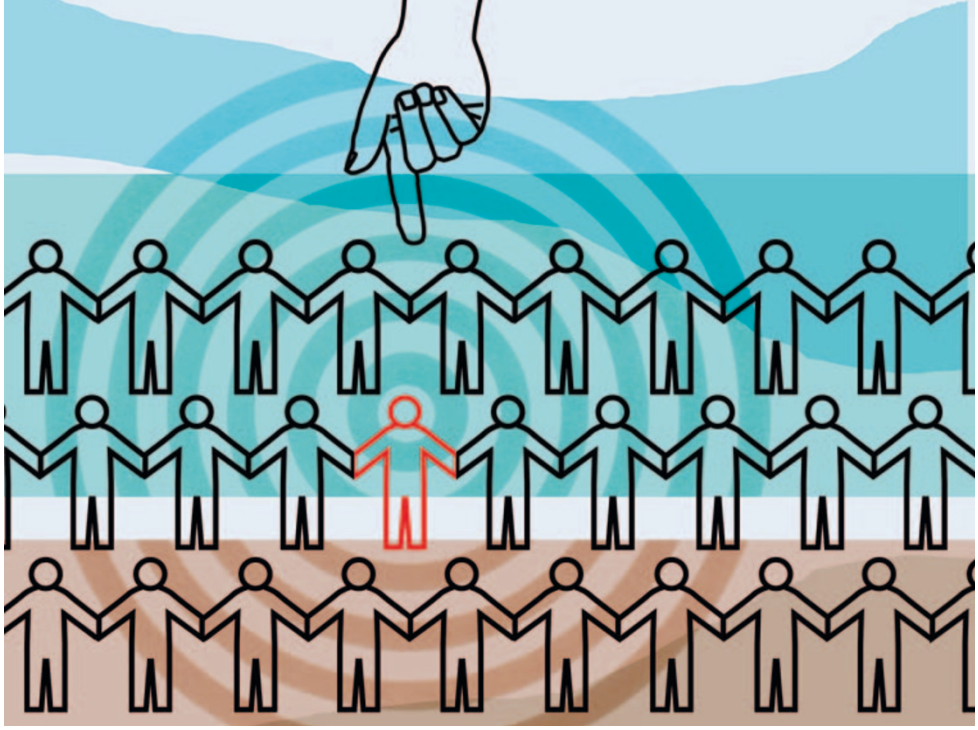

T-CELL ACTIVATION

CCL3 and CCL4 actively recruit CD8$^+$ T cells

It is clear that antigen-presenting cells, such as dendritic cells (DCs), are necessary mediators of the help provided by CD4$^+$ T cells to CD8$^+$ T cells. However, many questions remain regarding how these three cell types interact and whether such interactions are regulated or occur randomly. Answers to some of these questions have now been provided by a study published in *Nature* showing that naive CD8$^+$ T cells are actively recruited to sites of antigen-specific interactions between CD4$^+$ T cells and DCs.

In this study, Castellino *et al.* set out to test the hypothesis that CD8$^+$ T cells are actively recruited to DCs that are activated by CD4$^+$ T cells. When immunocompetent mouse recipients of OT-I T cells and OT-II T cells (CD8$^+$ and CD4$^+$ T cells that express a T-cell receptor specific for a peptide consisting of amino-acid residues 257–264 and 323–339 of ovalbumin (OVA), respectively) were immunized with OVA257–264 in adjuvant on both flanks, equal numbers of OT-I T cells were detected in both draining lymph nodes. However, if OVA323–339 was administered to one flank (with either OVA257–264 and adjuvant, or adjuvant alone being concomitantly administered to both flanks), the accumulation of OT-I T cells was greater in that draining lymph node than in the contralateral lymph node.

Furthermore, intravital two-photon microscopy showed that, in the presence of OT-II T cells, OT-I T cells came into contact with DCs pulsed with OVA323–339 more often than with unpulsed control DCs.

To investigate whether these observations were indicative of the active recruitment of CD8$^+$ T cells to DCs that are activated by CD4$^+$ T cells, the mice were administered antibodies specific for candidate chemokines. Antibodies specific for CC-chemokine ligand 3 (CCL3) or CCL4 inhibited the accumulation of OT-I T cells in lymph nodes containing activated OT-II T cells. Both CD4$^+$ T cells and DCs were found to produce CCL3 and CCL4 when activated. Consistent with a role for these chemokines in the recruitment of CD8$^+$ T cells, OT-I T cells isolated from lymph nodes draining the site of immunization expressed the receptor for CCL3 and CCL4, CC-chemokine receptor 5 (CCR5), whereas OT-I T cells from non-draining lymph nodes did not.

Furthermore, *Ccr5*$^{-/-}$ polyclonal CD8$^+$ T cells did not accumulate in lymph nodes containing activated CD4$^+$ T cells and (in the presence of OT-II T cells) contacted DCs presenting OVA323–339 with the same frequency as they contacted control DCs. Functionally, although administration of antibodies specific for CCL3 and CCL4 did not prevent the clonal expansion of OT-I T cells or their acquisition of effector function, the size and effectiveness of the memory OT-I T-cell population was markedly reduced.

This study provides clear evidence that the ability of CD4$^+$ T cells to provide help for the generation of an optimal memory CD8$^+$ T-cell population is not a result of random cell–cell interactions but is a highly regulated process.

Karen Honey

ORIGINAL RESEARCH PAPER Castellino, F. *et al.* Chemokines enhance immunity by guiding naive CD8$^+$ T cells to sites of CD4$^+$ T cell–dendritic cell interaction. *Nature* **440**, 890–895 (2006)

In the news

ROCKY ROAD FOR GENE THERAPY

Gene therapy — once heralded as a miracle cure for some genetic disorders — has had a chequered past, and recent developments do little to bestow confidence in this approach.

Although initially thought to be a success, a clinical trial that began in 1999 was temporarily halted when three out of eleven patients developed leukaemia following gene therapy to treat X-linked severe combined immunodeficiency (X-SCID). This unfortunate outcome led US-based scientists to re-evaluate this approach using mice to study its long-term effects. These scientists have now shown that treatment of immunodeficient mice by replacing the defective gene encoding the common cytokine receptor γ-chain (*Il2rg*) with the normal version, as was done in the human trial, caused lymphomas in a third of the animals in later life (*Nature*, 27 April 2006). Dr Niels-Bjarne Woods, one of the scientists who carried out the research, was "surprised by the strength of the association" (*BBC News*, 27 April 2006) and concluded that "preclinical experimental treatments involving transgenes should include long-term follow-up" (*Nature*, 27 April 2006).

Moreover, the development of cancer in the mice was not because insertion of the gene led to activation of the oncogene *Lmo2*, as was originally suggested to explain the complication in humans, but because IL-2Rγ itself has oncogenic properties. So, the development of leukaemia "may in fact have been an inevitable consequence of the treatment, not just a rare side effect" (*New Scientist*, 29 April 2006).

But Professor Adrian Thrasher, of Great Ormond Street Hospital, London, UK, who has successfully treated nine children using this approach and seen no cases of leukaemia, told the BBC that "The researchers have taken artificially high doses of these genes and given them to animals." (*BBC News*, 27 April 2006).

Lucy Bird