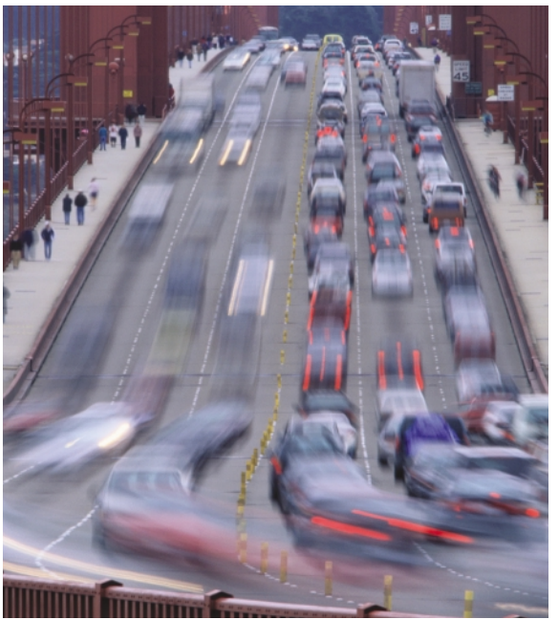
LYMPHOCYTE MIGRATION

Modes of transport



Cell migration is regulated by the Rho family of GTPases, which control membrane polarization and cytoskeletal dynamics. Activation of one family member, Rac, is crucial for generation of lamellipodia and for cell movement. Although several molecules have been identified which function as guanine nucleotide-exchange factors for Rac, the upstream signalling cascade leading to Rac activation is not well characterized. CDM family proteins might be involved in this cascade. Genetic studies have shown the importance of these proteins in cellular migration in *Caenorhabditis elegans* and *Drosophila melanogaster*, but the physiological relevance of these proteins in mammals is unknown. Fukui and colleagues now report in *Nature* a vital role for Dock2 — a haematopoietic cell-specific CDM family member — in lymphocyte, but not monocyte, chemotaxis.

To study the physiological role of Dock2, Fukui and colleagues generated *Dock2*$^{-/-}$ mice. The cellularity of secondary lymphoid organs was reduced in the *Dock2*$^{-/-}$ mice, although the proportion of monocytes was increased, indicating that lymphocyte homing might be impaired. To investigate the ability of lymphocytes to migrate to lymph nodes or spleen, fluorescently labelled *Dock2*$^{-/-}$ and *Dock2*$^{+/-}$ CD4^{+} T cells or B cells were injected into wild-type mice. The migratory capacity of the *Dock2*$^{-/-}$ cells was considerably reduced in comparison with the *Dock2*$^{+/-}$ cells.

Next, the authors analysed the movement of *Dock2*$^{-/-}$ splenic T and B cells in response to several chemokines. Whereas T and B cells from *Dock2*$^{+/-}$ mice migrated in response to secondary lymphoid tissue chemokine (SLC), stroma-derived factor 1 (SDF-1) and B-lymphocyte chemoattractant (BLC), *Dock2*$^{-/-}$ cells showed no response to these chemokines.

As *Dock2*$^{-/-}$ lymphocytes failed to respond to these chemokines *in vitro*, Fukui and colleagues carried out further analysis of the *Dock2*$^{-/-}$ mice to see if the lack of response affected their phenotype. Several abnormalities were identified, including: a defect in the emigration of mature thymocytes from the thymus, abnormal thymus architecture, atrophy of lymphoid follicles in peripheral lymphoid organs and loss of marginal zone B cells in the spleen. Several of these abnormalities were similar to those observed in mice lacking certain chemokine receptors. These results indicate that lymphocyte and myeloid cell migration are regulated by distinct signalling pathways.

Jenny Buckland

References and links

ORIGINAL RESEARCH PAPER Fukui, Y. *et al*. Haematopoietic cell-specific CDM family protein DOCK2 is essential for lymphocyte migration. *Nature* **412**, 826–831 (2001)

TUMOUR IMMUNOLOGY

Manipulating melanoma

Although tumour-specific T cells can be isolated from cancer patients, their ability to attack the tumour and induce regression is often impaired, possibly because tumour-antigen presentation is suboptimal. Several studies have addressed this issue by stimulating antigen-presenting cells with anti-CD40 antibodies, in conjunction with tumour-antigen immunization, to enhance weak anti-tumour T-cell responses. However, a recent study in *Proceedings of the National Academy of Sciences* now indicates that the anti-CD40 approach to manipulating tumour responses should be applied with caution — treatment of mice bearing melanoma tumours with anti-CD40 alone enhanced the deletion of tumour-specific CD8^{+} T cells.

Kedl and colleagues developed a mouse melanoma model system in which the B16 melanoma cell line transfected with an ovalbumin (OVA) peptide was injected intradermally, and CD8^{+} T-cell responses to the peptide were tracked using a major histocompatibility complex (MHC)-tetramer construct. Because OVA-specific CD8^{+} T cells — although transient and non-functional — were detected in mice challenged with the tumour alone, the authors reasoned that anti-CD40 treatment, in the absence of tumour-antigen immunization, might be sufficient to rescue the function of the tumour-specific CD8^{+} T cells. This approach would be beneficial because it would not be necessary to determine the specific tumour antigens for each patient. Surprisingly, anti-CD40 treatment accelerated the deletion of tumour-specific CD8^{+} T cells, and co-immunization with vaccinia virus expressing OVA was required to prevent this deletion.

There is a long way to go in determining the precise signals required for manipulating the immune response to tumours *in vivo*. This study suggests caution in the use of anti-CD40 therapy, and future work must focus on the additional signals required to induce functional T-cell responses to tumours.

Elaine Bell

References and links

ORIGINAL RESEARCH PAPER Kedl, R. M. *et al.* CD40 stimulation accelerates deletion of tumor-specific CD8^{+} T cells in the absence of tumor-antigen vaccination. *Proc. Natl Acad. Sci. USA* **98**, 10811–10816 (2001).

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