Using R331 renal carcinoma cells that express caspase-8 (FLICE)-like inhibitory protein (FLIP), which inhibits TRAIL-DR5-mediated apoptosis, the authors showed that DR5-mediated tumour-cell apoptosis was essential for trimAb-mediated tumour rejection. Interestingly, only a minor population (10%) of DR5-susceptible tumour cells in the tumour burden was necessary for tumour rejection to occur in response to trimAb therapy. This rejection required the activation of CD8⁺ T cells, indicating that both tumour-cell apoptosis through DR5 and tumour-specific CTL responses were required for tumour eradication by trimAb therapy.

So, combining agonistic monoclonal antibodies that activate T cells (CD40 and CD137) with an agonistic monoclonal antibody that induces tumour-cell apoptosis (DR5) is an effective tumour-specific immunotherapy in mice. This combination therapy might be a potential strategy for cancer immunotherapy in humans.

Olive Leavy

ORIGINAL RESEARCH PAPER Uno, T. *et al.*
Eradication of established tumors in mice by a combination antibody-based therapy. *Nature Med.* 7 May 2006 (doi:10.1038/nm1405)

transferred to naive mice that were deficient for both RAG2 and the common cytokine receptor γ -chain. These mice, in addition to being B-cell- and T-cell-deficient, also completely lack NK cells. Subsequent challenge with DNFB resulted in a vigorous CHS response in these mice, confirming the ability of sensitized NK cells to mediate a hapten-specific memory response independently of B cells and T cells. These transferable hapten-specific NK memory cells were shown to localize in the donor's liver but not in the spleen.

These results describe an unexpected function for NK cells and indicate that a B-cell- and T-cell-independent adaptive immune response exists in mammals.

Olive Leavy

ORIGINAL RESEARCH PAPER O'Leary, J. G., Goodarzi, M., Drayton, D. L. & von Andrian, U. H.
T cell- and B cell-independent adaptive immunity mediated by natural killer cells. *Nature Immunol.* 7, 507–516 (2006)

CYTOKINES

IL-25 expels worms

Two papers published recently in *The Journal of Experimental Medicine* provide new insight into the development of protective T helper 2 (T_H2)-cell responses *in vivo*: they show that the cytokine interleukin-25 (IL-25) is an important regulator of T_H2-cell responses.

It has been suggested that IL-25 (also known as IL-17E) is involved in the development of T_H2-cell responses. Because immunity to infection with parasitic helminths is usually associated with T_H2-cell responses, both groups studied the role of IL-25 in immunity and inflammation *in vivo* using mouse models of infection with such parasites.

Owyang *et al.* showed that, although AKR mice are normally susceptible to infection with *Trichuris muris*, treatment with recombinant IL-25 induced resistance to infection with this parasite. Resistance to infection was associated with a T_H2-cell response, including increased production of IL-4, decreased production of interferon- γ (IFN γ) and increased numbers of goblet cells in the caecum. Consistent with these observations, although wild-type C57BL/6 mice infected with *T. muris* mount an efficient T_H2-cell response and are resistant to infection, IL-25-deficient C57BL/6 mice infected with *T. muris* failed to mount a T_H2-cell immune response and were unable to clear the worms from the gastrointestinal tract.

Similarly, Fallon *et al.* found that IL-25-deficient mice were unable to clear the parasitic helminth *Nippostrongylus brasiliensis* as rapidly as wild-type mice. Delayed clearance of the parasite was associated with delayed induction of T_H2-cell responses. For example, whereas in the presence of IL-25 large amounts of the T_H2 cytokines IL-4, IL-5 and IL-13 were detected 5 days after infection, in the absence of IL-25 cytokines were not observed until 10 days after infection.

Owyang *et al.* found that blocking T_H1-cell responses in IL-25-deficient mice infected with

T. muris reversed the decrease in production of T_H2 cytokines and enabled the mice to clear the infection. Therefore, in addition to a role in the efficient induction of T_H2-cell responses, IL-25 might have a role in the suppression of T_H1-cell responses. Consistent with this anti-inflammatory role, chronically infected IL-25-deficient mice developed severe intestinal inflammation that was associated with high levels of pro-inflammatory cytokines such as IFN γ and IL-17 in the caecum.

Using mice expressing a lacZ reporter construct in the *Il25* locus, Owyang *et al.* were able to show that subsets of CD4⁺ and CD8⁺ T cells in the caecal patch (which is a lymphoid follicle closely associated with the mucosal surface) of mice resistant to infection with *T. muris* express IL-25. Furthermore, Fallon *et al.* showed that a population of non-B-cell, non-T-cell KIT⁺Fc ϵ RI⁺ cells responded to IL-25 by producing large amounts of IL-4, IL-5 and IL-13. In resistant mice, the number of these cells in the mesenteric lymph nodes increased following infection with *N. brasiliensis*, whereas in IL-25-deficient mice the number of these cells remained static. The correlation between the number of these cells and the ability of the mice to clear *N. brasiliensis* led the authors to suggest that these cells are an initial source of T_H2 cytokines following infection with *N. brasiliensis*.

These two studies clearly identify IL-25 as a regulator of T_H2-cell responses *in vivo* and, as Owyang *et al.* suggest, provide a new potential therapeutic target for the treatment of diseases associated with pathogenic T_H2-cell responses.

Karen Honey

ORIGINAL RESEARCH PAPERS Owyang, A. M. *et al.*
Interleukin 25 regulates type 2 cytokine-dependent immunity and limits chronic inflammation in the gastrointestinal tract. *J. Exp. Med.* 203, 843–849 (2006) | Fallon, P. G. Identification of an interleukin (IL)-25-dependent cell population that provides IL-4, IL-5, and IL-13 at the onset of helminth expulsion. *J. Exp. Med.* 203, 1105–1116 (2006)