rearrangements, but this has not been shown *in vivo* in non-receptor-transgenic mice. Using various approaches, the authors showed that, in their system, tolerance is the result of developmental arrest followed by receptor editing concomitant with upregulated expression of recombination-activating genes (*Rag1* and *Rag2*). It was not associated with clonal deletion of Igκ$^+$ B cells or proliferation of Igλ$^+$ cells.

This technique could, in theory, be used for any type of antigen receptor for which there is a specific monoclonal antibody. The authors also suggest that an adoptive-transfer approach, using macro-self-transgenic mice as hosts for the adoptive transfer of normal or mutant bone marrow, could speed up the screening of mutant mice for immune-tolerance phenotypes, which currently requires time-consuming and expensive crossing with receptor-transgenic mice.

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References and links

ORIGINAL RESEARCH PAPER Ait-Azzouzene, D. *et al*. An immunoglobulin Cκ-reactive single chain antibody fusion protein induces tolerance through receptor editing in a normal polyclonal immune system. *J. Exp. Med.* **201**, 817–828 (2005)

delayed or reduced T-cell-mediated immune response. For example, in the autoimmunity model, wild-type mice immunized with myelin oligodendrocyte glycoprotein rapidly developed experimental allergic encephalomyelitis, whereas in transgenic mice, there was a significant delay before symptoms began.

The authors conclude that, as they saw no intrinsic defects in proliferation or cell death of the transgenic T cells, the defective immune responses probably result from insufficient retention of circulating T cells in the lymph nodes, where they might meet cognate antigen. Downregulation of $S1P_1$ is therefore required to maximize T-cell priming, and the next step will be to identify the factors that regulate this *in vivo*.

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References and links

ORIGINAL RESEARCH PAPER Chi, H. & Flavell, R. A. Regulation of T cell trafficking and primary immune responses by sphingosine 1-phosphate receptor 1. *J. Immunol.* **174**, 2485–2488 (2005)

IN BRIEF

B-CELL DEVELOPMENT

Basal immunoglobulin signaling actively maintains developmental stage in immature B cells.

Tze, L. E. *et al*. *PLoS Biol.* **3**, e82 (2005).

This study shows that basal signalling through the B-cell receptor (BCR) of immature B cells is crucial to suppress expression of the recombination-activating genes (*RAG1* and *RAG2*) and to prevent 'back-differentiation' to the pro-B-cell stage. Therefore, such basal signalling is important to maintain allelic exclusion of the immunoglobulin light chains (which rearrange at this stage of development) and ensure self-tolerance. When basal IgM signalling in immature B cells was inhibited, microarray analysis and flow cytometry showed the upregulation of genes and proteins that are selectively expressed by pro-B cells. The requirement for basal signalling to maintain B-cell development could be an important quality-control mechanism to test for a functional BCR.

ANTIBODY RESPONSES

MutSα binds to and promotes synapsis of transcriptionally activated immunoglobulin switch regions.

Larson, E. D. *et al*. *Curr. Biol.* **15**, 470–474 (2005).

Class-switch recombination (CSR) — the process by which a new immunoglobulin constant region is joined to the rearranged heavy-chain variable (VDJ) region — requires activation-induced cytidine deaminase (AID) and the mismatch-repair heterodimer MutSα (MSH2–MSH6). This study clarifies the role of MutSα by showing that it specifically binds to regions of G4 DNA (four DNA strands associated through bonds between guanines) in transcribed switch regions that are produced during CSR and to the U•G mismatches that are created by AID. Binding of MutSα promoted interactions between the G-rich loops, thereby leading to switch-region synapsis.

NATURAL KILLER CELLS

A subset of natural killer cells achieve self-tolerance without expressing inhibitory receptors specific for self MHC molecules.

Fernandez, N. C. *et al*. *Blood* 22 Feb 2005 (doi:10.1182/blood-2004-08-3156).

Natural killer (NK) cells are thought to express at least one inhibitory receptor specific for a self-MHC class I molecule, and this is thought to maintain NK-cell self-tolerance. However, Fernandez *et al.* detected a population of NK cells that lack expression of all known inhibitory receptors specific for self-MHC class I molecules. These NK cells were hyporesponsive *in vitro* when cultured with either cells lacking cell-surface expression of MHC class I molecules or tumour cells expressing ligands for NK-cell activating receptors. Similar hyporesponsiveness was observed *in vivo*, as these NK cells were inefficient at mediating rejection of bone marrow lacking cell-surface expression of MHC class I molecules, indicating that, for some NK cells, self-tolerance is not a result of inhibitory-receptor interaction with self-MHC class I molecules but of hyporesponsiveness to self.