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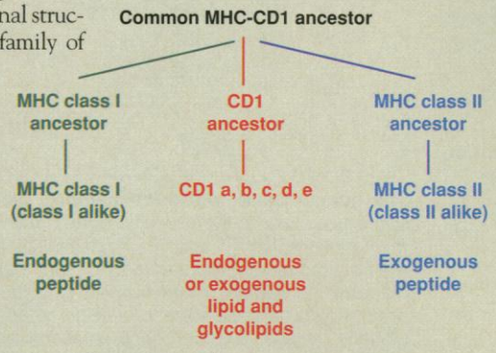
UPDATE: IMMUNOLOGY

Antigen Presentation: A Balanced Diet

Michael Brenner and Steven Porcelli

For much of the past decade, immunologists studying how the immune system recognizes foreign molecules have focused on the molecular mechanisms by which T cells recognize peptide antigens. A series of landmark crystallographic studies have revealed how peptide antigens are displayed on the surface of cells. Amino acid side chains of the peptide are anchored into specific pockets in the peptide binding grooves of the major histocompatibility complex (MHC) class I and class II membrane proteins. This determines which peptides can bind MHC, and thus which peptides have the potential to be recognized by T cell receptors. However, several remarkable findings suggest that an important part of the story has not yet been told. On page 339 of this issue, Zeng *et al.* present the three-dimensional structure of murine CD1d1, a representative of a family of conserved mammalian proteins that are distant cousins of MHC molecules (*1*) (see figure). This structure reinforces the view that CD1 proteins bind and present antigen in a way that offers T cells a fundamentally different look at the antigenic universe, one that includes lipids and glycolipids.



The CD1 genes are located on a different chromosome than the MHC and encode five isoforms (CD1a through e) in human and two homologs of CD1d in mice. These are nonpolymorphic proteins with barely 30% homology to MHC class I or II molecules (*2*, *3*). Despite this marked divergence from MHC structure, a role for CD1 in antigen presentation was shown by the finding that CD1b expression on antigen-presenting cells was required for the responses of certain T cell clones to *Mycobacterium tuberculosis* (*4*). Further studies in this system led to the surprising finding that the mycobacterial antigens recognized by CD1-restricted T cells are not peptides, but instead are lipids (mycolic acids) and glycolipids (lipoarabinomannan and phosphatidylinsositol mannosides) found in the cell walls of these bacteria (*5*, *6*). How could such antigens be presented? Has the immune system evolved a third family of antigen-presenting molecules capable of binding nonpeptide lipid antigens?

The structure described by Zeng *et al.* suggests that this is indeed the case. Although the overall structure of murine CD1d1 is strikingly like that of an MHC class I molecule, the region corresponding to the peptide binding groove of MHC molecules is significantly larger. Narrow at its opening, the CD1 groove descends into a deep cavity lined almost entirely by nonpolar or hydrophobic amino acid side chains. The multiple distinct pockets (generally six or more) for anchoring peptide antigen side chains seen in all MHC binding grooves seem to coalesce in the CD1 structure into just two large pockets. The cluster of tyrosines that contribute to the hydrogen bonding network that anchors the NH_2-terminus of peptides in MHC class I molecules is eliminated in the CD1 structure, and the large CD1 groove has less capacity for hydrogen bonding than any other antigen-presenting molecule yet examined.

The size and topography of the CD1 cavity weigh heavily against its being able to bind peptides after the manner of MHC molecules. Instead, the CD1 cavity appears ideally suited to bind markedly hydrophobic ligands, such as the lipid and glycolipid bacterial antigens that are presented to human CD1-restricted T cells. The mouse CD1 crystal structure contains a poorly defined, unbranched density within the pockets of the deep hydrophobic groove. Although the nature of this density has yet to be clarified, its unbranched structure suggests that it is not a peptide, and it may in fact represent a bound acyl chain. Given the data on antigen specificity of CD1-restricted T cells and the structure described by Zeng *et al.* (*1*), one might hypothesize that the lipid tails of microbial antigens like mycolic acids and lipoarabinomannan anchor in the hydrophobic cavity of CD1, leaving the hydrophilic glycan and oxygen-containing groups protruding out and accessible for interactions with T cell receptors. The putative CD1 antigen binding cavity begins to provide a molecular explanation for the immune system's balanced diet of antigens.

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