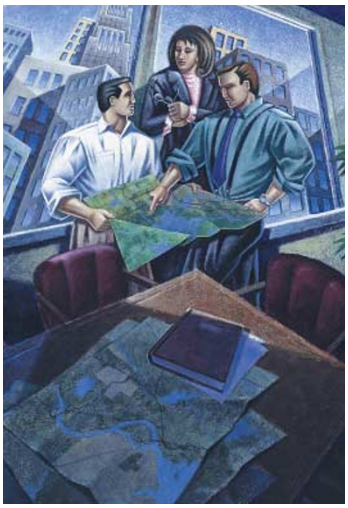
ANTIGEN PRESENTATION

Working out an alternative route

MHC class I molecules are classically ascribed the function of presenting peptides derived from endogenous antigens; cytosolic proteins are degraded by the proteasome and peptides are transported into the endoplasmic reticulum (ER) for loading onto MHC class I molecules. However, MHC class I molecules in certain antigen-presenting cells, particularly dendritic cells (DCs), can also present peptides derived from exogenous antigens — a process referred to as cross-presentation. Now, results from three groups bring us closer to understanding how this process works, and indicate that phagosomes are competent for cross-presentation.

The first indication that antigens in phagosomes might have access to ER-derived components came from a study by Michel Desjardins' group, in which they showed that phagocytosis in macrophages proceeds by the recruitment of ER membranes. In the present study (Houde *et al.*), proteomic analysis showed that various molecules required for cross-presentation can be detected on phagosomes. Latex beads labelled with fluorescent ovalbumin were phagocytosed and fluorescence could be detected in the cytoplasm, indicating that exogenous proteins are retro-translocated into the cyoplasm for degradation by proteasomes. Indeed, proteasomes and polyubiquitylated proteins were associated with the cytoplasmic side of the phagosome membrane.



So, are phagosomes capable of processing exogenous peptides and does this result in T-cell stimulation? The authors compared the processing of endogenous ovalbumin (expressed by macrophages after infection with vaccinia virus) and exogenous ovalbumin (delivered through phagocytosis). The cross-presentation of peptide–MHC class I complexes was partially inhibited by treatment with brefeldin-A (which blocks the secretory pathway), whereas conventional presentation was totally inhibited, supporting the idea that phagosomes are the source of the MHC class I complexes in the brefeldin-A-treated cells.

Guermonprez *et al.* purified phagosomes from immature DCs and found that various ER proteins were detectable on early phagosomes. Activity of the ER-resident enzyme glucose-6-phosphate was marked on the phagosome membrane. Components of the cross-presentation pathway (including the transporter for antigen processing (TAP), tapasin and calreticulin) were detected on early phagosomes. Functional assays showed that phagosomes are a site of TAP-dependent peptide loading onto MHC class I molecules, leading to T-cell stimulation.

The study by Ackerman *et al.* provided similar evidence to show that phagosomes from immature DCs have all the necessary components for cross-presentation. An interesting feature of this study was the use of US6 — a transmembrane protein from human cytomegalovirus that binds to the lumenal face of TAP. Exogenously added soluble US6 inhibited cross-presentation, showing that the TAP inhibition occurred in a location where internalized proteins have access to ER components.

Together, these three studies show that phagosomes are competent organelles for cross-presentation.

Elaine Bell

References and links

ORIGINAL RESEARCH PAPERS Houde, M. *et al.* Phagosomes are competent organelles for antigen cross-presentation. *Nature* **425**, 402–406 (2003) | Guermonprez, P. *et al.* ER–phagosome fusion defines an MHC class I cross-presentation compartment in dendritic cells. *Nature* **425**, 397–402 (2003) | Ackerman, A. L. *et al*. Early phagosomes in dendritic cells form a cellular compartment sufficient for cross presentation of exogeneous antigens. *Proc. Natl Acad. Sci. USA* 17 October 2003 (doi:10.1073/pnas.1735556100)
FURTHER READING Desjardins, M. ER-mediated phagocytosis: a new membrane for new functions. *Nature Rev. Immunol.* **3**, 280–291 (2003)