## WEB WATCH

**Developing-world focus**

- http://www.scidev.net

Advances in science and technology could be of profound benefit to people in developing countries; yet, these are often the people who have the least access to such information. *SciDev.Net* is a free-access web resource, launched in December 2001, that is dedicated to covering scientific and technology issues that are relevant to the needs of developing countries. *SciDev.Net* is a non-profit-making organization that is supported financially by several international agencies. It is run by a board of trustees, many of whom are based in developing countries, and the goal of the site is to provide, "informed debate on ways of applying science and technology to social and economic development in an environmentally responsible way". The site is sponsored by *Nature* and *Science*, both of which have agreed to provide free access to several articles each week.

The site contains news, feature articles, opinions, editorials and book reviews, as well as a section called 'How do I…?', which provides guidelines on topics such as writing research grants or becoming a science journalist. You can also search for meetings, and check for available jobs and grants from various agencies. The 'Dossier' section provides introductory material and resource guides. Future 'Dossier' topics to watch out for include AIDS/HIV, gender and science, GM crops and food, malaria, and technology transfer. The 'Links' section provides access to scientific organizations, news sources and journals, as well as aid and funding agencies. Future plans include regional gateways, with the possibility of some material being published in the appropriate language for that region.

*Elaine Bell*

TRANSPLANTATION

# Mismatch advantages

Allogeneic bone-marrow (BM) transplantation has greatly improved the treatment of leukaemia. Conventionally, BM transplants are performed between individuals that are matched at their MHC loci (but differ with respect to 'minor' antigens). Donor T cells that recognize recipient minor antigens mediate a graft-versus-leukaemia (GVL) effect, but can also cause graft-versus-host disease (GVHD). However, an MHC-matched donor can be found for only a proportion of patients. Full MHC-haplotype-mismatched BM grafts have been made possible by depleting T cells from the graft (which reduces the otherwise lethal GVH reactions across the MHC barrier), but this leads to a higher incidence of relapse due to a decrease in the GVL effect, and a greater risk of graft rejection. Now, Ruggeri and colleagues report in *Science* that certain MHC mismatches between BM donors and recipients might, in fact, be advantageous — donor natural killer (NK)-cell alloreactivity correlates with the elimination of leukaemia relapses and graft rejection, and protects patients against GVHD.

NK cells, unlike T cells, are activated when they recognize an absence of MHC class I molecules. When MHC class I ligands are present, killer inhibitory receptors (KIRs) on the NK cells are engaged and the cells are not activated. Ruggeri *et al.* reasoned that mismatched BM transplants might, therefore, trigger NK-cell alloreactivity. To assess the effect of

AUTOIMMUNITY

# Mistaken identity

**The long-standing puzzle of why nuclear antigens are targeted in systemic autoimmune diseases might have been resolved. Elizabeth Leadbetter and co-workers, reporting in *Nature,* show that autoreactive B cells can be triggered by self-antigens that look foreign to innate receptors.**

**All of us have potentially autoreactive B cells in our circulation, but these are normally kept in check. When tolerance breaks down, antibodies that are specific for DNA, RNA, nucleoproteins and immunoglobulins dominate the autoimmune response. But, it has never been clear why these specificities are selected.**

**Previous studies had indicated that transgenic B cells that are specific for IgG2a (a common autoantigen in systemic lupus erythematosus; SLE) can be activated by immune complexes but not monomeric antibodies. The authors have now shown that only certain immune complexes are effective — IgG2a–nucleosome complexes stimulate the B cells, but IgG2a–hapten complexes do not. Moreover, digestion with DNAse ablated the activating potential of IgG2a–nucleosome complexes, which showed that DNA was the key. It was predicted that the immune complexes activate B cells by simultaneously engaging the B-cell receptor (BCR) and a co-receptor.**

**Complement receptors — the most obvious co-receptor candidates — were ruled out, so the authors looked to the Toll-like receptors (TLRs). TLRs recognize conserved molecular signatures that are characteristic of microorganisms, such as hypomethylated CpG motifs in DNA. Importantly, mammalian DNA contains some CpG motifs, so it is possible that IgG2a–nucleosome immune complexes might co-ligate the IgG2a-specific BCR and a TLR.**

**To test this idea, the transgenic mice were crossed with mice that were deficient in Myd88, an adaptor molecule that is essential for most Tlr signalling pathways. Strikingly, *Myd88*$^{-/-}$ transgenic B cells were unresponsive to IgG2a–chromatin immune complexes.**

**The receptor that recognizes CpG motifs, Tlr9, is unique in that it requires endosome acidification for signalling, and specific inhibitors of endosome acidification, such as chloroquine, were shown to block the transgenic B-cell responses to IgG2a–chromatin complexes.**

this, they analysed the correlation of donor NK-cell alloreactivity with rejection, relapse and GVHD in patients with acute myeloid leukaemia (AML). Because NK cells distinguish between groups of MHC molecules, rather than single variants, Ruggeri *et al.* were able to divide the donor–recipient pairs into two groups on the basis of the presence or absence of KIR–ligand incompatibility in the GVH direction. KIR–ligand incompatibility correlated with protection of patients against graft rejection, leukaemia relapse and GVHD. The survival rate after five years for AML patients with KIR-mismatched donors was 60%, which is a much better outcome than for matched, unrelated donor transplants.

To explore this effect further, the group then performed experiments in mouse model systems. The transfer of human alloreactive NK-cell clones to non-obese diabetic (NOD) or severe combined immunodeficient (SCID) mice — which lack B cells and T cells — eradicated previously transplanted AML cells and prevented the death of the mice. In mismatched mouse transplants, the infusion of donor alloreactive NK cells also permitted the use of less drastic pre-transplant conditioning regimens. Infusion of NK cells after the BM transplant was able to convert mixed chimeras to stable full-donor chimerism. Importantly, the use of alloreactive NK-cell infusions permitted the use of otherwise lethal doses of allogeneic T cells for immune reconstitution — this NK-cell-mediated protection against GVHD seems to be due to the elimination of recipient antigen-presenting cells by the donor NK cells.

This new work has important implications for transplantation therapy. The most readily applicable concept is that choosing donors with KIR–ligand incompatibility in the GVH direction offers a striking advantage for survival. In the future, it will be interesting to see how the mouse models, in which donor alloreactive NK cells were infused as a supplement to pre-transplant conditioning, will translate to a clinical setting.

*Elaine Bell*


**References and links**

**ORIGINAL RESEARCH PAPER** Ruggeri, L. *et al.* Effectiveness of donor natural killer cell alloreactivity in mismatched hematopoietic transplants. *Science* **295**, 2097–2100 (2002)

**FURTHER READING** Murphy, W. J. *et al.* Immunobiology of natural killer cells and bone marrow transplantation: merging basic and preclinical studies. *Immunol. Rev.* **181**, 279–289 (2001)


**Co-ligation of the BCR and a TLR is an attractive mechanism to explain how autoreactive B cells that are specific for immunoglobulin or nuclear components become activated in autoimmunity. It might explain also why SLE patients benefit from chloroquine treatment.**

*Jennifer Bell*


**References and links**

**ORIGINAL RESEARCH PAPER** Leadbetter, E. A. *et al.* Chromatin–IgG complexes activate B cells by dual engagement of IgM and Toll-like receptors. *Nature* **416**, 603–607 (2002)

**FURTHER READING** Shlomchik, M. J., Craft, J. E. & Mamula, M. J. From T to B and back again: positive feedback in systemic autoimmune disease. *Nature Rev. Immunol.* **1**, 147–153 (2001)

**WEB SITES**

**Ann Marshak-Rothstein's lab:** http://www.bumc.bu.edu/Departments/PageMain.asp?Page=2831&DepartmentID=304

**Encyclopedia of Life Sciences:** http://www.els.net/

autoimmune disease: pathogenesis | immune tolerance mechanisms | antibody responses: development


# IN BRIEF

IMMUNE REGULATION

## A neuronal receptor, neuropilin-1, is essential for the initiation of the primary immune response.

Tordjman, R. *et al. Nature Immunol.* **3**, 477–482 (2002)

Neuropilin-1 is a transmembrane receptor that is involved in axon guidance. This study shows that neuropilin-1 is expressed by dendritic cells (DCs) and T cells, and mediates a homophilic interaction between these two cell types. Preincubation of either T cells or DCs with blocking neuropilin-1-specific antibodies blocked T-cell proliferation, which indicates that the expression of neuropilin-1 on both cell types is important for the initiation of an immune response.

T-CELL SIGNALLING

## c-Jun $NH_2$-terminal kinase (JNK)1 and JNK2 have distinct roles in $CD8^+$ T-cell activation.

Conze, D. *et al. J. Exp. Med.* **195**, 811–823 (2002)

## c-Jun $NH_2$-terminal kinase (JNK)1 and JNK2 signaling pathways have divergent roles in $CD8^+$ T-cell-mediated antiviral immunity.

Arbour, N. *et al. J. Exp. Med.* **195**, 801–810 (2002)

The c-Jun $NH_2$-terminal kinase (JNK) signalling pathway is induced by cytokine signalling and stress stimuli, and it has been implicated in the control of T-cell proliferation and differentiation. These studies used *Jnk1*$^{-/-}$ and *Jnk2*$^{-/-}$ mice to investigate the physiological role of these kinases in $CD8^+$ T-cell responses. Conze *et al.* showed that Jnk2 deficiency resulted in increased interleukin-2 (IL-2) production and the increased proliferation of $CD8^+$ T cells. By contrast, *Jnk1*$^{-/-}$ $CD8^+$ T-cell populations were unable to expand after antigen stimulation, even in the presence of endogenous IL-2. Arbour *et al.* investigated the role of JNKs in antiviral T-cell immunity. After viral infection, virus-specific $CD8^+$ T-cell expansion was reduced in *Jnk1*$^{-/-}$ mice compared with wildtype mice, but was increased in *Jnk2*$^{-/-}$ mice. Therefore, Jnk1 and Jnk2 have distinct roles in $CD8^+$ T-cell responses.

ISOTYPE SWITCHING

## The AID enzyme induces class switch recombination in fibroblasts.

Okazaki, I. M. *et al. Nature* **416**, 340–345 (2002)

The putative RNA-editing enzyme AID (activation-induced cytidine deaminase) is expressed only in activated B cells and is essential for class-switch recombination (CSR). To examine the molecular basis of CSR, an artificial substrate was developed that allows the detection of CSR by the expression of a green-fluorescent-protein-based marker. Using this substrate, the authors found that the ectopic expression of AID in non-B cells, such as fibroblast and T-cell lines, was sufficient to induce CSR, providing that the substrate was actively transcribed. This indicates that AID is the only B-cell-specific factor that is required for CSR at an active locus.