ANTIGEN PRESENTATION

T cells spot new antigen

CD1 molecules are a family of MHC class-I-like molecules involved in the presentation of lipid antigens to T cells. CD1a-restricted T cells specific for mycobacteria-infected cells have been shown to have an anti-bacterial effect; however, until this study in *Science* defined the CD1a-presented antigens as mycobacterial lipopeptides, their molecular identity had remained unknown.

To characterize the CD1a-bound mycobacterial antigens, Moody *et al.* analysed a reporter T-cell line that expresses the α- and β-chains of a CD1a-restricted, mycobacteria-specific T-cell receptor (TCR) — J.RT3.CD8-2 cells. Components of the cell wall of *Mycobacterium tuberculosis* were fractionated by chromatography, and only one fraction contained compounds that could stimulate J.RT3.CD8-2 cells. The ability of this fraction to mediate T-cell activation was shown to depend on CD1a presentation and to be TCR specific.

The compound was found to be similar to the known mycobacterial lipopeptide mycobactin. Didehydroxymycobactin (DDM) differed from mycobactin in that it contained lysine residues rather than hydroxylysines and the uncommon amino acid α-methyl serine. This indicated that DDM is probably an intermediate in mycobactin synthesis and provides new insight into the final molecular steps involved in generating mycobactin.

Activation of J.RT3.CD8-2 cells was not only a property of purified DDM, as infection of monocyte-derived dendritic cells with as few as five *M. tuberculosis* bacteria was sufficient to stimulate T cells. Previously it has been shown that mycobactin siderophores scavenge iron from host cells and are required for *M. tuberculosis* to adapt to its intracellular habitat. Therefore, a T-cell response to CD1a presentation of an intermediate of mycobactin synthesis could prove invaluable in the early detection of *M. tuberculosis* by the immune system.

Interestingly, although natural DDM isolated from *M. tuberculosis* stimulated J.RT3.CD8-2 cells to produce high levels of interleukin-2, several other related lipopeptides were unable to elicit any response. These lipopeptides differed only in the length and saturation of their fatty acyl chains and the presence of hydroxylysine residues, indicating that the T-cell response requires a specific peptide structure and fatty acyl chain. This led the authors to suggest that the polypeptide portion of the lipopeptide interacts with the TCR in a similar manner to peptide presented by classical MHC class I and II molecules.

These data identify a novel *M. tuberculosis* lipopeptide that can be presented in the context of CD1a, eliciting a specific T-cell response to the pathogen. Furthermore, the characterization of lipopeptides as a new class of T-cell antigen markedly expands the pool of antigens that the immune system can survey.

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References and links

ORIGINAL RESEARCH PAPER Moody, D. B. *et al.* T cell activation by lipopeptide antigens. *Science* **303**, 527–531 (2004)