ANTIGEN PRESENTATION

DCs spot the difference

A question that has puzzled immunologists for many decades is how the immune system discriminates between self- and non-self-antigens. Although this puzzle remains far from being solved, a recent paper published in *Nature* indicates that dendritic cells (DCs) can distinguish antigens taken up in the presence of Toll-like receptor (TLR) ligands from those taken up in the absence of such ligands.

During an infection, DCs efficiently phagocytose microorganisms, leading to DC activation (for example, through microbial ligation of their TLRs) and presentation of microbial peptides to $CD4^+$ T cells, thereby initiating an immune response. At the same time, these DCs are surrounded by large amounts of self-antigen (for example, apoptotic cells).

> "DCs can distinguish antigens taken up in the presence of TLR ligands from those taken up in the absence of such ligands"

So, Blander *et al.* set out to investigate whether there are regulatory mechanisms that prevent DCs from initiating an immune response to these self-antigens during an infection. Using fluorescently labelled apoptotic cells expressing ovalbumin (OVA) and bacteria expressing H2-Eα, it was shown that ~60% of DCs (either bone-marrow-derived DCs or splenic DCs) that had taken up the fluorescently labelled apoptotic cells had also taken up bacteria. However, only peptides derived from the bacteria were presented at the cell surface by MHC class II molecules; this was indicated by the observation that $CD4^+$ T cells specific for an H2-Eα peptide were induced to proliferate, whereas $CD4^+$ T cells specific for an OVA peptide were not. The authors then provided further evidence that the presence or absence of a TLR ligand in the phagocytosed material determines whether peptides derived from the material are presented at the cell surface by MHC class II molecules. They showed that although DCs that phagocytosed microspheres conjugated with both hen-egg lysozyme (HEL) and a TLR ligand (lipopolysaccharide; LPS) were able to stimulate HEL-peptide-specific $CD4^+$ T cells, DCs that phagocytosed a mixture of microspheres conjugated with HEL and microspheres coated with LPS, and DCs that had phagocytosed microspheres conjugated with HEL and were stimulated by exogenous LPS, were not.

Isolated phagosomes from DCs that had phagocytosed a mixture of microspheres conjugated with only HEL and microspheres conjugated with both HEL and LPS were separated and biochemically characterized. In phagosomes containing the microspheres conjugated with HEL and LPS, the invariant chain (Ii) — a chaperone molecule that assists in the assembly of nascent MHC class II molecules and whose degradation is required for the peptide-binding groove of MHC class II molecules to become available for peptide loading — was degraded, whereas in phagosomes containing the microspheres conjugated with only HEL, Ii degradation was not observed. Consistent with this, HEL-peptide–MHC-class-II complexes were only observed in phagosomes that contained microspheres conjugated with both HEL and LPS.

These data indicate that DC presentation of cell-surface peptide–MHC-class-II complexes is regulated in a TLR-dependent phagosome-autonomous manner, providing details of one mechanism to ensure that self-antigens that are phagocytosed by DCs during an infection are not presented to $CD4^+$ T cells.

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ORIGINAL RESEARCH PAPER Blander, J. M. & Medzhitov, R. Toll-dependent selection of microbial antigens for presentation by dendritic cells. *Nature* 19 Feb 2006 (doi:10.1038/nature04596)