

Functional dichotomy between CD1a and CD1b

with

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What is known about CD1 surface molecules?

Lucia Mori: CD1 molecules are MHC class I-like molecules with limited polymorphism, expressed by professional antigen-presenting cells (APC) (reviewed in 1). In humans there are 5 CD1 molecules, CD1a, b, c, d and e and, with the exception of CD1e, all are expressed on the cell surface. Surface CD1 molecules have the capacity to bind and present antigens to T cells. Lipids of self or of microbial origin are the molecules presented by CD1. As lipids are not soluble in aqueous solutions, they are usually associated with membranes or with lipid-transfer molecules and brought inside intracellular compartments where they associate with CD1 molecules. In some instances, small lipid molecules bind to cell surface CD1 and are directly presented without the need to be internalized and intracellularly processed by the APC. The binding of lipids to CD1 molecules and the generation of the antigenic complex is an interesting process ruled by both lipid and CD1 structural characteristics. To sim-

plify, the lipid must have one or more acyl tails of the appropriate length to fit into the hydrophobic pockets of the CD1. The hydrophilic part of the lipid, be this a glycolipid or a phospholipid, protrudes out of the CD1 groove and remains exposed and possibly interacts with the TCR of the T cell. The detailed description of these fine interactions has been made thanks to the resolution of the crystal structure of various CD1-lipid complexes (reviewed in 2). As CD1 molecules recycle in different intracellular compartments (reviewed in 3), the repertoire of lipid antigens presented by individual CD1 molecules will differ. For example, large bacterial lipoglycans which require trimming of big carbohydrate moieties are processed in late endosomes/lysosomes, the intracellular compartment where glycolipids are degraded. This explains why CD1b molecules, which recycle through these compartments, are in most cases the CD1 molecules presenting these microbial antigens.

Have exogenous lipids an influence on the stability of the CD1 surface molecules?

Lucia Mori: We have observed that in the absence of exogenous lipids in the milieu surrounding the cells, CD1a expression at the APC surface is altered. A large part of the cell surface CD1a molecules, although remaining on the plasma membrane, undergo changes in their conformation as detected by staining the cell surface of APC with a panel

of monoclonal antibodies specific for various CD1a epitopes (4). As a consequence, the immunological skills of the CD1a-expressing cells, *i.e.* the capacity to present to T cells, is also affected. However, CD1a molecules are very dynamic because when the lipid concentration in the milieu rises again, the previously altered CD1a molecules now reacquire

both their shape and functional capability of presentation to T cells. We have investigated in detail which lipid molecules can influence the immunological function of CD1a and found that the only lipids able to restore correct CD1a surface expression and

function are the ones able to efficiently bind to CD1a, like glycosphingolipids sulfatide, GM1 ganglioside, and sphingomyelin, but not phosphatidic acid, phosphatidyl ethanolamine, distearin or cholesterol, which have low CD1a binding capacities if any.

How can you explain the functional dichotomy between CD1a and CD1b?

Lucia Mori: The phenomenon just described is indeed peculiar for the CD1a molecules, because CD1b and MHC class I molecules are not affected by lipid deprivation. These differences in function can be explained by the different structures of these antigen-presenting molecules. Human CD1a is characterized by a relatively large F' pocket exposed to the cell surface which allows binding of exogenous lipids in the absence of acidification. The structure of this pocket might facilitate exchange of bound

lipids, and when empty, the molecule might collapse. In comparison human CD1b has a more intricate net of pockets which can probably only open up after acidification, and may be stabilized by a variety of self ligands.

We believe that loading of exogenous lipids stabilizes CD1a molecules and prolongs the persistence of the antigenic complex at the APC surface. In this way CD1a can work as a receptor, scanning the extracellular environment for detection of potentially antigenic lipids.

REFERENCES

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