ANTIGEN PRESENTATION

Bringing the outside in

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Normally, MHC class I molecules display peptides that are generated in the cytosol from the cell's own proteins. But in some cells, such as dendritic cells (DCs), proteins from the extracellular environment can gain access to cytosolic proteases that generate peptides for presentation by MHC class I molecules — a process known as cross-presentation. The mechanisms behind cross-presentation have been hotly debated. Now, a paper in *Immunity* provides evidence to indicate that the machinery for endoplasmic reticulum (ER) protein retrotranslocation operates in the phagosomes of DCs and is responsible for the transfer of exogenous antigens into the cytosol for cross-presentation.

The main route for cross-presentation requires that extracellular proteins that are taken up in phagosomes exit into the cytosol, are processed by the proteasome and are then transported into the lumen of the ER through TAP (transporter associated with antigen processing) for binding to MHC class I molecules. Ackerman and colleagues wanted to find out what mediates the phagosome-to-cytosol step in this process. Their first clue came from the earlier observation that phagosomes can contain proteins that normally reside only in the ER, possibly following fusion of the ER with the phagosome. Ackerman *et al*. provided support for this rather controversial concept using a new approach. They showed that beads coated with a peptide containing an N-glycosylation site could be N-glycosylated in DC phagosomes — a process that normally occurs exclusively in the ER.

Given that this ER-associated process could occur in phagosomes, the authors then asked whether activities assigned to the ER protein transporter SEC61 might occur in phagosomes and be involved in cross-presentation. SEC61 normally transports proteins from the cytosol into the ER, but it can also work in reverse transporting proteins from the ER to the cytosol for degradation. To assess phagosome-to-cytosol retrotranslocation, the authors made use of the viral protein ICP47, which must access the cytosol to carry out its function of inhibiting TAP-mediated peptide translocation. When given exogenously to DCs, ICP47 could indeed inhibit TAP and reduce MHC class I cell-surface expression, which is consistent with ICP47 entering the cytosol by retrotranslocation. Importantly, SEC61 was shown to be involved in the retrotranslocation of ICP47, as pre-incubation of the DCs with *Pseudomonas aeruginosa* exotoxin A, which inhibits SEC61-mediated retrotranslocation, reversed the ICP47-mediated inhibition of TAP. Exotoxin A also impaired the ability of DCs to cross-present exogenous ovalbumin, but it did not affect their ability to present endogenously expressed ovalbumin.

The role of SEC61-mediated retrotranslocation in cross-presentation was confirmed using a dominant-negative form of the ATPase p97, which is a crucial component of the ER retrotranslocation machinery. Similar to exotoxin A, dominant-negative p97 reduced the cross-presentation of exogenous ovalbumin by DCs.

This paper provides evidence for a model of cross-presentation involving ER components that facilitate the transfer of phagocytosed antigens to the cytosol and thereby their entry into the MHC class I pathway. Exactly how these ER components get into the phagosomes remains to be determined.

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ORIGINAL RESEARCH PAPER Ackerman, A. L., Giodini, A. & Cresswell, P. A role for the endoplasmic reticulum protein retrotranslocation machinery during crosspresentation by dendritic cells. *Immunity* **25**, 607–617 (2006)
FURTHER READING Rock, K. L. Exiting the outside world for cross-presentation. *Immunity* **25**, 523–525 (2006)