ANTIGEN PRESENTATION

Dressing up

Ever wished as a kid that you were just that little bit older so that you could get into the club that everyone was talking about? The alternative to maturity for many a teenager has long been presentation — dress yourself up and hope no one asks your age. Successful entry to an adaptive immune response also depends on these two factors. The maturation of antigen-presenting cells, such as dendritic cells (DCs), aids the stimulation of $CD4^+$ T cells, as does enhanced presentation of antigen on the MHC class II molecules of DCs. This study shows that Toll-like receptor 2 (TLR2) has an important role in both of these processes.

Signalling through TLR2 induces the maturation of DCs, but can ligands bound to TLR2 be internalized for presentation by MHC class II molecules? Schjetne and colleagues used an antagonistic TLR2-specific monoclonal antibody with κ light chains (TL2.1), which acts as a ligand for TLR2 without inducing signalling, to separate the maturation-inducing effects of TLR2 stimulation from the antigen-presenting effects. First, they showed that TL2.1 failed to induce the maturation of immature DCs. However, TL2.1 was still 100–1,000 times more efficient at stimulating the proliferation of Cκ-specific $CD4^+$ T cells by antibody-treated DCs than was an isotype-matched control antibody. In the absence of DC maturation, enhanced presentation of the Cκ epitope of TL2.1 by DCs must be responsible for the T-cell stimulation. The effect was shown to be specific for TLR2 binding, as antibodies specific for CD62 ligand or CXC chemokine receptor 1 did not enhance T-cell proliferation.

The response of Cκ-specific T cells to TL2.1 was almost completely abrogated by the addition of chloroquine, leupeptin or brefeldin A, which inhibit different stages in the lysosomal processing and presentation of MHC class II antigens. This indicates that ligands bound to TLR2 enter the conventional pathway for presentation by MHC class II molecules. This conclusion is supported by the authors' demonstration by fluorescent staining of the entry of TL2.1 into early endosomes.

It seems probable, therefore, that stimulation of TLR2 *in vivo* would lead to the development of an adaptive immune response by synergy between DC maturation and the enhanced presentation of antigens to T cells. This makes TLR2 an attractive target for vaccines. To get the right response, it seems to help if you are mature enough and dress like it.

Kirsty Minton

References and links

ORIGINAL RESEARCH PAPER Schjetne, K. W. *et al*. Link between innate and adaptive immunity: Toll-like receptor 2 internalizes antigen for presentation to $CD4^+$ T cells and could be an efficient vaccine target. *J. Immunol*. **171**, 32–36 (2003)

IN BRIEF

TUMOUR IMMUNOLOGY

Granzymes A and B are not essential for perforin-mediated tumor rejection.

Smyth, M. J. *et al. J. Immunol.* **171**, 515–518 (2003)

The importance of perforin in tumour surveillance is clear from studies of perforin-deficient mice, which spontaneously develop B-cell lymphomas. However, what is the function of the granzyme serine proteases that are released with perforin from the cytotoxic granules of cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells? Previous studies investigating this have produced contradictory results. Using five different tumour models, Smyth and colleagues show that granzymes A and B are not essential for CTL- or NK-cell-mediated rejection of spontaneous or experimental tumours. They conclude that perforin either acts alone, or acts with another granule content, possibly an alternative granzyme, to destroy tumour cells *in vivo*.

NATURAL KILLER T CELLS

Cross-presentation of disialoganglioside GD3 to natural killer T cells.

Wu, D. Y. *et al. J. Exp. Med.* **198**, 173–181 (2003)

α-Galactosylceramide — a glycolipid derived from marine sponges — is a universal ligand for mouse natural killer T (NKT) cells that express a Vα14–Jα18 T-cell receptor. This ligand is presented by CD1d molecules, but no natural ligand for mouse NKT cells has been identified yet. Wu and colleagues show that mouse NKT cells can recognize the tumour-associated ganglioside GD3 in the context of CD1d molecules. Because the human melanoma cell line used to immunize the mice was CD1d negative, the authors conclude that GD3 was cross-presented to NKT cells by CD1d-positive antigen-presenting cells. This study is the first to identify a natural ligand for mouse NKT cells and also to show cross-presentation to NKT cells. Whether GD3-specific NKT cells can be induced in immunized melanoma patients is the subject of future investigation.

TECHNIQUE

Cutting edge: a chemical genetic system for the analysis of kinases regulating T cell development.

Denzel, A. *et al. J. Immunol*. **171**, 519–523 (2003)

This study describes the use of ASKA (ATP analogue-sensitive kinase alleles) technology to regulate the activity of lymphocyte-specific protein tyrosine kinase (LCK) and assess its role in T-cell development. Previous attempts to assess the dose-dependent effects of LCK have required the generation of several lines of transgenic mice that express different levels of the transgene. ASKA is a chemical genetic approach that allows quantitative regulation of LCK activity rather than altering the expression levels of RNA or protein. Combining ASKA technology with reaggregate fetal thymic-organ cultures showed that there is a dose-dependent correlation between thymocyte development and LCK activity.