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

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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.