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# The role of group 1 and group 2 CD1-restricted T cells in microbial immunity

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**Abstract**

Group 1 and group 2 CD1 present both self and microbial lipid antigens to T cells. While group 1 CD1-restricted T cells are known for their ability to recognize mycobacterial glycolipid antigens, group 2 CD1-restricted T cells are recognized as regulatory T cells that can influence the outcome of innate and adaptive immune responses. The evidence that these T cells contribute to host defense against infectious diseases is reviewed.


*Keywords:* CD1; Microbial immunity; Natural killer T cells

## 1. Introduction

In 1992, human $CD4^{-}8^{-}$ T cells were discovered to recognize mycobacterial antigens presented by CD1b [1]. Subsequently, the mycobacterial cell wall lipid mycolic acid was the first purified antigen shown to be presented by CD1b [2]. Although CD1-restricted T cells have now been implicated in a variety of immunological processes, including tumor immunity, autoimmune disease, and immunoregulation, the impact of these original studies on the area of microbial immunity was enormous. The finding that CD1 presents lipids and glycolipids greatly expanded the number of potential microbial antigens recognized by T cells. Lipids and glycolipids are important structural components of many human pathogens and their structure is often sufficiently different from their eukaryotic counterparts that they may be considered "foreign". Therefore, these molecules have the potential to be highly antigenic. Furthermore, as lipids and glycolipids are the products of multi-step biosynthetic pathways, rapid variation of these antigens is unlikely to occur, in contrast to microbial protein antigens. Finally, unlike MHC antigen-presenting molecules, few CD1 alleles exist. This suggests that any CD1-presented antigens that elicit protective immunity would make useful vaccines, as even diverse ethnic groups should respond to them. This paper will review our current understanding of the role of CD1-restricted T cells in host defense against microbial pathogens.

The CD1 family of antigen-presenting molecules is an evolutionarily conserved family of genes that are found in mammals. The human CD1 genetic locus is found on chromosome 1 and consists of five genes: CD1A, -B, -C, -D, and -E. Based on their primary structure, the CD1 genes from humans and other species are classified as either group 1 (CD1A, -B, and -C) or group 2 (CD1D). Relevant to the discussion below, mice and rats lack group 1 CD1 genes and instead have only group 2 CD1 genes. The CD1 polypeptide pairs with $\beta_2$ microglobulin and has an overall topology that resembles class I MHC molecules. The three-dimensional crystal structure has been solved for human CD1a and CD1b, and murine CD1d [3–5]. All three molecules have antigen-binding grooves composed primarily of hydrophobic amino acids that create the perfect environment to bind lipid antigens. Important differences exist between their structures, particularly the size and shape of the antigen-binding groove, and these characteristics are likely to affect the size and nature of the lipid molecules that bind to the different CD1 isoforms.

One question is whether the structural differences that form the basis of classifying CD1 molecules as either group 1 or group 2, have any functional consequences. T cell recognition of CD1 in the absence of exogenous antigen has been observed for both group 1 and group 2 CD1-restricted T cells.

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The presentation of endogenous self-lipids is thought to be the basis for this type of direct recognition or "autoreactivity". While CD1a, -b, and -c also present microbial antigens to T cells, the recognition of microbial antigens by CD1d-restricted T cells has not yet been shown. In contrast, CD1d is recognized by natural killer (NK) T cells that, when activated, can affect many immunological processes, giving rise to the notion that these T cells function as immunoregulatory cells. In contrast to the group 1 CD1 proteins, which have only been shown to present antigens derived from mycobacterial species and not other microbes, CD1d-restricted T cells participate in host immunity to a variety of pathogens, including bacteria, fungi, parasites, and viruses [6]. One of the important issues in the CD1 field is whether this dichotomy represents a meaningful difference in the biology of group 1- and group 2-restricted T cells, or whether it is a bias that is due to the experimental approaches used to study group 1 CD1 (human) and group 2 CD1 (primarily rodent).

## 2. Group 1 CD1-restricted T cells

### *2.1. Group 1 CD1-restricted T cells recognize microbial antigens*

Group 1 CD1-restricted T cells are most remarkable for their ability to recognize non-peptide antigens. The first example of this was the human CD1b-restricted $CD4^{-}8^{-}$ T cell line DN1. The DN1 T cell line specifically recognizes mycolic acid (MA), which is unlike any previously described T cell antigen. Mycolic acids are a heterogeneous family of α-branched β-hydroxy carboxylic acids that contain two long acyl chains with a combined length of up to 90 carbons and are an important structural component of the mycobacterial cell wall. CD1b also presents other lipid molecules found in the cell wall of *Mycobacterium tuberculosis* to human T cells (see Table 1). For example, the T cell line LDN5 was isolated from a leprosy skin lesion, and it recognizes glucose monomycolate (GMM) [7]. GMM is a mycolic acid molecule that has been modified by the addition of glucose on the carboxylic acid function. The exquisite antigen specificity for antigen that is so characteristic of conventional T cells is also observed for CD1-restricted T cells and is exemplified by DN1 and LDN5. Although CD1b presents both MA and GMM, DN1 recognizes MA but not GMM; DN5 recognizes GMM but not MA. Thus, the presence or absence of a sugar molecule dramatically affects recognition of these antigens. Finally, another class of cell wall lipids, the phosphatidylinositol mannosides, can also be presented by CD1b to human T cells. All of these CD1b-restricted antigens have a similar structural motif: a polar head group and two acyl chains.

Table 1
Microbial antigens recognized by CD1-restricted T cells

| CD1 molecule | Bacterial and foreign antigens |
|---|---|
| CD1a | Didehydroxymycobactin |
| CD1b | Mycolic acid, GMM, phosphatidylinositol dimannoside (PIM), sulfoglycolipids, lipoarabinomannan (LAM) |
| CD1c | Mannosyl-β1-phosphoisoprenoid |
| CD1d | α–galactosylceramide |

Mycobacterial antigens presented by the other CD1 isoforms have also been identified. CD1c presents the mycobacterial mannosyl-β1-phosphoisoprenoids to the $CD8^{+}$ CD1c-restricted human T cell line CD8-1 [8]. These molecules differ from the CD1b antigens as they have a single acyl chain. The first CD1a-restricted antigen was recently identified and resembles mycobactin, a lipopeptide produced by *M. tuberculosis* [9]. Therefore, the paradigm of CD1-restricted antigens consisting of two acyl chains and a polar head groups needs to be modified to take into account these newly identified antigens. As additional antigens are identified, it will be interesting to learn whether each CD1 isoform selects a unique set of lipid structures that is presented to and recognized by T cells.

### *2.2. Intracellular CD1 trafficking patterns intersect with intracellular pathogens and antigens*

Differences in the spectrum of lipid antigens presented by each CD1 isoform could also emerge because each one has a distinct intracellular trafficking pattern. This insight is based largely on the work of Brenner and his colleagues, who have characterized the intracellular trafficking patterns of the different CD1 isoforms through the endosomal system of APC [10]. For example, once CD1b reaches the cell surface, it undergoes recycling and traffics through late endosomal and lysosomal compartments, intersecting with the MHC class II-containing compartment (MIIC), and then moves back to the surface. In contrast, CD1a is expressed primarily on the cell surface, and its recycling pathway only penetrates as deep as the recycling endosome. CD1c traffics through both early and late endosomal compartments. These findings have implications for the types of lipid antigens each isoform may encounter, particularly when a cell is infected with pathogens that may inhabit distinct intracellular niches within the cell. Clearly, this aspect of CD1 biology has most relevance to how CD1-restricted T cells identify infected cells. Although this is an attractive hypothesis, other pathways exist for the uptake of bacterial lipid and glycolipid molecules by APC. For example, transfer of mycobacterial lipids from infected cells to uninfected APC occurs, while other antigens, such as lipoarabinomannan, can be taken up by specific receptors [11,12].

### *2.3. Antimicrobial effector functions of CD1-restricted T cells*

CD1-restricted T cells have several characteristics that make them particularly effective effector T cells. Most CD1-restricted T cells are cytolytic and can lyse a variety of target cells in an antigen-specific and CD1-restricted manner. The molecular pathways used by CD1-restricted T cells to kill target cells have been characterized in some detail, and appear