IMMUNODEFICIENCY

Natural killers need *NEMO*

The natural killer (NK) cells of patients who have a defect in the NF-κB pathway are not up to the job, according to a new study in *The Journal of Clinical Investigation*. But, the good news is that treatment with interleukin-2 (IL-2) can restore their killer potential.

Hypohidrotic ectodermal dysplasia with immunodeficiency (HED-ID) is an X-linked syndrome that results from mutations in the *NEMO* gene — which encodes inhibitor of κB kinase-γ (IKK-γ). IKK-γ is essential for the formation of a functional IKK complex, which phosphorylates IκBα; this allows the translocation of NF-κB to the nucleus and gene transcription. The immunodeficiency that is seen in patients with HED-ID is variable, but defects in both T- and B-cell responses have been reported.

Orange and colleagues studied three patients that had HED-ID; two of these were shown to have new mutations in *NEMO*. One of these patients had recurrent infections with cytomegalovirus (CMV), which is indicative of defective NK-cell activity. This led the authors to examine all three patients for NK-cell defects. The numbers of NK cells in the peripheral blood of these patients were within the normal range. However, the cytotoxic activity of the NK cells against tumour-cell targets *in vitro* — a classic measure of NK-cell function — was completely abolished. A control experiment showed that the patients' NK cells were effective in an antibody-dependent cellular cytotoxicity assay, which indicates that the cytotoxic effector machinery was intact.

Next, the authors investigated whether it might be possible to correct the *NEMO*-dependent NK-cell defect. *In vitro* treatment with IL-2, which is a potent enhancer of NK-cell activity, restored the cytotoxic activity of NK cells from patients with HED-ID. An electrophoretic mobility-shift assay then showed that stimulation with IL-2 induced NF-κB activity in these NK cells. These *in vitro* findings provided the rationale for treating the patient who suffered from recurrent CMV infection with IL-2. Promisingly, *ex vivo* NK-cell cytotoxicity was apparent immediately and persisted for four weeks after treatment. So, in addition to defining a new molecular pathway in NK-cell activity, this study highlights a potential therapy to restore antiviral innate immunity in HED-ID patients.

Jennifer Bell

References and links

ORIGINAL RESEARCH PAPER Orange, J. S. *et al.* Deficient natural killer cell cytotoxicity in patients with IKK-γ/NEMO mutations. *J. Clin. Invest.* **109**, 1501–1509 (2002)

IN BRIEF

T-CELL SIGNALLING

Induction of T helper type 2 immunity by a point mutation in the LAT adaptor.

Aguado, E. *et al. Science* **296**, 2036–2040 (2002)

A LAT mutation that inhibits T-cell development yet induces lymphoproliferation.

Sommers, C. L. *et al. Science* **296**, 2040–2043 (2002)

The adaptor protein LAT (linker for activation of T cells) links the T-cell receptor (TCR) to downstream signalling effectors. Two groups have now generated mice that are homozygous for a mutation of a single LAT tyrosine residue (Tyr136) to investigate the role of this residue *in vivo*. Both groups report an early block in T-cell differentiation and the accumulation of polyclonal $CD4^+$ helper T cells in the periphery. Aguado *et al.* show that these T cells produce large quantities of type-2 cytokines, which results in tissue eosinophilia and the secretion of IgE and IgG1 by plasma cells. Sommers *et al.* analysed TCR signalling and showed that the activation of PLC-γ and NFAT, calcium signalling, IL-2 production and cell death are defective in these mice. These studies highlight the crucial role of LAT in T-cell development and homeostasis.

TRANSPLANTATION

Allogeneic β-islet cells correct diabetes and resist immune rejection.

Pericin, M. *et al. Proc. Natl Acad. Sci.* **99**, 8203–8206 (2002)

Usually, allogeneic MHC-incompatible cell grafts are rejected rapidly by immunocompetent hosts. Here, Pericin *et al.* successfully correct streptozotocin-induced diabetes by transplanting fully MHC-mismatched insulin-producing β-islet cells under the kidney capsule of recipient mice. This was made possible by the generation of a growth-regulated, transformed endocrine cell line that could be transplanted into recipients without contaminating passenger leukocytes. The grafts that controlled hyperglycaemia were not rejected for >100 days.

T-CELL RESPONSES

Programmed contraction of $CD8^+$ T cells after infection.

Badovinac, V. P., Porter, B. B. & Harty, J. T. *Nature Immunol.* **3**, 619–626 (2002)

Normally, the contraction phase of a T-cell response is correlated with clearance of the pathogen, but are these events mechanistically linked? This study indicates that for $CD8^+$ T cells, the contraction phase is actually pre-programmed and, unlike the expansion phase, it is not dependent on the continued presence of available antigen. The kinetics of the contraction phases of $CD8^+$ T-cell responses to viral or bacterial infection in mice were shown to be independent of the quantity of available antigen, duration of infection or magnitude of T-cell clonal expansion. These results indicate that the contraction of $CD8^+$ T-cell populations is programmed to occur even if a pathogen has not been cleared successfully.