ANTIGEN PROCESSING

DC maturation

It is well known that immature dendritic cells (DCs) are specialized for antigen capture, whereas mature DCs present peptide–MHC class II complexes for T-cell stimulation, but the mechanisms that regulate the antigen-processing capacity of DCs are not well understood. Now, Trombetta and colleagues show that regulation of lysosome

acidification is important for the proteolytic activity of lysosomal enzymes.

The authors measured the ability of immature and mature DCs to degrade internalized antigens. The lysosomes of immature DCs were loaded with horseradish peroxidase (HRP) in the presence or absence of lipopolysaccharide (LPS) as a maturation stimulus. Immature DCs retained 80% of the loaded HRP after 19 hours, whereas only 10% of the loaded HRP was detectable in mature DCs, indicating that lysosomal proteolysis had occurred. Yet no differences

were detected in the expression levels of the lysosomal enzymes cathepsins H, D, S and L and legumain (AEP) in immature and mature DCs. However, cathepsin L and AEP in immature DCs were present in the inactive pro-enzyme form, in contrast to the active form present in mature DCs. *In vitro* assays that assess the degradative capacity of lysosomes at different pH levels showed that the activity of proteolytic enzymes is highly pH dependent. So, the authors next measured the pH of lysosomes in living cells using the pH-sensitive reporter fluorescein isothiocyanate (FITC)–dextran. Lysosomes in immature DCs had a pH of ~5.4, whereas the pH of lysosomes in mature DCs was ~4.5. The enhanced acidification in mature DCs seems to be the result of a higher proportion of active ATP-dependent vacuolar proton pumps in the lysosomal membrane.

So, regulation of lysosome acidification is one mechanism that controls the ability of DCs to link the formation of peptide–MHC class II complexes to maturation stimuli.

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References and links

ORIGINAL RESEARCH PAPER Trombetta, E. S. *et al.*

Activation of lysosomal function during dendritic cell maturation. *Science* **299**, 1400–1403 (2003)

WEB SITE

Ira Mellman's lab: <http://info.med.yale.edu/cellbio/Mellman.html>

INFECTIOUS DISEASE

Immunotherapy for prion disease

Prion diseases, including Creutzfeldt-Jakob disease, are currently untreatable and result in fatal neurodegeneration. Previous attempts to develop therapies for these conditions have had limited success, with benefits only being seen if treatment begins before or close to inoculation with the infectious agent. However, a recent study from Simon Hawke's group, published in *Nature*, shows that monoclonal antibodies can inhibit prion replication and delay the development of prion disease, even when given considerably later in the incubation period.

Prion-disease pathogenesis involves the transformation of normal cellular prion protein (PrP^c) into an infectious disease-associated isoform, PrP^{Sc}. In this study, the authors generated prion-specific monoclonal antibodies (ICSM18 and ICSM35, which recognize PrP^c and PrP^{Sc} with differing affinities) and tested whether these could block the transformation of PrP^c to PrP^{Sc} *in vivo*.

Mice were inoculated intraperitoneally with a brain homogenate derived from terminally ill mice with scrapie and were treated twice weekly with ICSM18, ICSM35 or isotype-matched control antibodies. Even when given 30 days after prion infection (when the levels of PrP^{Sc} had reached a maximum in the inoculated mice), treatment with ICSM18 or ICSM35 resulted in considerably reduced levels of infectious protein in the spleens of treated mice compared with controls.

Does this treatment have positive effects on the health of the inoculated mice? Although the treatment was unsuccessful if given to mice after the onset of clinical disease, mice that were treated between 7 and 30 days after prion infection survived for up to 150% longer than isotype control-treated or untreated mice. Mice for which the treatment was continued remained healthy at the end of the study, showing no clinical signs of scrapie.

The authors conclude that although this treatment is not effective if given after clinical symptoms have developed and that there is a possibility that similar treatments could result in autoimmune side effects in patients, immunotherapeutic strategies for human prion diseases are worth pursuing.

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References and links

ORIGINAL RESEARCH PAPER White, A. R. *et al.* Monoclonal antibodies inhibit prion replication and delay the development of prion disease. *Nature* **422**, 80–83 (2003)

FURTHER READING Aguzzi, A. Peripheral prion pursuit. *J. Clin. Invest.* **108**, 661–662 (2001)