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CD1 Presentation of Microbial Nonpeptide Antigens to T Cells

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Introduction

It has long been recognized that T cells are an essential component of efficient cell-mediated immunity against intracellular pathogens. The central paradigm has been that T cells recognize foreign peptides in the context of MHC class I and II molecules. Upon activation, these T cells lyse infected macrophages, depleting the reservoir of cells harboring the pathogen. Furthermore, T cell recognition of antigen leads to the release of cytokines which activate macrophages to kill microbial organisms. For many such pathogens, considerable effort has been invested towards identifying peptide antigens which can engender cell-mediated immunity with the ultimate goal of developing vaccines against infectious disease. The drawback of this approach lies in the polymorphic nature of MHC molecules. Therefore, peptides which bind to one individual's MHC and activate that person's T cells, may not bind to another person's MHC and therefore cannot be recognized by their T cells. Thus, an effective vaccine requires the delineation of peptide antigens which can bind to and be presented by a variety of MHC molecules.

A new advance in our understanding of T cell biology has been the demonstration of T cell recognition of nonpeptide antigens. In one system, $\gamma\delta$ T cells were shown to recognize isopentenyl pyrophosphate and related structures in the isoprenoid family (1). The ability of $\gamma\delta$ T cells to recognize these antigens may occur in a manner independent of antigen-presenting molecules. In a second system, $\alpha\beta$ T cells have been shown to recognize lipid and lipoglycan antigen in the context of CD1 molecules (2–4).

CD1 family of MHC-related proteins

The human cluster of differentiation I (CD1)¹ gene family consists of five nonpolymorphic genes, CD1A, -B, -C, -D, and -E, mapped to a cluster on chromosome 1 (for review see reference 5). Human CD1 has a unique tissue distribution, with

CD1a, -b, and -c present on thymocytes but not peripheral blood T cells. Human CD1 are also present on professional antigen-presenting cells including dendritic cells, Langerhans cells, and mantle zone B cells. The structural homology of CD1 with class I and class II molecules suggests an antigen-presenting function. However, the amino acids encoded in the predicted antigen binding site, the $\alpha 1$ and $\alpha 2$ domains, are extremely hydrophobic.

Recognition of CD1 by human T cells

A unique function of human CD1 is the ability to present nonpeptide antigen to T cells. Specifically, human CD1b and CD1c have been shown to present lipid and lipoglycan antigens of *Mycobacterium tuberculosis* and *Mycobacterium leprae* to T cells (2–4, 6). Two major antigens have been elucidated, both derived from the cell wall of mycobacteria: mycolic acids and lipoarabinomannan. Mycolic acids are branched long chain fatty acids specifically found in mycobacteria. Lipoarabinomannan (LAM) contains an arabinose head, branched mannose core, and phosphatidyl inositol which contains two fatty acids: tuberculostearic acid and palmitic acid. For lipoarabinomannan, the data suggested that T cell recognition was at the level of the branched mannose core. These data do not preclude the possibility that human CD1 can present peptide antigen, as convincingly shown for murine CD1 (7).

CD1 antigen presentation pathway

CD1-restricted T cell recognition of nonpeptide antigens involves an intracellular presentation pathway (Fig. 1). The CD1 antigen presentation pathway has novel aspects, although it shares some features in common with the classical MHC class II pathway. It has been demonstrated that the macrophage mannose receptor is involved in the uptake of LAM, through binding of its mannose core. The mannose receptor delivers LAM to late endosomal and lysosomal vesicles, as well as to the MHC class II antigen loading compartment (MIIC). The uptake of LAM into endosomes and its presentation to LAM-reactive T cells are blocked by reagents which interfere with the mannose receptor (8).

In the MIIC compartment, the mannose receptor, LAM, and CD1b colocalize, suggesting that this is the place where LAM is loaded onto CD1b molecules. CD1b is endocytosed at the plasma membrane in coated pits and coated vesicle structures, transits to early endosomes, and is then delivered to the MIIC. In striking contrast to other MHC molecules, CD1b endocytosis and trafficking to the MIIC compartment were shown to be directed by a YXXZ (where Y is a tyrosine, X is any amino acid, and Z is a hydrophobic residue) motif contained in the cytoplasmic tail of the molecule (9). The endosomal localization motif is essential for antigen presentation by CD1b, suggesting that trafficking of CD1b through lysosomal compartments is required for loading of antigen into CD1b.

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1. Abbreviations used in this paper: CD1, cluster of differentiation I; LAM, lipoarabinomannan; MIIC, MHC class II antigen loading compartment.

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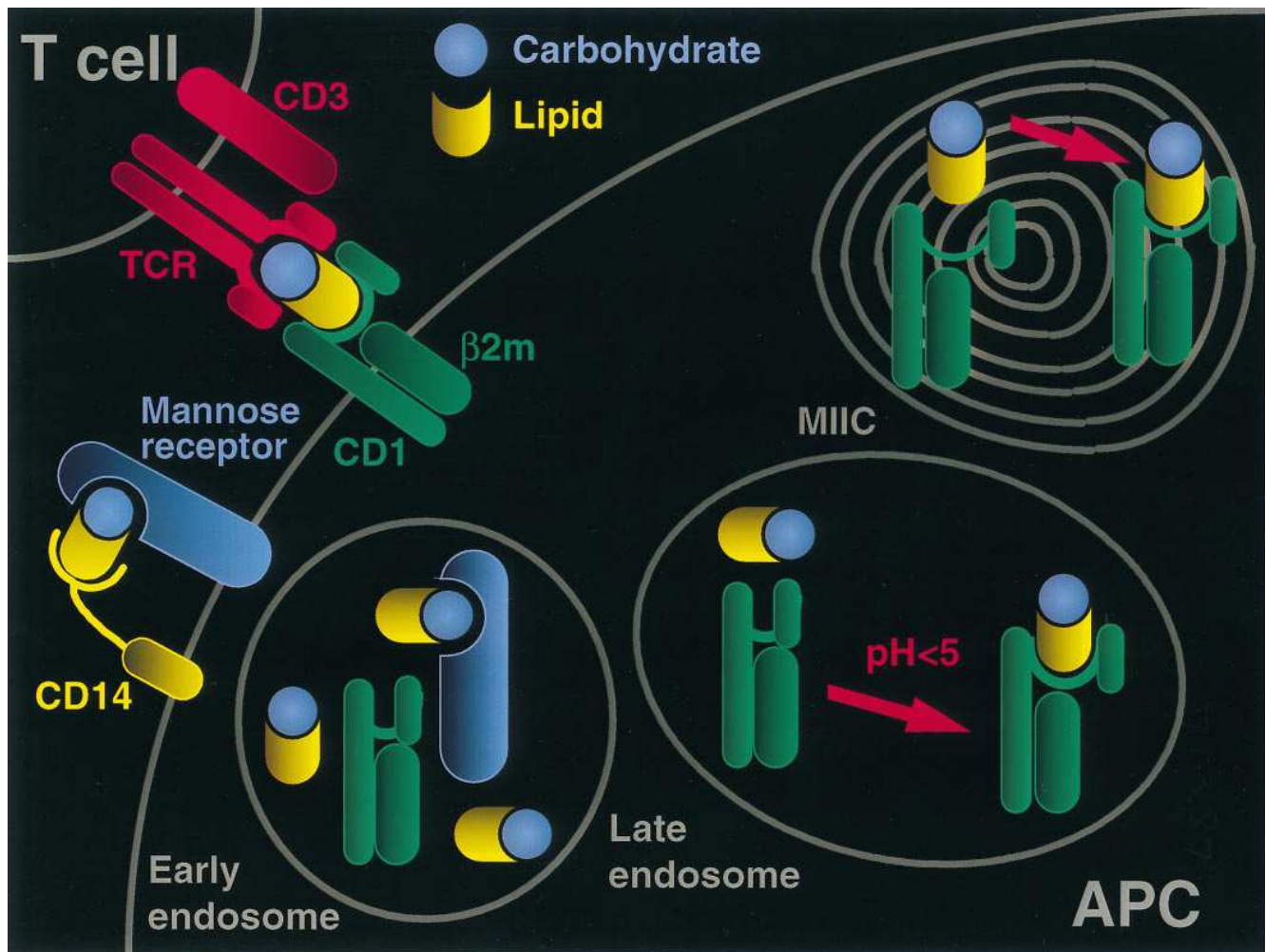


Figure 1. The CD1 antigen presentation pathway. Lipoglycan antigens bind to antigen-presenting cells via pattern recognition molecules such as CD14 and the mannose receptor. The mannose receptor can traffic such antigens through the endosomal pathway, where at acid pH, lipoglycans may bind via their lipid portions to CD1. The antigen-CD1 complex traffics to the cell surface where it is recognized by the appropriate T cell receptor.

The presentation of both LAM and mycolic acids is also dependent on the acidification of endosomes, since lysosomotropic drugs which prevent endosomal acidification block antigen presentation. At $\text{pH} < 5$, the biophysical properties of CD1b and CD1c are dramatically altered to facilitate the direct interaction of CD1 with nonpeptide ligands. Principally, at acid pH there is unfolding of the α -helical part of CD1. This can influence antigen binding, since the two α -helices of antigen-presenting molecules form the walls of the antigen-binding groove. This groove is believed to be deeper and narrower than the class I molecule groove as shown for the mouse CD1 (10). Indeed, for human CD1b and CD1c, the unfolding of the α -helices exposes a hydrophobic binding site which accommodates the lipid portion of LAM. At acid pH, the direct physical binding of LAM to CD1b is of high affinity, 3.2×10^{-8} M, comparable to high affinity peptide-MHC interactions (Ernst, W.A., M. Kronenberg, J. Maher, S. Cho, D. Chatterjee, and R.L. Modlin, manuscript submitted for publication).

This novel antigen presentation pathway bridges two arms of the immune system. Innate immunity pertains to those cells

which are preprogrammed to respond in certain ways, including macrophages, natural killer cells, and mast cells. The mannose receptor, a pattern recognition marker, is part of the innate immune response. In this manner, the mannose receptor is able to traffic antigen first recognized by the innate immune system to T cells, which are part of the acquired immune response since their selection and expansion involves the development of memory. In that manner, the CD1 antigen presentation pathway links together the innate immune system and the acquired immune response.

CD1-restricted T cells in microbial immunity

Investigation of human leprosy has provided direct evidence for the involvement of the CD1-restricted T cells in host response to infection. CD1a, -b, and -c were expressed on dendritic cells in the granulomas within the skin lesions of leprosy patients. Furthermore, the frequency of CD1+ cells correlated with the level of cell-mediated immunity to *M. leprae*, being 10-fold more abundant in the granulomas of patients with the immunologically responsive tuberculoid form of the disease, as

compared with the unresponsive lepromatous form (Sieling, P.A., M. Mehrali, T.H. Rea, M.B. Brenner, R.L. Modlin, and S. Porcelli, manuscript in preparation). It is likely that these differences are related to the level of GM-CSF in the lesions, being greater in the tuberculoid lesions. In addition, IL-10, which is specifically found at the site of infection in the lepromatous form, has been shown to downregulate CD1 expression (11). Further evidence for a role of CD1 presentation of antigens in immunity to mycobacterial infection in vivo includes the isolation of CD1-restricted T cells from patients with mycobacterial infection. Initially, a CD1b-restricted, *M. leprae*-specific T cell line was derived from a cutaneous leprosy lesion (4) and more recently, *M. tuberculosis*-reactive CD1-restricted T cell lines from the peripheral blood of patients with tuberculosis (12).

The study of CD1-restricted T cells from patients with mycobacterial infection as well as normal healthy donors has revealed certain shared functional features. First, all the CD1-restricted T cell lines isolated produce high levels of IFN- γ , but little or no IL-4 upon stimulation with mycobacterial antigen. This Th1 cytokine pattern can directly contribute to cell-mediated immunity against intracellular infection by enhancing T cell proliferation and macrophage activation. Secondly, CD1-restricted T cells also show a high degree of cytolytic activity against antigen-pulsed macrophages. Furthermore, these T cells can lyse macrophages infected with virulent *M. tuberculosis*. The induction of cytotoxicity is dependent on antigen presentation and T cell recognition since lysis is blocked by antibodies to CD1b. Lysis of highly infected macrophages can contribute to host defense either by directly killing the bacteria or indirectly by discharging the pathogen and thereby allowing freshly recruited macrophages to take up and more effectively dispose of the bacteria (13).

Two mechanisms of cell-mediated cytotoxicity differentially contribute to the outcome of infection with intracellular pathogens. CD4-CD8⁻ (double negative) CD1-restricted T cells lyse targets through the Fas/Fas-ligand pathway, while the lysis of targets by CD8⁺ cells depends on the release of granules containing perforin and granzymes. However, only the CD8⁺ subset of CD1-restricted T cells kills the intracellular *M. tuberculosis* during the lysis of the target cell. While the double negative T cells may have an immunoregulatory role by reducing the local cellular infiltration and thereby limiting tissue damage, the CD8⁺ T cells may have the greatest impact in combating intracellular pathogens (12). The mechanisms by which CD8⁺ T cells kill the bacteria remain to be determined and are of potentially important therapeutic interest.

Nonpeptide antigens of other pathogens

Description of the CD1 presentation pathway, its unique ability to present nonpeptide antigens, and evidence for its role in host immune responses were pioneered in the study of mycobacterial infections. However, nonpeptide antigens sharing very high structural similarity with LAM or mycolic acids are present in many other pathogens. Lipoteichoic acid in *Staphylococcus* and *Streptococcus* are analogous in structure to LAM. Similarly, the lipopolysaccharides of gram-negative organisms share structural homology with LAM. The capsular polysaccharides of some gram-negative organisms are linked to palmitic acid, making them logical candidates for presentation by CD1 to T cells. Homology can be found in the structural components of some parasitic organisms, for instance the lipophos-

phoglycan of *Leishmania*. We anticipate studies delineating involvement of CD1-restricted T cells in these and other infectious diseases.

Advantage of nonpeptide antigens as vaccine candidates

The discovery of nonpeptide lipid and glycolipid antigen recognition by CD1-restricted T cells defines a new paradigm for immune recognition and provides a distinct mechanism for host responses to infection. It may be possible to exploit this aspect of the immune response in the area of vaccine development. Current immunoprophylactic strategies use protein subunit vaccines, which may vary in effectiveness according to the MHC haplotype of the individual.

The advantage of antigens presented by CD1 resides in the nonpolymorphic nature of these antigen-presenting molecules. That is, everyone has the same CD1 molecules. Therefore, these nonpeptide antigens will bind to everyone's CD1 and can be recognized by everyone's T cells. The next critical step will be to determine whether CD1-restricted T cell responses to nonpeptide antigens are sufficient for protective immune responses to microbial pathogens.

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