The evolved functions of CD1 during infection

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CD1 proteins display lipid antigens to T cell receptors. Studies using CD1d tetramers and CD1d-deficient mice provide important insight into the immunological functions of invariant NK T cells (iNKT) during viral and bacterial infections. However, the mouse CD1 locus is atypical because it encodes only CD1d, whereas most mammalian species have retained many CD1 genes. Viewed from the perspective that CD1 is a diverse gene family that activates several of classes of T cells, new insights into lipid loading and infection response are emerging.

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CD1 antigen presentation was discovered using human T cells that recognize CD1a, CD1b, or CD1c proteins [1,2]. Separately, a distinct population of CD3+ cells that persist in MHC knockout mice were designated 'invariant NK T cells' (iNKT) based on their (nearly) invariant TCR Vα14 chains and Vβ chains, as well as natural killer (NK) locus encoded markers [3,4]. Later, mouse iNKT cells were found to recognize CD1d, so that the previously separate fields of CD1 and NKT cells merged [5]. Human T cells with Vα24 TCRs were found to have the same molecular recognition properties as Vα14 mouse iNKT cells [6,7] as well as a shared lineage-specific transcription factor, promyelocytic leukemia zinc finger (PLZF) [8••]. In addition, certain mouse and human T cells recognizing CD1d were found to lack the conserved TCRs [9] and antigen reactivity [10,11], that normally characterize iNKT, so that the NKT definition was expanded to include also 'diverse' NK T cells.

Here, we review recent advances in understanding the role of these various populations of CD1-reactive T cells during infection. Increasingly, differences in the cellular expression patterns, subcellular trafficking, antigen-binding grooves, and phenotypes of the responding T cells make the case that CD1a, CD1b, CD1c, CD1d, and CD1e proteins have distinct functions. Further, new insights into nonhuman CD1 genes show that CD1 gene families are large and vary from species to species. These studies emphasize that CD1-restricted T cells and NK T cells are not synonymous, and make the case that understanding the functions of CD1 involves looking at and beyond NKT.

CD1 presents lipids to the TCR

Many crystal structures of CD1 proteins bound to lipid antigens show that the alkyl chains are inserted into a hydrophobic groove, allowing presentation of carbohydrate, peptidic, or inorganic components of amphipathic antigens [12]. Recent studies of ternary complexes show how the T cell receptor α and β chains of iNKT contact the CD1–glycolipid complex to form a binding footprint [13••,14]. The NKT footprint is quite different from that of TCRs contacting peptide-MHC [15]. The iNKT TCRs are rotated and pushed laterally so that the α chain binds near the center of CD1d, and the TCR β chain makes limited contact at the margin of CD1d.

These new crystal structures explain in detail why certain Vα and Vβ chains are conserved in natural iNKT populations. The CDR3α loop plays the dominant role in binding to the CD1d platform, and the direct contacts with the protruding galactose unit are mediated by Jα18 residues. On the basis of mutational studies [16], molecular models [14], and other data [17], the global orientation of the TCR and other aspects of the recognition event visualized in these crystal structures are also likely conserved for natural α-linked glycolipid antigens (Figure 1) [17–19]. Whether this rotated and laterally displaced footprint is used by diverse TCRs that recognize the glycolipid, lipid, and lipopeptide antigens presented by CD1a, CD1b, CD1c, or CD1d, remains to be seen.

New bacterial targets

Unlike CD1a, CD1b, and CD1c, the CD1d protein is expressed in the liver and on certain gastrointestinal epithelia. Recent studies implicate CD1d and iNKT cells in controlling bacterial colonization of the gastrointestinal tract of mice [20]. Small intestinal colonization with both Gram-negative and Gram-positive organisms was increased in CD1d knockout mice, and organisms translocated across the intestinal epithelium. NKT cells

Figure 1
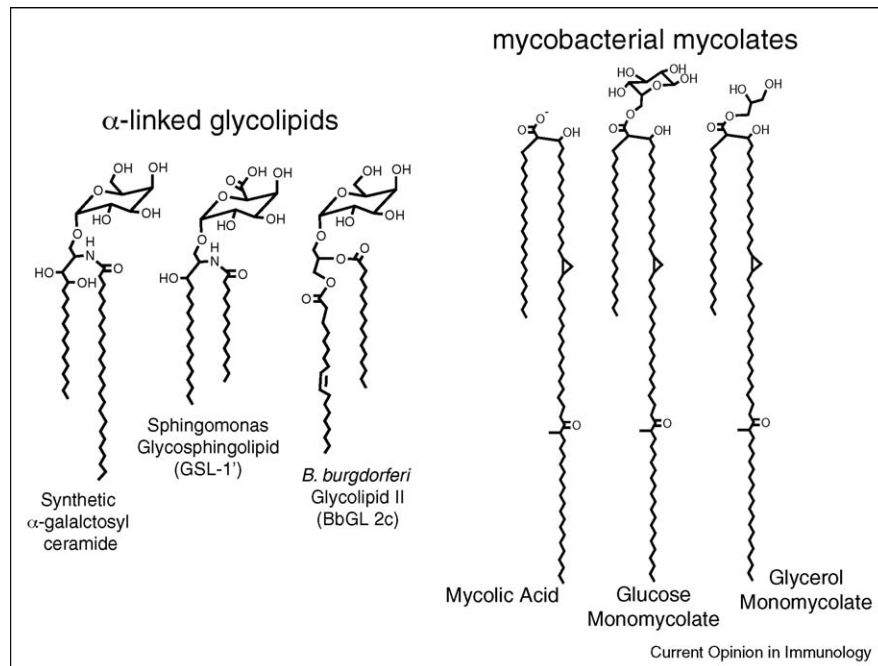
Structural homologies among CD1 ligands. Invariant NKT cells recognize structurally related glycolipid antigens that differ in the composition of their lipid anchors, but shared an α-linked galactose unit. Three types of mycobacterial mycolate antigens are recognized by CD1b-restricted T cells. These foreign molecules have lipid anchors (C72–86) that are much larger than most self diacylglycerols or sphingolipids. CD1b is the only CD1 protein that is known to have a groove large enough to accept this type of antigen.

triggered CD1d-expressing Paneth cells to secrete antimicrobial peptides [20].

Invariant NKT cells respond to *Borrelia burgdorferi*, the causative agent of Lyme disease. Mice that are usually resistant to infection become more susceptible when the CD1d gene is deleted [21], and levels of protective *Borrelia*-specific IgM are reduced [22]. An antigenic target of the response was identified as the *B. burgdorferi* glycolipid II (BbGL-II), an α-galactosyl diacylglycerol that constitutes 12% of lipid in this pathogen [17]. This antigen has obvious structural homology to α-galactosyl ceramide (Figure 1), and BbGL-II loaded CD1d tetramers stain liver NKT cells during infection, indicating that the molecular mechanism of activation involves CD1–glycolipid–TCR contact. Infection of Jα18-deficient mice with *B. burgdorferi* resulted in prolonged arthritis and bacterial persistence, raising the possibility that lipid recognition by iNKT is relevant to a chronic syndrome [23]. Lastly, the recognition of *Borrelia* antigens by mouse NKT cells may be relevant to human Lyme disease because human NKT cells recognize a variant of BbGL-II [17], and unpublished studies have identified CD1 gene expression in human skin affected by acute borrelial infection (Yakimchuk and Moody, unpublished).

For CD1a, CD1b, and CD1c proteins, the most extensively studied bacterial pathogens are *Mycobacterium tuberculosis* and *Mycobacterium leprae*. Following the discovery of free mycolic acid [24] and glucose monomycolate antigens [25], glycerol monomycolate isolated from *Mycobacterium bovis* was recently found to stimulate a human CD4+ T cell clone (Figure 1) [26•]. Additionally, polyclonal mononuclear cells from humans latently infected with *M. tuberculosis* produced IFN-γ in response to glycerol monomycolate at a higher frequency than cells from noninfected controls or actively infected tuberculosis patients. Along with studies of mannosyl phosphomycoketides, mycolic acids, glucose monomycolates, and sulfated trehalose lipids [27–29], this patient study supports the hypothesis that tuberculosis infection promotes expansion of human lipid reactive T cells *in vivo*. However, whether or not such responses are durable and subject to recall, such that vaccination might provide protection from infection, remains unknown.

CD1 responses to viruses

NKT cells respond to viral infections involving HIV [30] HSV [31], and influenza [32]. These new observations raise the question of whether the mechanism of virus recognition involves cognate recognition of a virally produced antigen by the TCR, indirect recognition of cellular changes induced by viruses, or both. To date, no virally derived CD1 ligands have been identified. However, new evidence shows that CD1c presents an N-terminally acylated lipopeptide similar in sequence to HIV nuclear envelope factor (Nef) [33•]. This finding

supports the hypothesis that cellular lipidation of viral proteins may generate antigens presented by CD1 [34]. In addition, viruses trigger Toll-receptors and cause other cellular changes in ways that can activate NKT cells indirectly via IL-12, altered CD1d expression, or increased production of endogenous sphingolipids [18,35,36]. For example, TLR ligation affects glycosphingolipid biosynthesis by dendritic cells and is associated with increased IFN-γ release by NKT cells [37,38].

Microbes upregulate CD1 expression

CD1d is constitutively expressed on thymocytes, B cells, monocytes, macrophages, and myeloid dendritic cells (DC) at various stages of maturation. In contrast, CD1a, CD1b, and CD1c proteins are absent on blood monocytes in the circulation, and two new studies help explain why. Serum immunoglobulin (Ig) and activators of the peroxisome proliferator activator receptor-γ (PPAR-γ) are present in the serum and tonically inhibit CD1a, CD1b, and CD1c on human monocytes [39,40]. A human patient with common variable immunoglobulin deficiency expressed CD1a, CD1b, and CD1c, and this expression was downregulated after restoring immunoglobulin (Ig) to physiologic levels. Thus seems to be Ig necessary and sufficient for control of CD1 expression on circulating monocytes [39].

When monocytes exit the circulation, they are presumably released from inhibitory signals found at high concentrations in the serum, and they also encounter stimuli that increase CD1a, CD1b, or CD1c gene expression when present in tissues, as seen in patients with autoimmune disease [41] or infection [42]. The localized upregulation of CD1a, CD1b, and CD1c proteins on maturing myeloid DCs at sites of inflammation may allow CD1-expressing DCs and CD1-restricted T cells to generate proinflammatory positive feedback loops [43]. These CD1-inducing signals involve GM-CSF, IL-4, Toll-like receptor (TLR) 2, and TLR 5 [44,45]. Mycobacteria produce both ligands for CD1 proteins and signals that induce CD1, so they might provide dual signals to promote CD1-restricted T cell activation at the site of infection [46].

Microbes downregulate CD1 expression

Several studies of monocyte derived DCs have found that CD1a-expressing, CD1b-expressing, and CD1c-expressing cells decline in number after exposure to mycobacteria in culture [47–50]. These *in vitro* studies led to the speculation that drastic losses of CD1 expression might occur at the site of mycobacterial infection *in vivo* and might represent a physiological means of immune evasion. However, other *in vitro* studies failed to confirm CD1 downregulation [44,51]. More importantly, studies of CD1 expression in the lungs, lymphoid tissues, and skin of humans with tuberculosis and leprosy do not support the immune evasion hypothesis because

CD1a-expressing, CD1b-expressing, and CD1c-expressing cells are found at high levels at sites of infection [42,45,52]. Although mycobacteria do not prevent CD1 expression in a general way in all humans, a subset of humans with the lepromatous form of leprosy have reduced levels of CD1 expression at the site of infection [42,53].

Viral infection also downregulates cell surface expression of CD1. The HIV peptide Nef interacts with human CD1d, leading to decreased expression on the cell surface and diminished activation of CD1d-restricted NKT cells [54]. Kaposi sarcoma-associated herpesvirus and herpes simplex virus 1 downregulate CD1 surface expression using distinct mechanisms involving ubiquitination and lysosomal targeting, respectively [31,55]. The detailed molecular mechanisms of rerouting identified here, as well as the precedent of virally mediated MHC class I immunoevasion, now provide a rationale to examine CD1d expression during *in vivo* infection with viruses.

CD1 beyond NKT cells

T cells recognizing human CD1a, CD1b, and CD1c or their mammalian orthologs do not fall under historical or modern definitions of NKT cells because they are not known to commonly express NK receptors or invariant TCRs, and they do not recognize CD1d (Figure 2). Lacking a catchy jargon term like iNKT, they are designated according to a simple, descriptive, and accurate naming convention: CD1x-restricted T cells, where x is the identifying CD1 gene (Figure 2). Many CD1-restricted T cells have functions that are distinct from iNKT cells because they express diverse TCRs, present chemically diverse antigens and recognize different types of cells (Figure 2). Also, the study of gene induction patterns on myeloid DCs makes clear that CD1a, CD1b, CD1c, and CD1e are linked to one another, whereas CD1d is different [44,56].

Emerging pictures of isoform-specific function

Further, each of the five CD1 human proteins is emerging to have a distinct personality (Figure 2). Such gene-specific functions can be most readily understood for CD1e. After exiting the endoplasmic reticulum to the golgi apparatus, CD1e is diverted directly to endosomes without evidence of expression at the surface, suggesting that CD1e does not display antigens at the cell surface [57]. Recent studies show that unlike other CD1 proteins, CD1e is released into the lumen by proteolytic cleavage [58], where it can float freely and promote the molecular trimming of phosphatidylinositol antigens and their subsequent presentation by CD1b [59,60].

CD1b is emerging as the CD1 isoform that focuses on presenting large, exogenous foreign antigens that are

Figure 2
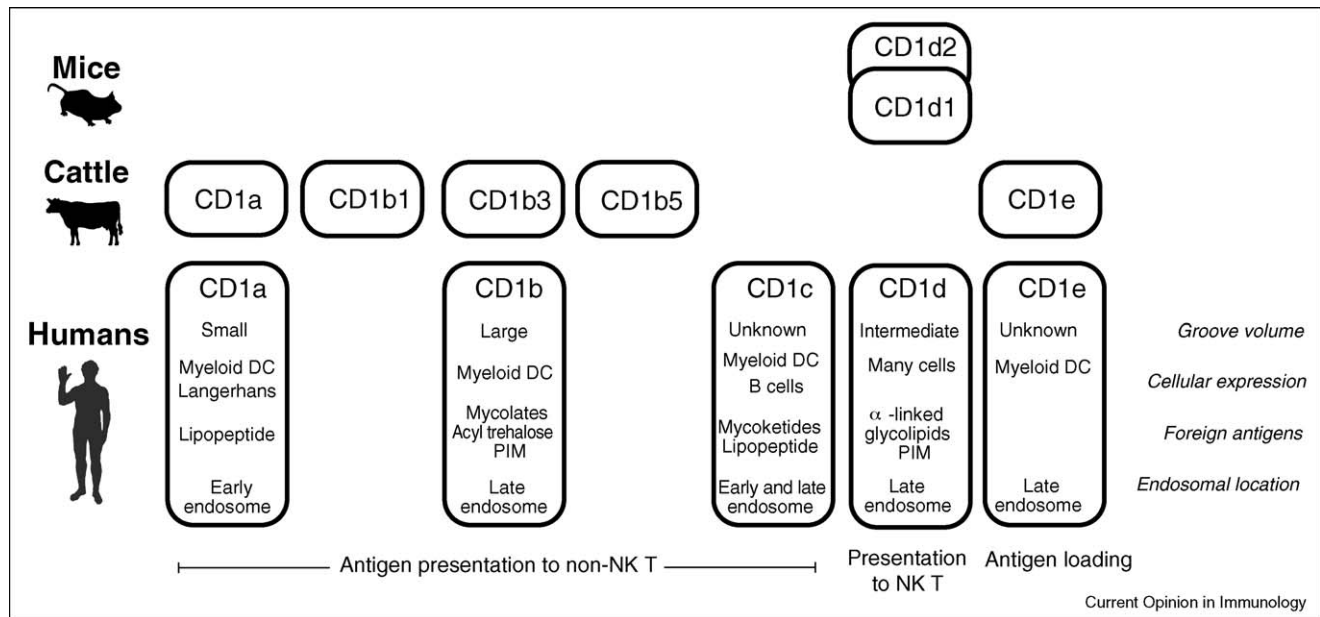
Humans, cows, and mice reflect differing patterns of CD1 gene conservation among mammalian species. Among CD1-restricted T cells, humans have NKT and non-NKT cells, whereas mice have only NKT cells, and cows have only non-NKT cells. Recent data suggest that the average number of CD1 genes in mammalian species is higher than in humans, so the mouse and other muroid rodents are distinctly atypical. CD1d1 and CD1d2 are highly homologous, but the three bovine genes that belong to the CD1b group have differing cytoplasmic tail sequences and differences in $\alpha1$ and $\alpha2$ domains that likely affect groove structure. This figure does not show the two bovine CD1b pseudogenes and the two bovine CD1d pseudogenes because they are predicted not to be translated into proteins.

taken up into lysosomes. With an interior volume of approximately 2300 cubic angstroms, the CD1b groove is much larger than that in CD1d and nearly twice the volume of the CD1a groove [61]. Correspondingly, the polyacylated trehaloses and mycolates, including the new glycerol monomycolate antigen, are lipids in the size range of C70–80, much larger than the C18–48 lipids presented by other CD1 isoforms. In fact, the longest C84–86 mycobacterial mycolates exceed the predicted volume of the CD1b groove and may protrude through a small opening at the bottom of the groove in the C′ pocket [62]. The insertion of such large lipids into CD1b may be more dependent on lipid transfer proteins and acid-mediated steric changes than seen for other CD1 proteins [59,63,64]. CD1a and CD1c proteins show fewer requirements for acid-mediated loading and less prominently accumulate in the most acidic lysosomal compartments [65,66]. These biophysical properties of CD1b suggest that it is specialized to capture exogenous long chain foreign lipids in preference to shorter self-phosphodiacylglycerols, sphingolipids, and other self-lipids that comprise mammalian membranes (Figure 2). Correspondingly, T cells autoreactive to CD1b have been less frequently observed than those directly recognizing CD1a or CD1c [1,41,67,68].

Surprising patterns of CD1 evolution

The discovery of an avian CD1 gene [69,70] and new evidence that it folds to form an antigen-binding pocket [71] proves that the CD1 system predates the emergence of mammals. However, unlike classical MHC class I molecules, which are present in all jawed vertebrates including fish, CD1 has not been identified in fish [72]. Also, recent studies suggest that CD1d proteins and NKT cells are apparently lacking in ruminants [73,74]. Figure 2 illustrates how modern species have survived while lacking any one of the five CD1 gene types. However most mammalian species have preserved large gene families, with up to 12 CD1 genes. Also, no mammalian species lacking all CD1 proteins has been identified since the discovery of the CD1 locus more than 20 years ago, implying that CD1 has an indispensable role in the mammalian immune system [75].

Thus, it appears CD1d and NKT cells per se are not universally conserved, but instead that the CD1 family is represented in some form in all amniote species. If all mammalian species express at least one CD1 protein, this implies that CD1 proteins have important immunological functions that were positively selected by evolutionary forces. Because one of the main functions of CD1 proteins is to present lipid antigens from pathogens, we speculate

that the size and composition of CD1 genes present in any given species reflects the results of pathogen exposure and selection pressure on an evolutionary time scale.

Acknowledgements

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Porcelli S, Brenner MB, Greenstein JL, Balk SP, Terhorst C, Bleicher PA: **Recognition of cluster of differentiation 1 antigens by human CD4−CD8-cytolytic T lymphocytes**. *Nature* 1989, **341**:447-450.

2. Porcelli S, Morita CT, Brenner MB: **CD1b restricts the response of human CD4−8-T lymphocytes to a microbial antigen**. *Nature* 1992, **360**:593-597.

3. Fowlkes BJ, Kruisbeek AM, Ton-That H, Weston MA, Coligan JE, Schwartz RH, Pardoll DM: **A novel population of T-cell receptor alpha beta-bearing thymocytes which predominantly expresses a single V beta gene family**. *Nature* 1987, **329**:251-254.

4. Budd RC, Miescher GC, Howe RC, Lees RK, Bron C, MacDonald HR: **Developmentally regulated expression of T cell receptor beta chain variable domains in immature thymocytes**. *J Exp Med* 1987, **166**:577-582.

5. Bendelac A, Lantz O, Quimby ME, Yewdell JW, Bennink JR, Brutkiewicz RR: **CD1 recognition by mouse NK1+ T lymphocytes**. *Science* 1995, **268**:863-865.

6. Spada FM, Koezuka Y, Porcelli SA: **CD1d-restricted recognition of synthetic glycolipid antigens by human natural killer T cells**. *J Exp Med* 1998, **188**:1529-1534.

7. Brossay L, Chioda M, Burdin N, Koezuka Y, Casorati G, Dellabona P, Kronenberg M: **CD1d-mediated recognition of an alpha-galactosylceramide by natural killer T cells is highly conserved through mammalian evolution**. *J Exp Med* 1998, **188**:1521-1528.

8. Savage AK, Constantinides MG, Han J, Picard D, Martin E, Li B,
•• Lantz O, Bendelac A: **The transcription factor PLZF directs the effector program of the NKT cell lineage**. *Immunity* 2008, **29**:391-403.
The transcription factor promyelocytic leukemia zinc finger (PLZF) controls development of the NKT cell lineage in mice and was lacking in other T cell populations, indicating that it is a lineage-specific transcription factor. Human NKT cells express PLZF mRNA, suggesting that PLZF may play a role in human NKT cell development.

9. Cardell S, Tangri S, Chan S, Kronenberg M, Benoist C, Mathis D: **CD1-restricted CD4+ T cells in major histocompatibility complex class II-deficient mice**. *J Exp Med* 1995, **182**:993-1004.

10. Jahng A, Maricic I, Aguilera C, Cardell S, Halder RC, Kumar V: **Prevention of autoimmunity by targeting a distinct, noninvariant CD1d-reactive T cell population reactive to sulfatide**. *J Exp Med* 2004, **199**:947-957.

11. Van Rhijn I, Young DC, Im JS, Levery SB, Illarionov PA, Besra GS, Porcelli SA, Gumperz J, Cheng TY, Moody DB: **CD1d-restricted T cell activation by nonlipidic small molecules**. *Proc Natl Acad Sci U S A* 2004, **101**:13578-13583.

12. Zajonc DM, Wilson IA: **Architecture of CD1 proteins**. *Curr Topic Microbiol Immunol* 2007, **314**:27-50.

13. Borg NA, Wun KS, Kjer-Nielsen L, Wilce MC, Pellicci DG, Koh R,
•• Besra GS, Bharadwaj M, Godfrey DI, McCluskey J *et al.*: **CD1d-lipid-antigen recognition by the semi-invariant NKT T-cell receptor**. *Nature* 2007, **448**:44-49.
The ternary structure of a human NKT TCR bound CD1d and α-galactosyl-ceramide explains why NKT cells naturally express certain conserved Vα and Vβ chains: the same chains present in natural iNKT mediate the contacts with antigen and CD1d. In contrast to observed interactions between human TCR and peptide-MHC, docking of NKT TCR and CD1d is parallel as opposed to diagonal in orientation.

14. Zajonc DM, Savage PB, Bendelac A, Wilson IA, Teyton L: **Crystal structures of mouse CD1d−iGb3 complex and its cognate Valpha14 T cell receptor suggest a model for dual recognition of foreign and self glycolipids**. *J Mol Biol* 2008, **377**:1104-1116.

15. Garcia KC, Adams EJ: **How the T cell receptor sees antigen — a structural view**. *Cell* 2005, **122**:333-336.

16. Scott-Browne JP, Matsuda JL, Mallevaey T, White J, Borg NA, McCluskey J, Rossjohn J, Kappler J, Marrack P, Gapin L: **Germline-encoded recognition of diverse glycolipids by natural killer T cells**. *Nat Immunol* 2007, **8**:1105-1113.

17. Kinjo Y, Tupin E, Wu D, Fujio M, Garcia-Navarro R, Benhnia MR, Zajonc DM, Ben-Menachem G, Ainge GD, Painter GF *et al.*: **Natural killer T cells recognize diacylglycerol antigens from pathogenic bacteria**. *Nat Immunol* 2006, **7**:978-986.

18. Mattner J, Debord KL, Ismail N, Goff RD, Cantu C III, Zhou D, Saint-Mezard P, Wang V, Gao Y, Yin N *et al.*: **Exogenous and endogenous glycolipid antigens activate NKT cells during microbial infections**. *Nature* 2005, **434**:525-529.

19. Kinjo Y, Wu D, Kim G, Xing GW, Poles MA, Ho DD, Tsuji M, Kawahara K, Wong CH, Kronenberg M: **Recognition of bacterial glycosphingolipids by natural killer T cells**. *Nature* 2005, **434**:520-525.

20. Nieuwenhuis EE, Matsumoto T, Lindenbergh D, Willemsen R, Kaser A, Simons-Oosterhuis Y, Brugman S, Yamaguchi K, Ishikawa H, Aiba Y *et al.*: **Cd1d-dependent regulation of bacterial colonization in the intestine of mice**. *J Clin Invest* 2009, **119(5)**:1241-1250.

21. Kumar H, Belperron A, Barthold SW, Bockenstedt LK: **Cutting edge: CD1d deficiency impairs murine host defense against the spirochete, *Borrelia burgdorferi***. *J Immunol* 2000, **165**:4797-4801.

22. Belperron AA, Dailey CM, Bockenstedt LK: **Infection-induced marginal zone B cell production of *Borrelia hermsii*-specific antibody is impaired in the absence of CD1d**. *J Immunol* 2005, **174**:5681-5686.

23. Tupin E, Benhnia MR, Kinjo Y, Patsey R, Lena CJ, Haller MC, Caimano MJ, Imamura M, Wong CH, Crotty S *et al.*: **NKT cells prevent chronic joint inflammation after infection with *Borrelia burgdorferi***. *Proc Natl Acad Sci U S A* 2008, **105**:19863-19868.

24. Beckman EM, Porcelli SA, Morita CT, Behar SM, Furlong ST, Brenner MB: **Recognition of a lipid antigen by CD1-restricted alpha beta+ T cells**. *Nature* 1994, **372**:691-694.

25. Moody DB, Reinhold B, Guy M, Beckman E, Frederique D, furlong S, Porcelli S: **Structural requirements for glycolipid antigen recognition by CD1b-restricted T cells**. *Science* 1997, **278**:283-286.

26. Layre E, Collmann A, Bastian M, Mariotti S, Czaplicki J, Prandi J,
• Mori L, Stenger S, De Libero G, Puzo G *et al.*: **Mycolic acids constitute a scaffold for mycobacterial lipid antigens stimulating CD1-restricted T cells**. *Chem Biol* 2009, **16**:82-92.
These studies provide evidence for a third type of mycolate antigen for CD1b. Interestingly, people latently infected with *M. tuberculosis* produced cytokines in response to glycerol monomycolate at levels higher than seen in patients with active tuberculosis. These findings implicate glycerol monomycolate specific T cells in the human immune response to *M. tuberculosis* and further enhance the argument that this isoform binds particularly large lipids.

27. Moody DB, Ulrichs T, Muhlecker W, Young DC, Gurcha SS, Grant E, Rosat J-P, Brenner MB, Costello CE, Besra GS *et al.*: **CD1c-mediated T-cell recognition of isoprenoid glycolipids in *Mycobacterium tuberculosis* infection**. *Nature* 2000, **404**:884-888.

28. Ulrichs T, Moody DB, Grant E, Kaufmann SH, Porcelli SA: **T-cell responses to CD1-presented lipid antigens in humans with**

Mycobacterium tuberculosis infection. *Infect Immun* 2003, **71**:3076-3087.

29. Gilleron M, Stenger S, Mazorra Z, Wittke F, Mariotti S, Bohmer G, Prandi J, Mori L, Puzo G, De Libero G: **Diacylated sulfoglycolipids are novel mycobacterial antigens stimulating CD1-restricted T cells during infection with *Mycobacterium tuberculosis***. *J Exp Med* 2004, **199**:649-659.

30. Moll M, Kuylenstierna C, Gonzalez VD, Andersson SK, Bosnjak L, Sonnerborg A, Quigley MF, Sandberg JK: **Severe functional impairment and elevated PD-1 expression in CD1d-restricted NKT cells retained during chronic HIV-1 infection**. *Eur J Immunol* 2009, **39**:902-911.

31. Yuan W, Dasgupta A, Cresswell P: **Herpes simplex virus evades natural killer T cell recognition by suppressing CD1d recycling**. *Nat Immunol* 2006, **7**:835-842.

32. De Santo C, Salio M, Masri SH, Lee LY, Dong T, Speak AO, Porubsky S, Booth S, Veerapen N, Besra GS *et al.*: **Invariant NKT cells reduce the immunosuppressive activity of influenza A virus-induced myeloid-derived suppressor cells in mice and humans**. *J Clin Invest* 2008, **118**:4036-4048.

33. Van Rhijn I, David C Young, Jenny Vazquez, Annemieke De Jong,
• Rahul Talekar, Joel T Katz, Richard Riese, Ruth Ruprecht, Peter B O'Connor, Catherine E. Costello, et al.: **CD1c trafficking to early endosomes allows presentation of lipopeptides that are sensitive to lysosomal degradation**. *J Exp Med* 2009, **206**(6) 1409–1422
These data show that human CD1c presents a lipopeptide antigen to T cells and that recognition is specific for peptide sequence. Whereas most studies focus on glycolipids, the discovery of lipopeptide antigens provides possible links to viral or self-antigens made through protein lipidation reactions.

34. Van Rhijn I, Zajonc DM, Wilson IA, Moody DB: **T-cell activation by lipopeptide antigens**. *Curr Opin Immunol* 2005, **17**:222-229.

35. Brigl M, Bry L, Kent SC, Gumperz JE, Brenner MB: **Mechanism of CD1d-restricted natural killer T cell activation during microbial infection**. *Nat Immunol* 2003, **4**:1230-1237.

36. Skold M, Xiong X, Illarionov PA, Besra GS, Behar SM: **Interplay of cytokines and microbial signals in regulation of CD1d expression and NKT cell activation**. *J Immunol* 2005, **175**:3584-3593.

37. Paget C, Mallevaey T, Speak AO, Torres D, Fontaine J, Sheehan KC, Capron M, Ryffel B, Faveeuw C, Leite de Moraes M *et al.*: **Activation of invariant NKT cells by toll-like receptor 9-stimulated dendritic cells requires type I interferon and charged glycosphingolipids**. *Immunity* 2007, **27**:597-609.

38. De Libero G, Moran AP, Gober HJ, Rossy E, Shamshiev A, Chelnokova O, Mazorra Z, Vendetti S, Sacchi A, Prendergast MM *et al.*: **Bacterial infections promote T cell recognition of self-glycolipids**. *Immunity* 2005, **22**:763-772.

39. Smed-Sorensen A, Moll M, Cheng TY, Lore K, Norlin AC, Perbeck L, Moody DB, Spetz AL, Sandberg JK: **IgG regulates the CD1 expression profile and lipid antigen-presenting function in human dendritic cells via FcgammaRIIa**. *Blood* 2008, **111**:5037-5046.

40. Leslie DS, Dascher CC, Cembrola K, Townes MA, Hava DL, Hugendubler LC, Mueller E, Fox L, Roura-Mir C, Moody DB *et al.*: **Serum lipids regulate dendritic cell CD1 expression and function**. *Immunology* 2008, **125**(3):289-301.

41. Roura-Mir C, Catalfamo M, Cheng T-Y, Marqusee E, Besra GS, Jaraquemada D, Moody DB: **CD1a and CD1c activate intrathyroidal T cells during Graves' disease and Hashimoto's thyroiditis**. *J Immunol* 2005, **174**:3773-3780.

42. Sieling PA, Jullien D, Dahlem M, Tedder TF, Rea TH, Modlin RL, Porcelli SA: **CD1 expression by dendritic cells in human leprosy lesions: correlation with effective host immunity**. *J Immunol* 1999, **162**:1851-1858.

43. Vincent MS, Leslie DS, Gumperz JE, Xiong X, Grant EP, Brenner MB: **CD1-dependent dendritic cell instruction**. *Nat Immunol* 2002, **3**:1163-1168.

44. Roura-Mir C, Wang L, Cheng T-Y, Matsunaga I, Dascher CC, Peng SL, Fenton MJ, Kirschning C, Moody DB: ***Mycobacterium tuberculosis* regulates CD1 antigen presentation pathways through TLR-2**. *J Immunol* 2005, **175**:1758-1766.

45. Krutzik SR, Tan B, Li H, Ochoa MT, Liu PT, Sharfstein SE, Graeber TG, Sieling PA, Liu YJ, Rea TH *et al.*: **TLR activation triggers the rapid differentiation of monocytes into macrophages and dendritic cells**. *Nat Med* 2005, **11**:653-660.

46. Moody DB: **TLR gateways to CD1 function**. *Nat Immunol* 2006, **7**:811-817.

47. Stenger S, Niazi KR, Modlin RL: **Down-regulation of CD1 on antigen-presenting cells by infection with *Mycobacterium tuberculosis***. *J Immunol* 1998, **161**:3582-3588.

48. Mariotti S, Teloni R, Iona E, Fattorini L, Romagnoli G, Gagliardi MC, Orefici G, Nisini R: ***Mycobacterium tuberculosis* diverts alpha interferon-induced monocyte differentiation from dendritic cells into immunoprivileged macrophage-like host cells**. *Infect Immun* 2004, **72**:4385-4392.

49. Gagliardi MC, Teloni R, Mariotti S, Iona E, Pardini M, Fattorini L, Orefici G, Nisini R: **Bacillus Calmette–Guerin shares with virulent *Mycobacterium tuberculosis* the capacity to subvert monocyte differentiation into dendritic cell: implication for its efficacy as a vaccine preventing tuberculosis**. *Vaccine* 2004, **22**:3848-3857.

50. Gagliardi MC, Lemassu A, Teloni R, Mariotti S, Sargentini V, Pardini M, Daffe M, Nisini R: **Cell wall-associated alpha-glucan is instrumental for *Mycobacterium tuberculosis* to block CD1 molecule expression and disable the function of dendritic cell derived from infected monocyte**. *Cell Microbiol* 2007, **9**:2081-2092.

51. Hava DL, van der Wel N, Cohen N, Dascher CC, Houben D, Leon L, Agarwal S, Sugita M, van Zon M, Kent SC *et al.*: **Evasion of peptide, but not lipid antigen presentation, through pathogen-induced dendritic cell maturation**. *Proc Natl Acad Sci U S A* 2008, **105**:11281-11286.

52. Buettner M, Meinken C, Bastian M, Bhat R, Stossel E, Faller G, Cianciolo G, Ficker J, Wagner M, Rollinghoff M *et al.*: **Inverse correlation of maturity and antibacterial activity in human dendritic cells**. *J Immunol* 2005, **174**:4203-4209.

53. Cruz D: **Host-derived oxidized phospholipids and HDL regulate innate immunity in human leprosy**. *J Clin Invest* 2008, **118**:2917-2928.

54. Cho S, Knox KS, Kohli LM, He JJ, Exley MA, Wilson SB, Brutkiewicz RR: **Impaired cell surface expression of human CD1d by the formation of an HIV-1 Nef/CD1d complex**. *Virology* 2005, **337**:242-252.

55. Sanchez DJ, Gumperz JE, Ganem D: **Regulation of CD1d expression and function by a herpesvirus infection**. *J Clin Invest* 2005, **115**:1369-1378.

56. Szatmari I, Gogolak P, Im JS, Dezso B, Rajnavolgyi E, Nagy L: **Activation of PPARgamma specifies a dendritic cell subtype capable of enhanced induction of iNKT cell expansion**. *Immunity* 2004, **21**:95-106.

57. Maitre B, Angenieux C, Salamero J, Hanau D, Fricker D, Signorino F, Proamer F, Cazenave JP, Goud B, Tourne S *et al.*: **Control of the intracellular pathway of CD1e**. *Traffic* 2008, **9**:431-445.

58. Angenieux C, Salamero J, Fricker D, Cazenave JP, Goud B, Hanau D, de La Salle H: **Characterization of CD1e, a third type of CD1 molecule expressed in dendritic cells**. *J Biol Chem* 2000, **275**:37757-37764.

59. de la Salle H, Mariotti S, Angenieux C, Gilleron M, Garcia-Alles LF, Malm D, Berg T, Paoletti S, Maitre B, Mourey L *et al.*: **Assistance of microbial glycolipid antigen processing by CD1e**. *Science* 2005, **310**:1321-1324.

60. Tourne S, Maitre B, Collmann A, Layre E, Mariotti S, Signorino-Gelo F, Loch C, Salamero J, Gilleron M, Angenieux C *et al.*: **Cutting edge: a naturally occurring mutation in CD1e impairs lipid antigen presentation**. *J Immunol* 2008, **180**:3642-3646.

61. Moody DB, Zajonc DM, Wilson IA: **Anatomy of CD1-lipid antigen complexes**. *Nat Rev Immunol* 2005, **5**:387-399.

62. Cheng TY, Relloso M, Van Rhijn I, Young DC, Besra GS, Briken V, Zajonc DM, Wilson IA, Porcelli S, Moody DB: **Role of lipid trimming and CD1 groove size in cellular antigen presentation**. *EMBO J* 2006, **25(13)**:2989-2999.

63. Winau F, Schwierzeck V, Hurwitz R, Remmel N, Sieling PA, Modlin RL, Porcelli SA, Brinkmann V, Sugita M, Sandhoff K *et al.*: **Saposin C is required for lipid presentation by human CD1b**. *Nat Immunol* 2004, **5**:169-174.

64. Relloso M, Cheng TY, Im JS, Parisini E, Roura-Mir C, DeBono C, Zajonc DM, Murga LF, Ondrechen MJ, Wilson IA *et al.*: **pH-dependent interdomain tethers of CD1b regulate its antigen capture**. *Immunity* 2008, **28**:774-786.

65. Sugita M, Grant EP, van Donselaar E, Hsu VW, Rogers RA, Peters PJ, Brenner MB: **Separate pathways for antigen presentation by CD1 molecules**. *Immunity* 1999, **11**:743-752.

66. Briken V, Jackman RM, Watts GF, Rogers RA, Porcelli SA: **Human CD1b and CD1c isoforms survey different intracellular compartments for the presentation of microbial lipid antigens**. *J Exp Med* 2000, **192**:281-288.

67. Vincent MS, Xiong X, Grant EP, Peng W, Brenner MB: **CD1a-, b-, and c-restricted TCRs recognize both self and foreign antigens**. *J Immunol* 2005, **175**:6344-6351.

68. Shamshiev A, Donda A, Carena I, Mori L, Kappos L, De Libero G: **Self glycolipids as T-cell autoantigens**. *Eur J Immunol* 1999, **29**:1667-1675.

69. Miller MM, Wang C, Parisini E, Coletta RD, Goto RM, Lee SY, Barral DC, Townes M, Roura-Mir C, Ford HL *et al.*: **Characterization of two avian MHC-like genes reveals an ancient origin of the CD1 family**. *Proc Natl Acad Sci U S A* 2005, **102**:8674-8679.

70. Salomonsen J, Sorensen MR, Marston DA, Rogers SL, Collen T, van Hateren A, Smith AL, Beal RK, Skjodt K, Kaufman J: **Two CD1 genes map to the chicken MHC, indicating that CD1 genes are ancient and likely to have been present in the primordial MHC**. *Proc Natl Acad Sci U S A* 2005, **102**:8668-8673.

71. Zajonc DM, Striegl H, Dascher CC, Wilson IA: **The crystal structure of avian CD1 reveals a smaller, more primordial antigen-binding pocket compared to mammalian CD1**. *Proc Natl Acad Sci U S A* 2008, **105**:17925-17930.

72. Wang C, Perera TV, Ford HL, Dascher CC: **Characterization of a divergent non-classical MHC class I gene in sharks**. *Immunogenetics* 2003, **55**:57-61.

73. Van Rhijn I, Koets AP, Im JS, Piebes D, Reddington F, Besra GS, Porcelli SA, van Eden W, Rutten VP: **The bovine CD1 family contains group 1 CD1 proteins, but no functional CD1d**. *J Immunol* 2006, **176**:4888-4893.

74. Looringh van Beeck FA, Reinink P, Hermsen R, Zajonc DM, Laven MJ, Fun A, Troskie M, Schoemaker NJ, Morar D, Lenstra JA *et al.*: **Functional CD1d and/or NKT cell invariant chain transcript in horse, pig, African elephant and guinea pig, but not in ruminants**. *Mol Immunol* 2009, **46(7)**:1424-1431.

75. Calabi F, Milstein C: **A novel family of human major histocompatibility complex-related genes not mapping to chromosome 6**. *Nature* 1986, **323**:540-543.