured with MIC ligands, and growth of NKG2D$^-$CD8$^+$ T cells was inhibited.

However, unlike CD8$^+$ T cells, prolonged exposure to MIC ligands does not seem to lead to the downregulation of NKG2D by CD4$^+$ T cells. Therefore, the authors conclude that in tumours that express MIC ligands, activation of T cells expressing NKG2D will result in proliferation and the secretion of CD95L that could lead to the elimination of CD95-sensitive tumour cells. However, after prolonged exposure to MIC ligands, CD8$^+$ T cells will downregulate the NKG2D receptor and become susceptible to the growth-suppressive effects of CD95L, which is continually produced by the expanding population of NKG2D$^+$CD4$^+$ T cells.

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ORIGINAL RESEARCH PAPER
Groh, V., Smythe, K., Dai, Z. & Spies, T. Fas ligand-mediated paracrine T cell regulation by the receptor NKG2D in tumor immunity. *Nature Immunol.* 28 May 2006 (doi:10.1038/ni1350)

AUTOIMMUNITY

Multipronged effects of *FOXP3* mutations

Mutations in the transcription factor forkhead box P3 (*FOXP3*) are responsible for a rare autoimmune disease in young boys known as IPEX (immunodysregulation, polyendocrinopathy and enteropathy, X-linked syndrome). At least in mice, FOXP3 has a crucial role in the development and function of CD4$^+$CD25$^+$ regulatory T (T_{Reg}) cells. Therefore, it has been suggested that a lack of these regulatory cells might contribute to disease in humans, as has been shown in the mouse model of the disease, Scurfy mice. However, Maria Grazia Roncarolo and colleagues now report that the human disease is not necessarily the result of a deficiency of T_{Reg} cells but instead because these cells are dysfunctional. Moreover, they show that effector T cells from patients with IPEX also have a functional defect.

To carry out their studies, four children with IPEX of varying disease severity and with various *FOXP3* mutations were studied, and so correlations could be drawn between different *FOXP3* mutations and T_{Reg}-cell generation and function. The authors were surprised to see that T_{Reg}-cell numbers were normal in most of the patients and were comparable to those of age-matched control donors. Moreover, these T_{Reg} cells had a normal phenotype, including expression of GITR (glucocorticoid-induced tumour-necrosis-factor-receptor-related protein) and CTLA4 (cytotoxic T-lymphocyte antigen 4), and they displayed normal T_{Reg}-cell characteristics, such as anergy and lack of interferon-γ (IFNγ) production after activation.

However, the ability of T_{Reg} cells from the IPEX patients to suppress the proliferation of CD4$^+$CD25$^-$ effector T cells was reduced compared with T_{Reg} cells from normal donors. The degree of defective suppression varied depending on the type of *FOXP3* mutation, the strength of the activation stimuli and the genotype of the target effector T cells. For example, when provided with a 'weak' stimulus (CD3-specific antibody presented by allogeneic antigen-presenting cells), T_{Reg} cells from IPEX patients who express the mutant FOXP3 protein could suppress *in vitro* proliferation of effector T cells from control donors. But when provided with a 'strong' stimulus (beads coated with CD3- and CD28-specific antibody), T_{Reg} cells from these same patients failed to suppress effector T-cell proliferation. Notably, activated T_{Reg} cells from a patient with a *FOXP3* mutation that completely ablated FOXP3 expression were unable to suppress effector T-cell proliferation.

During these studies the authors also noted that, when autologous effector T cells were used as targets for suppression, activated T_{Reg} cells from all four patients were unable to suppress *in vitro* proliferation, independent of the activation conditions used. This led the authors to investigate whether the effector T cells from IPEX patients were defective. Despite their disparate clinical phenotypes, effector T cells from all four patients had a markedly reduced ability to secrete interleukin-2 and IFNγ following T-cell receptor (TCR)-mediated activation compared with cells from normal donors. This defect was not apparent when the cells were activated with phorbol ester and ionomycin, which activate T cells in a TCR-independent manner. This finding indicates that FOXP3 could have a role in regulating the effector T-cell functions that depend on TCR signalling, as well as in regulating T_{Reg}-cell function.

So, these findings indicate that, in contrast to the disease in Scurfy mice, human IPEX is not necessarily due to the absence of T_{Reg} cells but rather to their impaired suppressive function, together with altered effector T-cell function.

Lucy Bird

ORIGINAL RESEARCH PAPER Bacchetta, R. *et al.* Defective regulatory and effector T cell functions in patients with *FOXP3* mutations. *J. Clin. Invest.* **116**, 1713–1722 (2006)