ANTIGEN PRESENTATION

Prime time: insights into cross-presentation

Cross-presentation — the display of peptides derived from exogenous antigens on MHC class I molecules — is important for effective immune responses to tumours and viral infections. Although classical antigen processing pathways are well characterized, the pathways that lead to cross-presentation are less clear. How can a cell physically separate endogenous from externally derived peptides and select which are presented on MHC class I molecules? Two studies published in *Nature Immunology* have now defined two distinct pathways for cross-presentation in different subsets of dendritic cells (DCs).

Burgdorf *et al.* report that the intracellular routes of endogenous and exogenous peptides destined for presentation on MHC class I molecules are distinct. Based on studies of mouse bone-marrow-derived conventional DCs (cDCs) presenting the soluble antigen ovalbumin (OVA), it was found that exogenously derived OVA transits from endosomes into the cytosol and is degraded by the proteasome before transport to, and MHC class I loading in, the same endosomes. These endosomes, identified as essential cellular compartments for cross-presentation but not endogenous antigen presentation in cDCs, contained TAP (transporter associated with antigen processing), which is normally found in the endoplasmic reticulum. Selective endosome-specific inhibition of TAP abrogated the ability of cDCs to cross-present OVA, but did not affect the presentation of endogenous antigens. Furthermore, signalling through Toll-like receptor 4 (TLR4) and the adaptor protein MyD88 increased the recruitment of TAP to endosomes, thereby leading to more effective cross-presentation by cDCs. So, this study provides evidence for how processing of endogenous and cross-presented antigens are mechanistically and spatially separated, and suggests that this pathway is most active under conditions of TLR activation.

In the second article, Di Pucchio *et al.* characterized a different pathway of cross-presentation in human plasmacytoid DCs (pDCs). pDCs are important in host defence against viruses owing to their capacity to produce large amounts of type I interferon, but their ability to stimulate virus-specific T-cell proliferation is not well understood. In this study, pDCs exposed to influenza virus for a short period of time were found to be highly effective stimulators of virus-specific $CD8^+$ T-cell proliferation compared with myeloid DCs (mDCs). In contrast to the pathway characterized by Burgdorf *et al.*, cross-presentation by pDCs did not rely on proteasomal degradation or cytosolic transit. Instead, viral antigens were routed directly to recycling endosomes containing TLR7 and TLR9, which are crucial for viral recognition. The endosomes of pDCs, but not mDCs, acted as large intracellular stores of presynthesized MHC class I molecules that were redistributed to the cell surface early after exposure to influenza virus. Therefore, pDCs are unique in their capacity to rapidly cross-present viral antigens, owing to endosomal compartments that are specialized for viral recognition and processing.

Together, these studies further our understanding of cross-presentation pathways and clarify the functional roles of DC subsets in priming the adaptive immune response. Based on the pDC-specific, kinetically distinct pathway identified by Di Pucchio *et al.*, it seems plausible that cross-presentation by different DC subsets serves different purposes over the course of an infection. As proposed by Di Pucchio *et al.*, rapid cross-presentation by pDCs might be important for early priming of memory $CD8^+$ T-cell responses, whereas priming by both mDCs and pDCs at later time points could enhance both recall and new responses to a pathogen.

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ORIGINAL RESEARCH PAPERS Burgdorf, S., Schölz, C., Kautz, A., Tampé, R. & Kurts, C. Spatial and mechanistic separation of cross-presentation and endogenous antigen presentation. *Nature Immunol.* 30 March 2008 (doi:10.1038/ni.1601) | Di Pucchio, T. *et al.* Direct proteasome-independent cross-presentation of viral antigen by plasmacytoid dendritic cells on major histocompatibility complex class I. *Nature Immunol.* 30 March 2008 (doi:10.1038/ni.1602)