Processed sugar

Peptides presented by major histocompatibility complex (MHC) proteins activate T cells. So too, it seems, do sugars.

Zwitterionic capsular polysaccharides from pathogenic bacteria trigger abscess formation *in vivo* that is $CD4^+$ T cell dependent. In *Cell*, Cobb *et al.* show that after engulfing bacteria, antigen-presenting cells (APCs) degrade the polysaccharide capsules and present the resultant lower-molecular-weight sugars on MHC class II molecules to T cells. Confocal microscopy of APCs conjugated with T cell showed colocalization of labeled polysaccharide, MHC class II and T cell receptors in immune synapses. Oxidation of polysaccharides by inducible nitric oxide synthase (iNOS) was crucial: iNOS-deficient mice do not develop abscesses when challenged *in vivo*. But iNOS-deficient splenocytes given pre-processed zwitterionic oligosaccharides could activate T cells *in vitro*. Thus, T cells can detect 'processed' sugar–MHC complexes. *LAD*

Cell **117**, 677–687 (2004)

Food for cross-priming

'Cross-priming' is the activation of $CD8^+$ T cells with antigen not produced by the presenting cell. How this process is different from 'direct' priming with endogenous antigens is unclear.

Wolkers *et al.* report in *Science* that epitopes located in the signal sequence of a protein are poor candidates for cross-priming. In contrast, cross-priming of T cells is much more efficient for epitopes derived from mature proteins. This distinction does not apply for the direct priming of endogenously expressed antigens. Although the molecular mechanism of this process remains unclear, data from Norbury *et al.* in the same issue suggest that processed antigens, such as the rapidly degraded signal sequences, are not efficiently cross-presented. Thus, Norbury *et al.* show that *in vivo* cross-priming requires donor cells that express stable proteins but not processed peptides. These reports provide important new information for the rational design of vaccine antigens presented via cross-priming. *PTL*

Science **304**, 1314–1317 & 1318–1321 (2004)

Processing EBV

The glycine-alanine (GAr) domain of the Epstein-Barr virus (EBV)–encoded nuclear antigen (EBNA1) can mediate immune escape by blocking its own proteosomal degradation, and it would seem, its antigen presentation. Thus it is unclear how the EBNA1-specific T cells seen in some EBV-infected individuals are generated.

In the *Journal of Experimental Medicine*, Tellam *et al.* find that EBNA1 protein resists degradation in B cells, yet B cells are sensitive to EBNA1-specific cytotoxic T lymphocyte (CTL) lysis, suggesting good antigen presentation. EBNA1 epitopes in B cells were processed in a proteosome- and TAP-dependent way. However, T cell activation by EBV-transformed B cell lines was abolished if fresh protein synthesis in the B cells had been blocked. Thus, the peptide presented to T cells is likely to arise from defective EBNA1 translation products that had no GAr sequences, making them susceptible to proteosomal degradation. *JDKW*

J. Exp. Med. **199**, 1421–1431 (2004)

Research notes written by Laurie A. Dempsey, Peter T. Lee and Jamie D.K. Wilson.

Spliced peptide epitopes

The peptide-binding cleft of MHC class I molecules places strict limits on the length of peptides that are presented to $CD8^+$ T cells. Typically, these peptides are thought to derive from contiguous amino acids. In *Science*, Vigneron *et al.* identified the second example of human CTLs recognizing a tumor epitope generated by peptide splicing. The mature melanoma epitope was generated by excision of four internal amino acids from a precursor peptide, followed by religation of the N- and C-terminal fragments.

Proteasome inhibitors blocked such processing *in vivo* and *in vitro*, suggesting that the proteasome is responsible for this activity. Peptide splicing by purified proteasomes *in vitro* did not require exogenous energy sources; presumably transient covalent bonds form between proteasomes and the N-terminal peptide, conserving bond energy for transpeptidation. Future work should determine if peptide splicing is a common form of antigenic epitope generation. *LAD*

Science **304**, 587–590 (2004)

Quality control in the ER

Retro-translocation of misfolded proteins from the endoplasmic reticulum (ER) to the cytosol is exploited by the cytomegalovirus (CMV)–encoded glycoproteins US2 and US11, which catalyze the retro-translocation of MHC class I heavy chains. In *Nature*, two groups have identified a key component of the retro-translocation machinery. Lilley and Ploegh showed that US11 recruits the heavy chains to a human homolog of yeast Der1p, called DERtrin-1 or Derlin-1. This protein was essential for US11-dependent, but not US2-dependent, heavy chain degradation.

Rapoport *et al.* report that another protein, VIMP, recruits the ATPase p97 to DERtrin-1. The ATPase p97 is known to capture retro-translocation substrates as they emerge on the cytosolic side of the ER. DERtrin-1 also associated with other substrates undergoing retro-translocation, and a DERtrin-1 'knockdown' in *Caenorhabditis elegans* induced ER stress, which indicates the accumulation of misfolded proteins in the ER. Together these data suggest that DERtrin-1 is an important mediator in the mammalian retro-translocation machinery. *JDKW*

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Calreticulin's true color

The assembly and loading of MHC class I molecules is a multistep process involving various protein chaperones, including calreticulin. However, the precise function of this chaperone has been hard to elucidate because the substrates it binds during the folding of class I molecules are transient monoglucosylated glycans. In the *Journal of Biological Chemistry*, Wearsch *et al.* developed an expression system to produce MHC class I heavy chain with the appropriate *N*-linked oligosaccharide. Calreticulin was found to efficiently bind the monoglucosylated glycan, but it does not discriminate between native and non-native conformations of MHC class I. Thus, although calreticulin associates with class I during folding and peptide loading, its function is not to sense peptide occupancy. Instead, it recruits the enzyme Erp57, which rearranges disulfide bonds within the peptide-loading complex to promote release of MHC class I from the complex. *PTL*

J. Biol. Chem. **279**, 25112–25121 (2004)