CELL MIGRATION

Regulating 'stickiness': a key role for RAPL

Chemokine-triggered cell adhesion and integrin-mediated migration are crucial steps in the control of efficient immune-cell trafficking, yet the signalling molecules involved in these processes have been poorly defined. Now, Katagiri and colleagues report in *Nature Immunology* that the effector molecule RAPL (regulator of cell adhesion and polarization enriched in lymphoid tissues) has a vital role in immune-cell trafficking.

Recently, these researchers identified RAPL as an effector molecule for the GTPase RAP1, which is known to activate integrins, such as lymphocyte function-associated antigen 1 (LFA1) and very late antigen 4 (VLA4), and invoke cell polarization and motility. So, to investigate whether RAPL is important in immune-cell trafficking *in vivo*, they generated RAPL-deficient mice. T and B cells isolated from these mice had reduced ability to adhere to ICAM1 or VCAM1 (the ligands for LFA1 and VLA4, respectively) when exposed to chemokines, even though expression levels of the integrins or chemokine receptors were indistinguishable from those of wild-type cells. In addition, in the presence of chemokines, the RAPL-deficient lymphocytes had impaired adhesion and transmigration through endothelial-cell monolayers. In wild-type cells, chemokine-stimulated LFA1 activation by RAP1 is accompanied by lymphocyte polarization; however, the authors did not see a redistribution of LFA1 in the RAPL-deficient cells following chemokine stimulation, indicating a crucial role for RAPL in integrin activation.

Owing to these functional defects in lymphocyte adhesion and migration, RAPL-deficient mice had reduced T- and B-cell numbers in the spleen and lymph-node follicles, indicating impaired homing to peripheral lymphoid organs. Similarly, in the absence of RAPL, $CD11c^+$ splenic dendritic cells (DCs) and epidermal Langerhans cells showed markedly reduced migration to the white pulp of the spleen or draining lymph nodes after exposure to an inflammatory stimulus.

In addition to the key role of RAPL in cell trafficking to lymphoid organs, the authors showed that it was also required for movement within and out of lymphoid organs. Accordingly, mature T cells accumulated in the thymi of RAPL-deficient mice because of defective emigration of thymocytes. Also, the maturation of B cells in RAPL-deficient spleens was impaired, resulting in reduced numbers of mature B cells in the marginal zones and blood, consistent with a requirement for integrin-mediated compartmentalization during splenic B-cell maturation.

Together, these results confirm that RAPL is a key regulator of cell 'stickiness' through integrin activation and is thereby crucial for effective immune-cell adhesion and migration.

Lucy Bird

References and links

ORIGINAL RESEARCH PAPER Katagiri, K. *et al*. Crucial functions of the RAP1 effector molecule RAPL in lymphocyte and dendritic cell trafficking. *Nature Immunol*. 7 September 2004 (doi:10.1038/ni1111).

FURTHER READING Price, L. S. & Bos, J. L. RAPL: taking the Rap in immunity. *Nature Immunol*. **5**, 1007–1008 (2004).

IN BRIEF

NATURAL KILLER T CELLS

CD1d-restricted T cell activation by nonlipidic small molecules.

Van Rhijn, I. *et al*. *Proc. Natl Acad. Sci. USA* **101**, 13578–13583 (2004).

The natural killer T (NKT)-cell population contains cells expressing a diverse repertoire of T-cell receptors (TCRs), in addition to those expressing invariant Vα14 or Vα24 TCRs in mice and humans, respectively. Van Rhijn *et al.* derived a human CD1d-restricted T-cell line expressing a Vα2/Vβ21 TCR. This T-cell line was shown to be specific for small sulphated polyaromatic structures, and the magnitude of the T-cell response induced by these structures varied depending on their pattern of hydroxylation and methylation. Although these antigens are not physiological, they have similar chemical features to several commonly used antibiotics and anti-inflammatory drugs known to induce strong hypersensitivity reactions in humans, leading the authors to suggest that these drugs might function as NKT-cell antigens.

CYTOKINES

Itch E3 ligase-mediated regulation of TGF-β signaling by modulating Smad2 phosphorylation.

Bai, Y. *et al*. *Mol. Cell* **15**, 825–831 (2004).

Transforming growth factor-β (TGF-β) receptor signal-transduction pathways are known to involve protein ubiquitylation. In this study, using mouse embryonic fibroblasts deficient in the E3 ubiquitin ligase ITCH, the authors show that the TGF-β-induced arrest in cell growth is markedly reduced in the absence of ITCH. This correlated with decreased phosphorylation of SMAD2, a signal transducer activated by the TGF-β receptor. Further analysis indicated that ITCH interacts with SMAD2 and mediates its ubiquitylation, and that ITCH, SMAD2 and the TGF-β receptor associate in cells stimulated with TGF-β. Together, these observations led the authors to conclude that ITCH positively regulates TGF-β-induced SMAD2 phosphorylation by enhancing the interaction of SMAD2 with the TGF-β receptor in a ubiquitylation-dependent manner.

B-CELL SIGNALLING

Regulation of B-cell survival by BAFF-dependent PKCδ-mediated nuclear signalling.

Mecklenbräuker, I. *et al*. *Nature* 8 September 2004 (doi:10.1038/nature02955).

Serine/threonine protein kinase C-δ (PKC-δ)-deficient mice develop a lupus-like autoimmune phenotype similar to that of mice transgenic for the B-cell survival factor BAFF (B-cell activating factor). To investigate the mechanism of disease in PKC-δ-deficient mice, the authors studied the effects of BAFF-mediated signals on PKC-δ deficiency and observed that, in the absence of PKC-δ, B cells were unresponsive to the effects of BAFF-receptor signalling. Further analysis revealed that nuclear localization of PKC-δ had a pro-apoptotic effect on B cells and that recombinant BAFF prevented nuclear accumulation of PKC-δ. Together, these data indicate the existence of a novel pathway by which BAFF regulates B-cell survival — preventing PKC-δ localization to the nucleus.