T-CELL RESPONSES

Team tactics

Cooperation and coordination are the key to an effective type-2 immune response, but every team needs its captain. That's the conclusion of a study in *Immunity* by Fallon *et al.* Using compound cytokine-knockout mice, they have clarified the functional redundancy of the T helper 2 (T_H2) cytokines and confirmed that interleukin-4 (IL-4) is the 'David Beckham' of the 'T_H2 team'.

Previous analysis of cytokine-knockout mice has shown that deletion of a single gene often leads to no discernible phenotype. Furthermore, as IL-4 is crucial for the generation of T_H2 cells, its deletion also leads to the reduced expression of IL-5, IL-9 and IL-13 by T_H2 cells. Therefore, it is not possible to determine which functions are IL-4 specific and which are dependent on the other cytokines in a single IL-4-knockout animal. To resolve these issues, the authors created a panel of compound T_H2 cytokine-deficient mice, ranging from single to quadruple knockouts of IL-4, IL-5, IL-9 and IL-13. A first analysis of the immune function of these mice has been carried out in two *in vivo* models — intestinal challenge with the nematode parasite *Nippostrongylus brasiliensis*, which induces a T_H2 response, and a pulmonary granuloma model.

In the parasite model, Fallon *et al.* show that both IL-5 and IL-9 have a synergistic role in worm expulsion, but that even in the absence of the other T_H2 cytokines, IL-4 is effective. Eosinophilia and the goblet-cell response (mucus production) have been linked previously to IL-5 and IL-13, respectively, but these new studies show that IL-4 can independently induce both processes. Only when all four cytokines are absent does the immune response deviate to a T_H1 pattern.

In the T_H2 granuloma model, however, IL-4 alone was unable to induce the goblet-cell response, although IL-5-independent eosinophilia was still observed. In the absence of IL-5, IL-9 and IL-13, IL-4 was sufficiently potent to induce a T_H2 granuloma. By contrast, in a T_H1 granuloma model, knockout of all four cytokines enhanced the magnitude of granuloma formation, which demonstrates the reciprocal relationship between the T_H1 and T_H2 cytokines.

But, what is really interesting about these mice is the potential for future experiments. These mice offer a unique opportunity to study the T_H2 cytokines as an interdependent unit. Given the importance of the T_H2 response in human atopic diseases such as asthma, these mice will be a useful tool to investigate disease pathogenesis and design new therapies. Further experiments could help us to fully analyse the team tactics of the T_H2 response.

Kirsty Minton

References and links

ORIGINAL RESEARCH PAPER Fallon, P. G. *et al.* IL-4 induces characteristic Th2 responses even in the combined absence of IL-5, IL-9 and IL-13. *Immunity* **17**, 7–17 (2002)

FURTHER READING Mak, T. W., Penninger, J. M. & Ohashi, P. S. Knockout mice: a paradigm shift in modern immunology. *Nature Rev. Immunol.* **1**, 11–19 (2001)

HIV

Raft required for entry

The targeting of CD4 to non-raft domains of the cell membrane can block HIV-1 infection, according to work from del Real and colleagues published in *The Journal of Experimental Medicine.*

Rafts (cholesterol-enriched lipid domains in the plasma membrane) are known to be important for regulating both cell signalling and pathogen infection of cells. The HIV-1 protein gp120 binds to CD4, which forms a complex with a chemokine receptor (CCR5 or CXCR4); HIV-1 needs this receptor complex to infect target cells. Although the role of rafts in CD4-mediated signalling is well established, it is not known whether the association of CD4 with rafts is important for the entry of HIV-1 into cells.

To answer this question, the authors generated CD4 chimaeras and mutants (in which the transmembrane and cytoplasmic domains were affected) and investigated the effect of these mutations on the partitioning of CD4 to raft or non-raft domains, CD4 signalling and HIV-1 infection. Of the mutants, only CD4-LDL — generated by replacing the CD4 transmembrane and cytoplasmic domains with those from the low-density lipoprotein (LDL) receptor — partitioned to the non-raft plasma-membrane fraction in transfected cells; all of the other mutants retained raft partitioning. Furthermore, CD4-LDL failed to activate the tyrosine kinase LCK after CD4 crosslinking and also failed to mediate HIV-1 entry (although it bound as well as wild-type CD4 to gp120). All mutants that retained raft partitioning mediated both CD4-induced LCK activation and HIV-1 entry.

Why is CD4 raft partitioning required for HIV-1 entry? Confocal microscopy studies showed that cells transfected with wild-type CD4 formed raft-associated complexes of CD4, gp120 and CXCR4 after gp120 induction. However, in CD4-LDL-transfected cells, CD4 and gp120 co-localized in non-raft membranes, but these did not coalesce with CXCR4-containing rafts. So, the partitioning of CD4 to rafts is required for gp120-induced receptor clustering.

These results show that the partitioning of CD4 to rafts is required for HIV-1 entry, and they establish that HIV-1 exploits rafts as host-cell entry sites, which might enable new strategies for preventing HIV-1 infection to be developed.

Jenny Buckland

References and links

ORIGINAL RESEARCH PAPER del Real, G. *et al.* Blocking of HIV-1 infection by targeting CD4 to nonraft membrane domains. *J. Exp. Med.* **196**, 293–301 (2002)

FURTHER READING Doms, R. W. & Trono, D. The plasma membrane as a combat zone in the HIV battlefield. *Genes Dev.* **14**, 2677–2688 (2000)