ANTIGEN PROCESSING

Traffic control

CD1 molecules are non-polymorphic MHC class-I-like molecules that present lipid antigens to certain T cells, including natural killer T (NKT) cells. We know a lot about the biology of CD1 molecules, but our knowledge of intracellular trafficking by CD1 molecules does not yet compare to our knowledge of the MHC class I and II pathways. Two papers in the December issue of *Immunity* now shed light on this aspect of CD1 biology. The results show that CD1 trafficking differs from MHC class I and II trafficking, and that components of the MHC class II pathway are important for normal CD1 trafficking.

Tyrosine-based motifs in the cytoplasmic tails of CD1 molecules direct them to the endocytic pathway. Previous studies revealed that in the steady state, CD1 isotypes (CD1a, b, c, d and e) are differentially distributed in the endocytic pathway, leading to the idea that they have specialized roles in surveying different endosomal compartments. Now, Albert Bendelac's group have examined the dynamics of CD1d trafficking. Pulse-chase experiments were consistent with the idea that CD1d can traffic directly from the trans-Golgi network to the cell surface. Furthermore, CD1d undergoes several rounds of internalization and recycling to the cell surface, and CD1d molecules ultimately accumulate in late endosomes/lysosomes. Co-precipitation experiments revealed an unexpected association between the invariant chain (Ii) and CD1d. The authors investigated whether this is a functional association, using CD1-TD, a CD1d molecule in which the tyrosine-based endosomal targeting motif was deleted. In rat basophil leukaemia cells, CD1-TD is present mostly at the cell surface in the steady state, but transfection with Ii resulted in redistribution of CD1-TD into endosomal compartments. Consistent with this, the steady-state level of wild-type CD1d at the cell surface was increased in Ii-deficient cells.

The results from the study by Chapman and colleagues also indicate a role for Ii in CD1d trafficking. Surprisingly, mice deficient in the cysteine protease cathepsin S, which is important for degradation of Ii and MHC class II maturation, had decreased numbers of CD1-restricted NKT cells that were functionally impaired. Presentation of the CD1-restricted molecule α–galactosylceramide was reduced in the cathepsin $S^{-/-}$ mice. Confocal localization studies revealed that CD1d accumulates in endosomes of cathepsin-S-deficient mice, and associates with MHC class II and Ii molecules. The results support the idea of a functional interaction between CD1d and Ii molecules.

Taken together, these new results reveal that CD1d molecules can traffic directly to the cell membrane, and that components of the MHC class II pathway — cathepsin S and Ii — have an unexpected role in CD1d trafficking. The functional significance of this unusual trafficking pathway remains to be determined.

Elaine Bell

References and links

ORIGINAL RESEARCH PAPERS Jayawardena-Wolf, J., Benlagha, K., Chiu, Y.-H., Mehr, R. & Bendelac, A. CD1d endosomal trafficking is independently regulated by an intrinsic CD1d-encoded tyrosine motif and by the invariant chain. *Immunity* **15**, 897–908 (2001) | Riese, R. J. *et al.* Regulation of CD1 function and NK1.1+ T cell selection and maturation by cathepsin S. *Immunity* **15**, 909–919 (2001)

WEB SITES

Albert Bendelac's lab: http://www.molbio.princeton.edu/research_facultymember.php?id=37

Harold Chapman's lab: http://pulmonary.ucsf.edu/faculty/chapman.html

VIRAL IMMUNITY

Week on, week off

Highly active antiretroviral therapy (HAART) is an effective treatment for many HIV-infected patients. However, the benefits of continuous treatment with these drugs come at a price, both financially and physiologically, due to the toxic side-effects of the drugs used. To address these issues, Fauci and colleagues have been investigating ways in which the amount of these drugs given to patients can be reduced without altering the effectiveness of the treatment. In *Proceedings of the National Academy of Sciences*, this group now publish a study that confirms the feasibility of a short-cycle structured intermittent therapy (SIT) HAART regimen, which halves the amount of retroviral therapy given to patients.

Chronically infected HIV patients who controlled their plasma HIV RNA while receiving continual HAART were treated with a SIT regimen consisting of 7 days on HAART followed by 7 days off HAART. Viral replication in peripheral blood and at reservoir sites was successfully suppressed in all patients who remained on this regimen. The $CD4^+$ T-cell counts were maintained in these patients and no significant increases in $CD4^+$ or $CD8^+$ T cells expressing activation markers or producing interferon-γ in response to HIV were seen. The toxic side-effects (as indicated by increased levels of serum cholesterol and triglycerides) were reduced and there was no evidence to suggest that resistance to antiretroviral therapies developed.

This study shows that SIT HAART regimes may be an effective way to significantly reduce the cost and toxicity of antiretroviral therapy. These results are particularly important for resource-poor countries where the cost of antiretroviral agents means that treatment is currently limited.

Jenny Buckland

References and links

ORIGINAL RESEARCH PAPER Dybul, M. *et al*. Short-cycle structured intermittent treatment of chronic HIV infection with highly active antiretroviral therapy: effects on virologic, immunologic, and toxicity parameters. *Proc. Natl Acad. Sci. USA* **98**, 15161–15166 (2001)