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Review

Diverse antigen presentation by the Group 1 CD1 molecule, CD1c☆

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ABSTRACT

CD1 molecules are Major Histocompatibility Complex (MHC) class I-like proteins that present diverse lipid antigens to T cells. Most of our understanding of CD1 lipid presentation and T cell recognition has come from study of the invariant Natural Killer T cell recognition of CD1d. However, in addition to CD1d, humans possess three additional CD1 molecules: CD1a, CD1b and CD1c, referred to as the Group 1 CD1s. The lack of an appropriate murine molecule to probe the function and disease relevance of these molecules has hindered understanding their precise immunological role, despite their pivotal role in human immunity. In this perspective, we discuss the progress of functional and molecular studies of CD1c. CD1c has been shown to specifically present lipids from *Mycobacterium tuberculosis* and other related pathogenic mycobacteria. αβ T cells reactive to these lipids presented in the context of CD1c have been characterized and upon stimulation secrete IFN-γ, an important cytokine in tuberculosis disease clearance. Other ligands characterized for CD1c include PI and PC, a lipopeptide with a dodecameric peptide moiety and sulfatides. These structurally and chemically diverse ligands suggest that CD1c has the capacity to present a wide repertoire of antigens to reactive T cells. Indeed, a substantial percentage (~2%) of the circulating αβ T cell population is reactive to CD1c presenting endogenous antigens, suggesting that this particular Group 1 molecule may play an important role in the human immune response.

1. Introduction

CD1c belongs to the family of Major Histocompatibility Complex (MHC) class I like proteins that serve to present lipid-based antigens to T cells. Located outside of the MHC region on chromosome 1 in humans and chromosome 3 in mouse, the CD1 genes are essentially monomorphic, unlike the highly polymorphic MHC classical class I genes that encode the peptide-presenting classical MHC molecules. In humans there are five CD1 molecules that have been grouped, based on their genomic organization, sequence homology and cellular functions into Group 1 (CD1a, CD1b, and CD1c) and Group 2 (CD1d) (Brigl and Brenner, 2004). Both Group 1 and Group 2 CD1 molecules have been shown to present lipid antigens on the cell surface in humans, whereas CD1e is found predominantly intracellularly and is thought to perform chaperone functions. Two *CD1D* genes are present in the mouse, however mice lack the Group 1 and *CD1E* genes likely due to a deletion of the region surrounding the Group 1 genes via a chromosomal translocation. Representatives of both the Group 1 and Group 2 CD1 molecules have been characterized in other species such as guinea pigs, rabbits, pigs, cows, dogs and sheep, therefore the Group 1 deletion appears to be specific to the rodent lineage (Brigl and Brenner, 2004). The lack of Group 1 CD1 molecules represent a distinct difference in lipid antigen presentation potential between humans and mice and thus poses a challenge when extrapolating CD1 function from the mouse model. CD1c, the focus of this perspective, is found in multiple copies in the guinea pig and as a single copy in the dog but has not been characterized in other species. Our understanding of the role of CD1c in human immunity is becoming better-understood thanks to structural information, characterization of CD1c specific T cells and humanized-mouse models where CD1c and the T cells that respond to it can be more easily manipulated. Our current understanding of the structure and function of CD1 molecules, CD1c in particular, is discussed below (Fig. 1).

2. Current status

2.1. Intracellular trafficking and cellular expression profiles of CD1c compared to the other CD1 isoforms

CD1c and the other CD1 molecules are synthesized in the endoplasmic reticulum where they are loaded with endogenous lipids and then trafficked to the cell surface via the secretory pathway (Brigl and Brenner, 2004). Internalization of the CD1 molecules then occurs, and their pathway through the endosomal compartment is dictated by specific sequence motifs in their cytoplasmic tails. CD1c is unique in that it broadly traffics through all compartments, but

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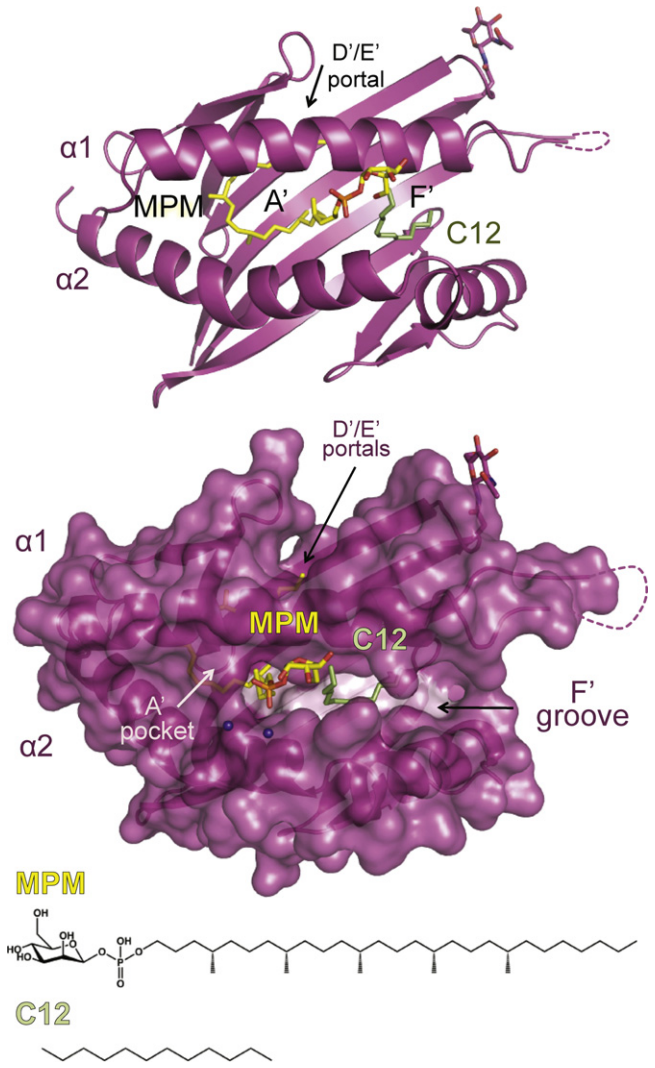

Fig. 1. The structure of the Group 1 CD1 molecule, CD1c, is shown in magenta in ribbon (top) and surface (bottom). CD1c is presenting the mycobacterial lipid derived from M. tuberculosis, mannosyl-β1-phosphomycoketide (MPM), shown in yellow. Apparent in the structure was also a C12 spacer hydrocarbon chain, shown in pale green. The chemical structures of these lipids are shown at the bottom. CD1c has the canonical A′ and F′ pockets, however CD1c has a modified structure, including a unique exit portal (D/E portal) and an open F′ pocket resembling a groove-like structure. These modifications allow CD1c to present a unique repertoire of lipid antigens such as mycoketides and lipopeptides.

the other CD1 isoforms vary in the depth of their trafficking. CD1a does not contain a clear sorting motif and thus is trafficked to early recycling endosomes, whereas CD1b primarily surveys late endosomes and lysosomes. CD1d sorts through early and late endosomes but not in recycling endosomes and is only partially localized in lysosomes. After surveying their respective compartments, where lipid transfer is presumed to occur, the CD1 molecules return to the cell surface where they present their newly loaded lipid antigens. The trafficking pattern of each CD1 type is a key parameter in what lipid antigens they are exposed to, both in proximity and via facilitated transfer through lipid chaperone molecules. Thus, different CD1 isoforms will be exposed to a different repertoire of lipid antigens depending on how they are trafficked. In addition, biochemical parameters such as pH (due to differential acidification of the endosomal compartments) will also have profound affects on lipid loading and protein stability. Other features, such as protein structure, also shape the lipid repertoire presented by each CD1 isoform and are discussed in more detail below.

The unique expression and regulation patterns of the Group 1 CD1 isoforms are another key feature that distinguishes human CD1 molecules from that of the mouse model (Brigl and Brenner, 2004). CD1d, the only CD1 isoform in mouse, is expressed broadly on professional antigen presenting cells (APCs), immature and mature thymocytes and peripheral T cells, in the liver and on the gastrointestinal epithelium. Human CD1d is also broadly expressed; it is detected at low levels on most monocytes, highly expressed on circulating and splenic B cells and also found on thymocytes, epithelial cells, parenchymal cells and vascular smooth muscle in the gut and liver. CD1d expression, however, is characteristically low and does not appear to be up-regulated on mature professional APCs. The Group 1 CD1 molecules, CD1c in particular, are characteristic markers for dendritic cells and other professional APCs. CD1c is found on Langerhans cells, and is unique in its expression on subsets of B cells, including lymph node mantle zones and germinal centers, in splenic marginal B zones and on certain circulating B cells in fetal and adult human blood. CD1c, in combination with the other CD1 family members, likely coordinate to present chemically and structurally divergent classes of self and foreign lipids to T cells, and this coordination may play key roles in combating specific infections or diseases. The study of the structural and biochemical features of lipid presentation by CD1c as well as how these complexes are recognized by CD1c specific T cells will be key steps forward in our understanding of the coordinated functioning of these molecules in the immune response. Furthermore, the established role for CD1c presentation of lipids from pathogenic mycobacteria (*Mycobacterium tuberculosis* for example, see below) makes this a potential candidate for vaccine development against important human diseases such as tuberculosis.

2.2. CD1c lipid presentation and its role in disease

Lipid presentation by CD1 molecules typically involves lipids with two fatty acid chains. These come in the form of phospholipids (like the self lipids phosphatidylcholine (PC) and phosphatidylinositol (PI)) and glycolipids (both self and foreign forms, typically differing in the linkage of their sugar head group). β-Linked carbohydrates are found in both eukaryotes and prokaryotes, however α-linked glycolipids are not found in mammals; this linkage is therefore an ideal sensor for bacterial infection (Brigl and Brenner, 2004). Most of what is known about CD1 lipid presentation has been derived from work on mouse and human CD1d, mainly due to their restriction by invariant Natural Killer T cells (iNKT) (Bendelac et al., 2007). This work has shown that subtle modifications in the length and/or saturation of the fatty acid chains can have profound affects on the effector functions of the reactive T cells, and can influence disease outcome in animal models of multiple sclerosis, rheumatoid arthritis and inflammatory bowel disease. This approach is now being extended to the Group 1 CD1s, and our understanding of what range of lipid antigens these molecules present is improving. Work that we and others have done have demonstrated that CD1c can bind and in some cases present to T cells glycolipids classically presented by CD1d, such as α-galactosylceramide (α-GalCer), GT1b, sulfatides as well as others. Endogenous lipids for CD1c have recently been characterized and include different isoforms of PC and PI (Haig et al., 2011). In addition, through very elegant studies, two unique classes of lipid antigens have been defined for CD1c: (1) those derived from pathogenic bacteria strains such as *M. tuberculosis and M. avium* that contain methylated (isoprenoid) mono-alkyl chains (such as phosphodolichols and phosphomycoketides) (see Brigl and Brenner, 2004) and (2) N-terminally acylated lipopeptides, such as those seen in myristoylated proteins (Van Rhijn et al., 2009). Both of these classes have only one hydrocarbon tail and thus suggest that CD1c may preferentially bind lipids of this type.