ANTIGEN PROCESSING

Accessibility is the key

Recognition of major histocompatibility complex (MHC) class II/peptide complexes by the T-cell receptor is a crucial step in the activation of $CD4^+$ T cells. Peptides for presentation on class II molecules are generated by proteolytic cleavage of extracellular proteins in the acidic environment of endosomes and lysosomes in antigen-presenting cells (APC). Reporting in *Science*, Maric and colleagues describe the role of a component of the processing pathway called γ-interferon-inducible lysosomal thiol reductase, GILT (also known as Ifi30), which catalyses the reduction of disulphide bonds and enhances protease access to the antigen.

In this study, Maric and colleagues cloned mouse GILT and generated a knockout mouse to investigate the role of GILT in antigen processing. Hen egg lysozyme (HEL), which contains four disulphide bonds, was used as a model antigen. The T-cell proliferative response of GILT-deficient mice that were immunized with HEL was about one-tenth that of wild-type littermates. In *in vitro* assays, HEL epitope-specific T cells were used to detect the presence of four specific HEL peptides presented on MHC class II molecules. Interestingly, the results were not quite as clear cut as might be expected. Whereas the response to one of the cysteine-containing epitopes was eliminated, two others were efficiently presented in the absence of GILT, indicating that proteases can access these epitopes in the absence of protein unfolding. By contrast, a cysteine-negative epitope was poorly presented in GILT-deficient mice, indicating that efficient presentation of this epitope requires the reduction of disulphide bonds outside the epitope.

So, this study shows that proteases alone are insufficient to generate the full complement of peptides from a specific antigen, and that GILT improves protease accessibility to antigen in the MHC class II processing pathway.

Elaine Bell

References and links

ORIGINAL RESEARCH PAPER Maric, M. *et al.* Defective antigen processing in GILT-free mice. *Science* **294**, 1361–1365 (2001)

ENCYCLOPEDIA OF LIFE SCIENCES
Antigen processing

WEB SITE
Peter Cresswell's lab:
http//info.med.yale.edu/immuno/fac_cresswell.html

INNATE IMMUNITY

Self-defence is a sweaty business

Whether its the Scandinavian sauna, the Russian bania, the Turkish hamman or the American Indian sweatlodge, sweating is something we sometimes like to do. Sweating is also beneficial, as evaporation from the skin lowers body temperature. New findings published in the December issue of *Nature Immunology* show another benefit of sweating. Researchers led by Birgit Schittek show that human sweat contains a new antibiotic peptide called dermcidin.

Anti-microbial peptides and proteins are components of the innate defence system. Proteins with anti-bacterial activities include phospholipase A2, lysozyme and granzyme B. Anti-microbial peptides include defensins, histatins and cathelicidins, some of which are in development as new anti-microbial agents. Some anti-microbial peptides and proteins are constitutively expressed, whereas others are induced during inflammation or by specific cytokines.

While screening a subtracted complementary DNA library of skin cells, Schittek and colleagues isolated the gene encoding a new anti-microbial peptide, dermcidin. They analysed the sequence and found that the peptide has no homology with other known anti-microbial peptides. The protein is specifically and constitutively expressed in sweat glands and secreted into sweat. Dermcidin is proteolytically processed, but it is not clear whether this processing takes place in the sweat gland cells or after it has been secreted into sweat. The purified peptide showed broad activity against pathogenic bacteria and fungi, which was maintained over a broad pH range and in high salt concentrations. These results show that human sweat contains at least one anti-microbial protein that might have a role in the regulation of skin flora and in innate immune responses.

Unlike most anti-microbial peptides, such as defensins, which are enriched in arginine and lysine residues leading to a net positive charge, dermcidin has a net negative charge of –5. The mode of action of the cationic defensins is to bind to anionic components in the target membrane and kill the microorganims by pore formation and permeabilization of the cell membrane. It seems probable that the mode of action of dermcidin will differ, and it remains to be seen whether dermcidin will be active against microorganisms that are resistant to current antibiotic therapies.

Melanie Brazil, Associate Editor,
Nature Reviews Drug Discovery

References and links

ORIGINAL RESEARCH PAPER Schittek, B. *et al.* Dermcidin: a novel human antibiotic peptide secreted by sweat glands. *Nature Immunol.* **2**, 1133–1137 (2001)