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Role of Group 1 CD1-restricted T Cells in Host Defense and Inflammatory Diseases

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Abstract

Group 1 CD1-restricted T cells are members of the unconventional T cell family that recognize lipid antigens presented by CD1a, CD1b, and CD1c molecules. While they developmentally mirror invariant natural killer T (iNKT) cells, they have diverse antigen specificity and functional capacity, with both anti-microbial and autoreactive targets. The role of group 1 CD1-restricted T cells has been best established in *Mycobacterium tuberculosis* (Mtb) infection in which a wide variety of lipid antigens have been identified and their ability to confer protection against Mtb infection in a CD1 transgenic mouse model has been shown. Group 1 CD1-restricted T cells have also been implicated in other infections, inflammatory conditions, and malignancies. In particular, autoreactive group 1 CD1-restricted T cells have been playing a role in several skin inflammatory conditions. The prevalence of group 1 CD1 autoreactive T cells in healthy individuals suggests the presence of regulatory mechanisms to suppress autoreactivity in homeostasis. The more recent use of group 1 CD1 tetramers and mouse models has allowed for better characterization of their phenotype, functional capacity, and underlying mechanisms of antigen-specific and autoreactive activation. These discoveries may pave the way for the development of novel vaccines and immunotherapies that target group 1 CD1-restricted T cells.

Keywords

CD1; Antigen presentation; T cells; Infection; Inflammation; Autoimmunity; Tumor immunity; animal models

I. INTRODUCTION

Group 1 CD1 molecules (CD1a, CD1b and CD1c) are antigen presenting molecules capable of binding to a diverse set of lipids and glycolipids. Because of their ability to recognize nonpeptide antigens, group 1 CD1-restricted T cells are thus members of the unconventional or innate-like T cell family. Unlike other members of this family such as invariant natural killer T (iNKT) cells and mucosal-associated invariant T (MAIT) cells, group 1 CD1-

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restricted T cells are not defined by an invariant TCR, but by their ability to bind to group 1 CD1-lipid complexes. While most of group 1 CD1-restricted T cells express diverse αβ TCRs, some γδ T cells can also recognize group 1 CD1 molecules.[1, 2] Group 1 CD1-restricted T cells are found in $CD4^+$, $CD8^+$, and double negative ($CD4^-CD8^-$) population and can recognize both self and foreign lipid antigens. This diversity poses a challenge in defining the exact phenotype and function of these T cells. In this review, we will consolidate findings from various animal models, microbial infections, and inflammatory conditions with the aim to provide a holistic view of the role of group 1 CD1-restricted T cells in host defense and inflammatory diseases.

Much of the early research on group 1 CD1-restricted T cells was focused on its potential role in *Mycobacterium tuberculosis* (Mtb) infection.[3, 4] Mtb lipid-specific T cells remain the cornerstone of our knowledge in the development, phenotype, and functional capacity of group 1 CD1-restricted T cells. Broadening of the field has been stymied due to the lack of specific reagents to identify group 1 CD1-restricted T cells in humans and a suitable small animal model, since wild-type mice do not express group 1 CD1 molecules. The development of several group 1 CD1 tetramers as well as the hCD1 transgene (hCD1Tg) mouse are key achievements that have ushered in a new wealth of knowledge.[5, 6] Significant headway has been made in implicating group 1 CD1-restricted T cells in infections such as *Staphylococcus aureus* (SA), inflammatory conditions in the skin, and protection against malignancies.[7-11] We will review how these findings could pave the way for new treatments and vaccines.

II. STRUCTURE AND CHARACTERISTICS OF GROUP 1 CD1 MOLECULES

A. Structure of group 1 CD1 molecules

CD1 molecules are a family of MHC class I-like antigen presenting molecules, which are specialized in presenting lipid antigens to T cells. Three major groups of CD1 isoforms have been identified in humans. Group 1 CD1 is composed of CD1a, CD1b, and CD1c, and group 2 CD1 consists of CD1d, which are expressed on the surface of various cell types. Group 3 CD1 molecule CD1e, which is expressed intracellularly and facilitates lipid loading.[12] The CD1 family of glycoproteins are found across the mammalian kingdom.[13, 14] Nonhuman primates, guinea pigs, and cattle express some or all of group 1 CD1 molecules in differing copy numbers and have thus been used as animal models.[15] Wild-type mice do not express group 1 CD1 molecules, and thus we developed the first transgenic group 1 CD1-expressing mouse model [5], which along with previously mentioned animal models and human *ex vivo* work, forms the basis for our understanding of group 1 CD1-restricted T cells.

Group 1 CD1 molecules are largely nonpolymorphic and their antigen binding cleft comprise of two main hydrophobic pockets (A' and F') with variable number of additional pockets.[14, 16] CD1b has the largest antigen binding cleft, followed by CD1c and CD1a.[17] CD1a has a large and open F′ channel, thus leading to less stringent requirements for antigen loading.[18] CD1b contains additional interconnected antigen pockets and portals which allow for the presentation of more complex lipids with long alkyl chains.[19, 20] CD1c likewise contains additional accessory portals, although smaller and fewer than CD1b, that allow for presentation of oversized alkyl chains.[21]

B. Intracellular trafficking and lipid loading of group 1 CD1 molecules

CD1 molecules assemble and are loaded with endogenous lipids in the endoplasmic reticulum through the assistance of microsomal triglyceride transfer protein.[22, 23] They then migrate through the Golgi apparatus to the cell surface and potentially bind exogenous lipids as they are exposed to the exterior of the cell. CD1b and CD1c are then internalized into clathrin-coated vesicles through the binding of tyrosine-based motifs in their cytoplasmic tails to adaptor protein complex 3 and 2 (AP-3, AP-2) and routed to the late and early endosomes, respectively.[24] Both CD1b and CD1c are also able to access the lysosomal compartment which may be important for the loading of microbial lipids that require modification or processing by lysosomal enzymes prior to loading.[25] CD1a, which lacks the cytoplasmic tail tyrosine-based endosomal targeting motif, is still able to recycle through early endocytic compartment and thus loads unique lipids found in this environment such as sulfatides and other endogenous lipids.[26] Thus, each of the group 1 CD1 isoforms have distinct cellular loading tropisms which, along with the unique architecture of their antigen binding grooves, dictate the types of lipids they can bind and present.

C. Expression of group 1 CD1 molecules

Group 1 CD1 molecules are largely expressed on professional antigen presenting cells (APCs) and thymocytes, with slight differences in expression pattern among different isoforms.[27] CD1b has the most restricted expression pattern, confined primarily to a subset of dendritic cells (DCs), while CD1c can also be found on macrophages and B cells, and CD1a has extensive expression on Langerhans cells.[28, 29] Group 1 CD1 molecules are expressed on double positive ($CD4^+CD8^+$) thymocytes, where they likely play a role in thymic selection.[30, 31] Culturing $CD14^+$ monocytes or bone marrow-derived cells with IL-4 and GM-CSF induces their differentiation into group 1 CD1-expressing DCs.[32-34] In addition to their role as antigen presenting molecules, group 1 CD1 molecules have been used as markers for several specific subsets of APCs. CD1c is expressed on mantle zone B cells and has been recently shown to define a group of IL-12 producing DCs that can efficiently prime cytotoxic T cells.[35, 36] $CD1a^+$ monocyte-derived DCs produced significantly higher levels of CCL1 and IL-12 and less IL-10 than their $CD1a^-$ counterparts.[37] The expression pattern of group 1 CD1 molecules in hCD1Tg mouse model is similar to that seen in humans, making it a useful small animal model to probe mechanistically the role of group 1 CD1-restricted T cells in various diseases.[5]

III. RECOGNITION OF LIPID ANTIGENS BY GROUP 1 CD1-RESTRICTED T CELLS

Most CD1-lipid complexes are arranged such that hydrophobic lipid tails reside within the groove of group 1 CD1 molecules, while polar carbohydrate, peptide, phosphate, or sulfate ester head groups are exposed at the surface and thus interact with TCRs. There are also several headless lipids that have been shown to reside within CD1 grooves and have no direct contacts with TCRs. Under basal conditions, group 1 CD1 molecules are loaded with endogenous lipids, which stabilize CD1 molecules and allow them to traffic to the cell surface. Therefore, even so-called unloaded CD1 tetramers or crystal structures

contain associated lipids. Some endogenous lipids may also act as spacers which work in concert with exogenous lipid antigens, loading into antigen-binding grooves.[38-40] The shape of the CD1 molecules also allows for certain TCRs to bind directly to their A' roof, without interaction or disruption by lipid ligands.[41]

Unlike conventional T cells, many lipid antigens that bind to group 1 CD1 molecules appear to prevent rather than allow for T cell recognition. Binding and presentation of lipid antigens by group 1 CD1 molecules can thus lead to 3 possible outcomes: (a) CD1/ lipid complex recognition by foreign lipid specific TCR, (b) CD1/lipid complex recognition by autoreactive TCR, or (c) CD1/lipid complex prevents the recognition by autoreactive TCR (Fig. 1). The first situation is most applicable to the presentation of foreign lipid antigens in the context of infection and malignancy in which group 1 CD1-restricted T cells may play a protective role, analogous to the established conventional T cell paradigm. Instances (b) and (c) relate to the role of group 1 CD1-restricted T cells in inflammatory conditions, in which at baseline conditions endogenous lipids block autoreactive T cell recognition, whereas disruption of lipid homeostasis or introduction of foreign lipids allows for direct binding of CD1 molecules to autoreactive T cells. This phenomenon has been well-studied in the context of CD1a on Langerhans cells in the skin[11, 42, 43] and will be further discussed in the section on the role of group 1 CD1-restricted T cells in inflammatory conditions. Of note, autoreactive group 1 CD1-restricted T cells may not be strictly pathogenic and have also been shown to provide immunity against infection and malignancy.[9, 44] Table 1 provides an overview of the endogenous, microbial, and inflammatory-associated lipid antigens recognized by group 1 CD1-restricted T cells.

IV. DEVELOPMENT AND PHENOTYPE OF GROUP 1 CD1-RESTRICTED T CELLS

Historical knowledge of human group 1 CD1-restricted T cells is largely based on T cell clones expanded from the blood of tuberculosis patients or healthy volunteers.[3, 45] This process may introduce some bias for the types of T cell clones derived. The development of several human and primate group 1 CD1 tetramers and dextramers loaded with Mtb and other microbial lipids as well as the hCD1Tg mouse model has allowed for a better understanding of polyclonal and *in vivo* behavior of this family of T cells.[5,6,31,44,46,47] In this section we will highlight distinct characteristics of group 1 CD1-restricted T cells regarding their development, surface phenotype, and functional capacity, correlating these findings within the human and mouse models.

A. Development of group 1 CD1-restricted T cells

Group 1 CD1-restricted T cell biology is often understood through the lens of its better studied cousin, the CD1d-restricted iNKT cells. Unlike conventional T cells which are selected by thymic epithelial cells, iNKT cells are selected by DP thymocytes in the thymus and their interactions with signaling lymphocytic activation molecules (SLAMs) enhance TCR signaling, likely contributing to a distinct pre-activated state.[48] Similarly, T cells from two transgenic mouse models expressing distinct CD1b-restricted TCRs in hCD1Tg background were found to be positively selected by hematopoietic-derived cells,

likely CD1b-expressing DP thymocytes.[31, 44] Despite their similar selection requirements, these two types of transgenic T cells had vastly different activation profiles. CD1b-autoreactive HJ1 T cells expressed transcription factor PLZF and surface marker NK1.1, and thus possessed pre-activated phenotype similar to iNKT cells.[44] Meanwhile, mycolic acid (MA)-specific CD1b-restricted DN1 T cells did not express PLZF and NK1.1 and behaved more similarly to conventional T cells.[31] The existence of both pre-activated and conventional-like group 1 CD1-restricted T cells is likewise seen in humans as both naïve and effector/memory group 1 CD1-restricted T cells have been detected in a study using non-biased dilution-based clonal screening.[49] Therefore, selection by hematopoietic cells is not sufficient for a pre-activated phenotype, and antigen specificity as well as strength of TCR-CD1 interaction both likely play a further role. Most group 1 CD1-restricted T cells are likely selected by group 1 CD1 expressing DP cortical thymocytes. More research in both animal models and human-derived tissues is needed to better understand the generalizability of these findings to the group 1 CD1-restricted T cell population at large.

B. TCR diversity and co-receptor usage of group 1 CD1-restricted T cells

The TCR of group 1 CD1-restricted T cells can be either composed of αβ or γδ TCR with a variety of antigen specificity. While no single invariant TCR seems to encompass the majority of group 1 CD1-restricted T cells to the same extent as iNKT and MAIT cells define their respective families, germline-encoded mycolyl-reactive (GEM) T cells have been identified as a type of donor-unrestricted T cell (DURT), which can be found among a wide swath of the human population due to its TCR's similarity to the un-recombined TCR sequence.[46] The α chain of the GEM TCR is formed without addition of N nucleotides and therefore is more likely to be shared across many individuals. GEM T cells are CD1b-restricted, $CD4^+$ T cells specific for Mtb antigen glucose monomycolate (GMM) and their TCR consists of a nearly invariant α chain (TRAV1-2-TRAJ9) and variable β chain but biased towards usage of TRBV6-2. GEM T cells can be found both in tuberculosis patients as well as healthy controls.[50] Another group of CD1b-restricted GMM-specific T cells were found in several unrelated donors and carry a TCR bias towards TRAV17 and TRBV4-1. They are known as LND5-like T cells due to their shared GMM-specificity and the TCR's similarity to a previously discovered clone.[51] In addition, CD1b and CD1c-restricted γδ T cells were shown to have a bias towards Vδ1 chain which provided the necessary specificity for binding to their respective molecules in an antigen dependent or independent manner.[1, 2]

While most of the human T cell clones originally identified as group 1 CD1-restricted T cells were either $CD8^+$ or DN, more recent direct staining of polyclonal T cells using group 1 CD1 tetramers has revealed that many more, if not most, appear to be $CD4^+$.[3,6,52] This bias appears to be particularly true for polyclonal CD1a-restricted autoreactive T cells which are largely $CD4^+$.[42,53] Similarly, group 1 CD1-restricted T clones derived from hCD1Tg mice could express either CD4, CD8αα, CD8αβ, or be DN. In addition, polyclonal group 1 CD1-restricted T cells from Mtb-infected mice were found in $CD4^+$, $CD8^+$, and DN T cell populations.[5] Furthermore, CD1c-restricted GMM-specific T cells in BCG vaccinated nonhuman primates can express CD4, or CD8, or be DN.[54, 55] Thus, group 1 CD1-restricted T cells encompass diverse subsets of T cells. It remains to be seen whether and how co-receptor usage may affect the selection and function of group 1 CD1-restricted T cells.

C. Activation and cytokine production

Group 1 CD1-restricted T cells can be activated through co-culture with CD1-expressing APCs, with or without antigen for antigen-specific or autoreactive T cells, respectively. Activation can be further modulated through the addition of adjuvants and cytokines, such as IL-12 and IL-18.[9,44] Upon activation, group 1 CD1-restricted T cells in hCD1Tg mice upregulate the expression of typical activation markers such as CD44, CD69, and CD25.[31, 44, 56] In humans likewise, group 1 CD1-restricted T cells appear to express conventional T cell markers of activation as demonstrated by the upregulation of CD25, CD69, and CD45RO and downregulation of CD45RA and CCR7 upon activation.[2,6,47,49,55,57] PBMC derived from both Mtb-infected humans and rhesus macaques showed a population of group 1 CD1-restricted Mtb lipid-specific T cells with $CCR7^{-}CD45RA^{-}$ (effector memory) phenotype.[55, 58]

In both humans and hCD1Tg mice, activated group 1 CD1-restricted T cells appear to mostly produce T_H1 and T_H17-like cytokines including IFN-γ, TNF-α, IL-2, and IL-17.[10,31,44,47,56] T_H2 cytokines such as IL-4 was shown to be produced by some CD1b and CD1c autoreactive clones.[47, 59] CD1a-restricted skin resident T cells are enriched in skin-homing subsets $(CLA)^{+}CD45RO^{+}$ and $CCR6^{+}CCR4^{+}CCR10^{+}$. Furthermore, they primarily produce IL-22, which plays a key role in skin homeostasis through the regulation of keratinocyte proliferation, and to a lesser extent IL-17 or IFN-γ, suggesting these cells are part of the T_H22 family.[42, 53] The diversity of group 1 CD1-restricted T cell phenotype is illustrated in Fig. 2.

D. Properties of group 1 CD1-restricted memory T cells

While conventional T cells have distinct naïve, effector, and memory phenotypes, innate-like T cells generally are thought to be pre-activated and to not develop a memory phenotype.[60] Given that group 1 CD1-restricted T cells appear to possess qualities associated with both types of T cells, it is not immediately obvious whether a definitive memory phenotype would exist. However, there is evidence that group 1 CD1-restricted T cells from Mtb lipid vaccinated hCD1Tg mice have distinct activation kinetics. Peak response to primary immunization with Mtb lipids pulsed DCs occurred at 7 days post immunization, while peak response to booster immunization, given 4 weeks after primary, occurred 5 days post immunization with greater magnitude. Such an effect would only be possible if initial immunization led to an expansion and differentiation of group 1 CD1-restricted T cells. Similar evidence exists in humans, Montamat-Sicotte et al. showed that MA-specific T cells could still be detected in PBMC from Mtb-infected individuals long after the infection is cleared.[58] These T cells were $CD4^{+}CD45RA^{-}CCR7^{-}$ and, upon restimulation with MA, could expand and produce IL-2 and/or IFN-γ comparably to ESAT-6-specific T cells. Furthermore, a recent study looking at CD1b-restricted GMM or MA-specific T cells using CD1 tetramers in TB active/latent/negative human cohorts in Peru and Boston found both $CD45RO^{+}$ and $CD45RO^{-}$ populations, suggesting the existence of a memory phenotype.[57] Thus, there is evidence that at least a proportion of group 1 CD1-restricted T cells can differentiate into a memory-like phenotype. Further research is needed to establish whether memory group 1 CD1-restricted T cells can provide protection to infections.

V. GROUP 1 CD1-RESTRICTED T CELL RESPONSES IN INFECTIOUS DISEASE

A. *Mycobacterium tuberculosis* infection

In 2019, Mtb infection caused approximately 1.4 million deaths worldwide.[61] The only approved vaccine, Bacillus Calmette–Guérin (BCG), is only effective in preventing childhood TB, but not adult disease.[62, 63] The development of additional TB vaccines is imperative. Mtb has a complex cell wall which contains many unique lipids,[64] making them attractive targets for immune recognition in host defense. Indeed, many of Mtb lipid antigens recognized by group 1 CD1-restricted T cells have been identified. Didehydroxymycobactin (DDM), a mycobacterial lipopeptide, has been shown to be recognized by CD1a-restricted T cells.[45] CD1b binds and presents the most diverse array of mycobacterial lipids, which include MA,[65] GMM,[66] glycerol monomycolate,[67] phosphatidylinositol mannosides,[68, 69] lipoarabinomannans[70-72] and diacylated sulfoglycolipids (Ac2SGL).[73] Mannose-1-β-phosphomycoketide (MPM) and its biosynthetic precursor, phosphomycoketide (PM), can bind to CD1c and activate CD1c-restricted T cells.[74] Given that protective immunity against Mtb is thought to be primarily mediated by T cells, providing protection by targeting Mtb lipid-specific T cells may offer a stronger heterogenous immune response. In the following section, we will summarize findings from studies of Mtb lipid-specific group 1 CD1-restricted T cells using various CD1/Mtb lipid tetramers (Table 2) and discuss the role of these T cells in Mtb infection and vaccination settings.

1. GMM-specific T cells—MA and modified mycolates such as GMM are major and essential components of the outer Mtb membrane and therefore could be an important immunological target.[64] The first group 1 CD1 tetramer was used to identify CD1b-restricted GMM-specific T cells in patients with latent and active TB at a frequency of 0.01% relative to all $CD3^+$ T cells.[6] Using this tetramer Van Rhijin et al. were able to discover two patterns of recurring TCR clonality and thus identify GEM T cells and LND5-like T cells, which were described in the TCR and co-receptor usage section of the review.[46, 51] Both types of CD1b/GMM-specific T cell express T_H1 cytokines (IFN-γ and TNF-α), suggesting they may play an anti-mycobacterial role.[51] Crystal structure of a GEM TCR bound to the CD1b/GMM complex revealed that the TCR α and β chains of GEM T cells acted as tweezers to surround and grip the glucose moiety of GMM.[75] A recent study used CD1b/GMM tetramers and high-throughput immunosequencing approach validated the donor unrestricted nature of GEM T cells, but also showed that they constituted a minority of GMM-specific TCRs detected.[76] Instead, this study revealed a diverse TCR α and TCR β repertoire of CD1b/GMM-specific T cells. Furthermore, TCR clonality could be used to distinguish active TB patients from latent and healthy controls, confirming the expansion of CD1b/GMM-specific T cells during active disease.[76] A CD1b-GMM tetramer assay was standardized by Seshadri's group which would allow profiling of other Mtb patient cohorts and verify GMM immunogenicity in future vaccines.[77]

While most of human research relies on PBMC obtained from the blood, recent work by Ogongo et al. provides a glimpse into the unconventional T cell populations in the human

lung.[50] The group performed high-throughput TCR sequencing of cells isolated from the blood as well as lung resections of TB patients with and without HIV coinfection.[50] They found that GEM T cells were depleted in the blood of TB-infected or HIV/TB-coinfected individuals but were not enriched in the lungs of these individuals, like MAIT cells.[50] They also identified additional non-TRAV1-2, most commonly TRAV3-1, GMM-specific TCRs which were both more abundant than GEM TCRs and were expanded in the prior TB compared to active TB cohorts.[50]

A recent large scale study with CD1b/GMM tetramers found both GEM T cells and TRBV4-1$^+$ LDN5-like GMM-specific T cells were detectable in two healthy human cohorts from different areas, Peru and Boston.[57] Unlike previous studies, there was no significant difference in the frequency or the CD45RO$^+$ expression among individuals with differing TB disease status (active, latent, negative) within a given area, but Peruvian cohort had a higher frequency of CD1b/GMM tetramer$^+$ T cells than Boston cohort. The authors suggested that this discrepancy may be due to the use of different screening methodology or higher rate of prior exposure to mycobacterial antigens in Peruvian subjects.[57]

While most of GMM-specific T cells in humans are CD1b-restricted, CD1c-restricted GMM-specific T cells comprise a larger proportion than CD1b-restricted ones in nonhuman primates (NHP) [54, 55]. Using Mamu CD1c/GMM tetramers, Layton et al. found GMM-specific T cells expanded in the blood of rhesus macaques 4 wk. after i.v. BCG vaccination with a predominant effector memory T cell phenotype (CD45RA$^-$CCR7$^-$). Furthermore, CD1c/GMM tetramer$^+$ T cells expressing T_{RM} markers CD69 and CD103 were also detectable in bronchoalveolar lavage (BAL) from Mtb-infected rhesus macaques.[55]

2. Additional polyclonal Mtb antigen-specific T cell populations—Besides GMM-specific T cells, several other Mtb lipid-specific T cells have been characterized using CD1 tetramers. DDM-specific CD1a-restricted T cells were identified in the PBMC of active and latent TB patients using CD1a/DDM dextramers.[78] Two mycoketides, PM and MPM, can be recognized by CD1c-restricted T cells. CD1c/PM tetramers, but not CD1c/MPM tetramers, were able to detect polyclonal T cells from PBMC of donors with latent TB.[74] Besides αβ T cells, polyclonal T cells identified and expanded from PBMC of healthy controls using CD1c/PM tetramers were found to largely express Vδ1$^+$ TCRδ chain.[1] While expanded T cell clones had the strongest affinity for PM, there was also some affinity for endogenous lipids including lysophosphatidylcholine (LPC), lysophosphatidic acid (LPA), and sulfatide.[1] It is unclear whether these CD1c-restricted γδ T cells could expand during Mtb infection.

As CD1b allows for the loading of more complex lipid antigens, several mycobacterial lipids have been successfully loaded on CD1b tetramers. α-, keto- and methoxy-MA loaded CD1b tetramers have been generated and validated with several human MA-specific T cell clones. Individual T cell clones were found to have specific reactivity patterns to these three types of MA/CD1b tetramers, suggesting T cell response to three forms of MA found in Mtb may not be identical.[57, 79] These CD1b/MA tetramers can recognize T cells in PBMC from both healthy and Mtb-infected individuals.[57, 79] Another study found that CD1b tetramers loaded with synthetic mycobacterial diacyl trehalose (DAT) can

recognize a human CD1b-restricted DAT-specific T cell line as well as T cells obtained from human PBMC.[80] No significant difference in CD1b/DAT tetramer$^+$ T cells were observed in subjects with different TB disease status, with frequencies comparable to T cells detected by CD1b/GMM and CD1b/MA tetramers.

3. Role in protective immunity—The identification of group 1 CD1-restricted T cells in Mtb-infected individuals provides correlative evidence of their role in Mtb protection. Busch et al. were able to take a step further and determine that CD1b-dependent T cell activation is a major contributor to limiting Mtb growth in BAL of active and latent TB infections.[81] They also identified LAM, a glycolipid in the Mtb cell wall and major virulence factor, as the main lipid recognized by T cells from healthy human PBMC, and that latently, but not actively, infected patients had CD1b-restricted LAM-specific T cells with polycytotoxic functionality (CD8$^+$, granulysin$^+$, granzyme B$^+$, perforin$^+$).[81] Given that latently infected patients are better able to suppress disease progression than actively infected patients, this study strongly supports a protective role of group 1 CD1-restricted T cells in human TB.

In hCD1Tg mice, group 1 CD1-restricted T cells were able to recognize and expand in response to Mtb lipid vaccination and Mtb infection.[5] A booster Mtb lipid vaccination led to faster peak response and magnitude, providing the first evidence of a memory phenotype.[5] Kinetics and phenotype of MA-specific T cells in Mtb infection was evaluated using a transgenic mouse model with the MA-specific DN1 TCR.[31] DN1 T cells produced various cytokines IFN-γ, TNF-α, and IL-13 in a group 1 CD1-restricted manner and could lyse Mtb-infected BMDCs. Furthermore, adoptively transferred DN1 T cells decreased bacterial burden in Mtb-infected Rag2$^{-/-}$ mice in a group 1 CD1-dependent manner.[31] This finding constituted the first direct evidence that group 1 CD1-restricted T cells could offer protection to Mtb.[31]

Current mouse research on group 1 CD1-restricted T cells still heavily relies on indirect methods of identification such as restimulation with Mtb lipids-pulsed DCs or specific T cell clones due to a lack of suitable tetramer system. Current group 1 CD1tetramers have thus far not had sufficient specificity or affinity in the hCD1Tg mouse model, and even though CD1b-MA tetramers which work on the human DN1 T cell line exists, it does not have significant staining on DN1 T cells isolated from DN1Tg/hCD1Tg/Rag2$^{-/-}$ mice. While no clear explanation for discrepancy exists, potential reasons include the existence of an additional receptor that facilitates tetramer binding to human T cells that is not expressed by mice or expression of additional surface molecules on mouse cells which lead to off-target binding.

4. Vaccine development—A notable advantage of including group 1 CD1-presented Mtb lipid antigens in vaccine development is that CD1 proteins are largely non-polymorphic. Thus, genetically diverse populations will likely have similar antigen presenting capacity and thus similar vaccine efficacy profiles. In addition, Mtb lipid antigens are highly conserved, making them attractive vaccine candidates. Vaccination of guinea pigs, cattle, and hCD1Tg mice with Mtb lipid antigens was shown to elicit group 1 CD1-restricted Mtb lipid-specific T response.[5, 82-84] A nanoparticle vaccine was able to effectively deliver

MA and lead to the activation and proliferation of adoptively transferred MA-specific DN1 T cells as well as polyclonal MA-specific T cells in hCD1Tg mice.[56] Given the failure of several protein-based subunit vaccines for TB in the recent years, a subunit vaccine containing both Mtb protein and lipid antigens that simultaneously stimulates MHC-restricted and CD1-restricted T cells may provide increased protective efficacy against Mtb infection and be adapted for other infectious diseases.

B. Infection with other microbial pathogens

Group 1 CD1-restricted T cells have been shown to recognize microbial lipid antigens from a few infectious agents including several mycobacterial species (*Mycobacterium leprae, Mycobacterium smegmatis, Mycobacterium phlei*), and other bacterial species *Borrelia burgdorferi, Salmonella typhimurium, Brucella melitensis*, and *Staphylococcus aureus* (SA).[29, 47] Hunger et al. first showed that CD1a-restricted T cell clones could recognize total lipid sonicates from the aforementioned mycobacterial species and determined these cells recognizing antigens within the mycolyl arabinogalactan peptidoglycan fraction.[29] CD1b-restricted T cells sorted and expanded from healthy human PBMC using CD1b dextramers loaded with total lipids from SA, *Brucella melitensis*, and *Salmonella Typhimurium* were found to be autoreactive and recognize phosphatidylglycerol (PG).[47] PG is a lipid commonly found on bacterial species and less so in mammalian cells, therefore group 1 CD1-restricted T cells may have little exposure to PG at steady state. Attempts to identify CD1b-restricted T cells specific to BbGL-II, a lipid found in *Borrelia burgdorferi*, the causative agent of Lyme disease, with CD1b tetramers from healthy controls and Lyme disease patients lead to the identification of additional autoreactive CD1b-restricted T cells.[85] In this case, expanded T clones recognized diacylglycerols (DAG), a moderately abundant self-lipid antigen.[85] Work thus far on CD1b-restricted T cells derived using microbial lipid antigens have shown there is significant cross-reactivity with self-lipid antigens.

Group 1 CD1-restricted T cells were found to contribute to protection against systemic SA infection.[10] SA-infected hCD1Tg$^+$ mice displayed markedly lower kidney inflammation and pathology compared with WT littermate controls.[10] Group 1 CD1-restricted T cells were found to be able to recognize SA-PG leading to the production of IL-17A and IFN-γ.[10] In SA-infected hCD1Tg mice, group 1 CD1-restricted T cell activation kinetics more closely resemble conventional T cells rather than the innate-like NKT cells.[86] Adoptive transfer of polyfunctional group 1 CD1-restricted SA-lipid specific T cells was protective against systemic SA infection by significantly reducing CFU burdens in the kidney.[10] This work constitutes the first direct evidence that group 1 CD1-restricted T cells can offer protection in an infection other than TB.

Despite their recognition of self-lipids, autoreactive CD1b-restricted T cells were shown to be able to provide protection against *Listeria monocytogenes* (LM) infection.[44] Mouse derived CD1b autoreactive T cell clone HJ1 could produce proinflammatory cytokines (IL-17A, IFN-γ, TNF-α) and induce lysis of hCD1Tg$^+$ cell line.[44] HJ1 T cell activation could be further augmented through TLR-mediated signaling, raising the possibility that these cells have the ability to be further activated in a TCR-independent manner.[44] HJ1 T cells adoptively transferred to hCD1Tg mice conferred protection against LM infection.[44]

This finding suggests that autoreactive CD1b-restricted T cells may play a role in host defense against various infections, although it is not clear how autoreactivity is suppressed in steady state conditions.

VI. GROUP 1 CD1-RESTRICTED T CELLS IN INFLAMMATORY CONDITIONS

The first group 1 CD1-restricted T cells identified were CD1a-restricted and CD1c-restricted DN T cells.[52] The authors noted they were able to isolate additional autoreactive T cell clones from synovial tissue of rheumatoid arthritis and systemic lupus erythematosus (SLE) patients, suggesting that these cells may be implicated in various autoimmune conditions.[52] Since then the role of autoreactive CD1-restricted T cells has been best established in several skin inflammatory conditions, including psoriasis, atopic dermatitis, and contact dermatitis.[87, 88] Most surprisingly, autoreactivity appears to be the rule rather than the exception, as several studies that have attempted to enrich and characterize group 1 CD1-restricted T cells from PBMC have discovered more autoreactive T cell lines.[42, 47, 49, 53, 85] While original works relied on sorting, co-culture with group 1 CD1-expressing DCs, and limiting dilution analysis, which could bias towards autoreactivity, more recent works using expanded populations from CD1 tetramer sorting yielded similar results.[42, 47, 49, 53, 85]

At this time, it is not clear whether the prevalence of autoreactive group 1 CD1-restricted T cells is due to biases associated with methods of purification and expansion or a reflection of the real TCR repertoire. In either instance, autoreactivity in group 1 CD1-restricted T cells is vastly common, and therefore begs the question of how these cells are not causing havoc at steady state conditions. One possible explanation is that endogenous CD1-associated lipid will impede binding by otherwise autoreactive T cells.[11, 43, 89] Some autoreactivity is directed at rarer lipid species such as PG, which is mostly contained within the mitochondria, however, there are also works describing autoreactivity against more commonly found lipids.[47, 90] Autoreactivity may also be kept at bay by the restricted expression of group 1 CD1 molecules, particularly CD1b, which can only be found on a subset of myeloid DCs and may be altered under disease conditions.[91, 92] Finally, additional cytokines or TLR signaling present in the *in vitro* coculture conditions may be absent *in vivo*, limiting the activation of autoreactive T cells. Additional research is needed to understand the regulation of group 1 CD1-restricted T cell autoreactivity and how this may impact various inflammatory and autoimmune conditions.

C. Properties of CD1b and CD1c-restricted autoreactive T cells

Studies in both humans and hCD1Tg mice attempting to obtain individual group 1 CD1-restricted T cell clones have yielded largely autoreactive clones.[5, 49, 53] Group 1 CD1-restricted T cells were estimated to constitute 7% of $CD4^+$ and 0.2% of DN TCR αβ cells in PBMC from healthy donors.[49] CD1c-restricted autoreactive T cells were found to constitute 0.06–3.0% of circulating T cells in healthy humans.[89] In a study investigating CD1c-restricted Mtb-specific T cells, CD1c-restricted $V\delta1^+$ T cells, identified using CD1c-PM tetramer, were found to also bind to CD1c loaded with endogenous lipids LPA, LPC, and sulfatide [1]. More recently, Wun et al. used CD1c tetramers loaded with endogenous

lipids to sort CD1c-restricted autoreactive T cells from healthy human controls.[89] Two obtained clones, $CD4^+$ and $CD4^-$, best bound to the smaller monoacylglycerol (MAG) loaded CD1c tetramer while lipids with larger headgroups such as phosphatidylcholine (PC), sphingomyelin (SM), and PM blocked binding.[89] Based on the crystal structure of clone 3C8, one mechanism of CD1c autoreactivity was found to be due to the TCR bind to CD1c centrally, plugging the F' portal, and thus explaining why large polar headgroups interfered with proper docking.[89]

Early findings of widespread CD1a and CD1c-restricted autoreactive T cells lead the field to conclude that autoreactivity to CD1b is limited. However, several CD1b-restricted T cell lines derived from bacterial lipids-loaded CD1b dextramers$^+$ T cells were found to be autoreactive and specifically recognize PG.[47] These CD1b autoreactive T cell lines produced a variety of cytokines, including IL-2, IL-4, IL-8, IL-13, TNF, IFN-γ, macrophage inflammatory protein-1α (MIP-1α), MIP-1β, oncostatin M, CXCL13, GM-CSF, and soluble tumor necrosis factor receptor type II,[47] in response to stimulation with CD1b-transfected C1R cells. Thus, autoreactive group 1 CD1-restricted T cells are polyfunctional and therefore may be play a role in a variety of disease processes.

The mechanism of CD1b autoreactivity was distinct to what was previously established with CD1c and CD1a. CD1b-restricted T cell autoreactivity to PG was determined to be due to an escape channel formed through the binding of the TCR with CD1b. As such, the nonpolar lipid tails are embedded within the CD1b molecule and the TCR recognizes the phosphate in the a neck portion of the lipid molecule, while the polar head group protrudes out and has no interactions with the TCR [90]. Another study on sorted and expanded CD1b-restricted endogenous lipid-specific δ1$^+$ T cells showed different modes of autoreactivity.[2] Two of the derived clones recognized endogenous lipid, while a third clone was able to bind to CD1b with no apparent interaction with the loaded lipid through its Vδ1 TCR chain.[2] Curiously, this clone could also recognize butyrophilin through its Vγ4 TCR chain, thus allowing it to potentially bind to two different targets simultaneously on the same cell and strengthen its interaction.[2] While group 1 CD1-restricted autoreactive T cells have different structural mechanisms behind their autoreactivity, each autoreactive TCR possesses a set of permissive and non-permissive endogenous lipids.

The development and functionality of autoreactive T cells was further assessed through a transgenic mouse line with the CD1b-autoreactive HJ1 T cell line. HJ1 T cells selectively responded to phospholipids, including PG, PC, phosphatidylethanolamine (PE), phosphatidylinositol (PI) but not phosphatidylserine (PS).[9] Unlike MA-specific T cell clone DN1, HJ1T cells exhibited an activated phenotype ($CD44^{hi}CD69^+CD122^+$) in naïve mice.[44] Co-culture of HJ1 T cells with hCD1Tg$^+$ BMDCs lead to the production of IFN-γ, IL-17A, and IL-22, but not IL-4, which could be further enhanced by TLR-mediated signaling or cytokines IL-12 and IL-18.[44] Additional work is needed to determine whether this phenotype and functional capacity can be observed among other mouse and human group 1 CD1 autoreactive T cells.

D. Autoreactive group 1 CD1-restricted T cells implicated in skin inflammatory conditions

The most compelling evidence for the role of group 1 CD1-restricted T cells in inflammatory and autoimmune conditions is in the skin, particularly for CD1a-restricted T cells, although some evidence also exists for CD1b-restricted T cells.[87, 88, 93] Autoreactive CD1a-restricted T cells were estimated to be 0.02 - 0.4% of blood memory T cells.[53] Given that skin resident Langerhans cells constitutively express CD1a, there was strong reason to believe CD1a-restricted T cells would preferentially home to the skin. This fact was confirmed when CD1a-restricted T cells were found to be overrepresented in two subsets: cutaneous lymphocyte antigen $(CLA)^+CD45RO^+$ and $CCR6^+CCR4^+CCR10^+$, another demarcation of skin-homing T cells.[53] T cell clones expanded from PBMC were found to be autoreactive and largely produce IL-22, but not IFN-γ or IL-17, suggesting CD1a-restricted T cells are a part of the T_H22 family.[53] Findings were further confirmed by extraction of skin CD1a-restricted T cells which showed similar phenotype.[53] Following work showed that headless lipids such as squalene and wax esters could bind to CD1a and allow for the activation of autoreactive CD1a-restricted T cells.[94] These lipids are generally restricted to the surface of the skin and sebaceous glands and would therefore not be accessible in steady-state conditions, preventing CD1a-mediated activation.[94]

In a recent study, Cotton et al. used a 3D culturing technique which relies on the migratory nature of skin T cells to obtain an unbiased population of CD1a-restricted T cells, which were then further enriched using CD1a tetramers loaded with endogenous lipids paired with staining optimization techniques.[42] Polyclonal CD1a-restricted T cells were found to account for 1% of skin T cell population, express CD4, and produce IL-22 upon restimulation.[42] Unsurprisingly given the use of a CD1a-endo tetramer, these CD1a-restricted T cells were found to be autoreactive and bind to CD1a loaded with several self-lipids including DAG, ceramide, PC, PI, and LPC, but not sulfatide and common SM.[42] This binding occurred through the A' roof of CD1a with no lipid contact, but larger lipid head groups could disrupt it.[42] Follow-up work by the group showed that the rarer 42:1 and 42:2 SM, lipids with particularly long tails, but not 36:1 SM, could block CD1a binding to polyclonal autoreactive T cells.[43] Despite constituting a minority of SM lipids, very long-chain fatty acids containing SMs including 42:1 and 42:2 were overrepresented in their binding to CD1a.[43] This finding suggests that CD1a autoreactivity is inhibited by selective binding to nonpermissive endogenous lipids.[43]

We and de Jong et al. have recently published two reviews on the role of CD1 and CD1a-restricted T cells in skin disorders and therefore this topic will be addressed here briefly.[87, 88] Group 1 CD1-restricted T cells have been implicated in psoriasis, atopic dermatitis, and contact dermatitis through autoreactive T cells. Cheung et al. showed that neolipids generated by PLA2 could be found in exosomes of psoriatic plaques and could activate CD1a-restricted T cells, and further induce the production of IFN-γ in psoriatic lesioned skin, but not healthy tissue.[95] CD1b-restricted autoreactive HJ1 T cells were shown to cause a psoriatic-like condition in an IL-17 dependent manner in the hyperlipidemic background induced via apoE-deficiency in mice through their recognition of phospholipids.[9]

CD1a-restricted T cells are also thought to a play a role in atopic dermatitis (AD)/eczema and contact dermatitis through the binding of allergens to CD1a or creation of neoantigens generated by PLA2. In AD, CD1a-restricted T cells have been shown to produce several inflammatory cytokines including IFN-γ, IL-13, and GM-CSF in response to neoantigens created by house dust mite induced PLA2.[96, 97] Similarly, PLA2 in bee venom could lead to the production of free fatty acids leading to CD1a-restricted T cell activation.[98] Two studies identified known allergens to be CD1a ligands, including 2,4-dinitrochlorobenzene and antigens contained in balsam of Peru oil, and showed they could effectively activate CD1a-restricted T cells.[11, 99] Nicolai et al. found unexpectedly that a group of similarly shaped bulky structured allergens could localize within CD1a A' cleft and thus allow for TCR recognition of CD1a by autoreactive group 1 CD1-restricted T cells.[11] While there is clear evidence that CD1a-restricted T cells can recognize allergens or neoantigens and produce inflammatory cytokines, more research is needed to determine whether these cells play a critical role in conditions such as AD, contact dermatitis, and psoriasis and thus whether their inhibition could prevent disease progression.

D. Additional inflammatory and autoimmune conditions

Group 1 CD1 molecules and group 1 CD1-restricted T cells have also been found in several human autoimmune diseases. Autoreactive CD1c-restricted T cells from patients with SLE could produce both IL-4 and IFN-γ, while CD1c-reactive T cells from healthy controls produce only IFN-γ.[59] When co-cultured with $CD1c^+$ B cells, CD1c-restricted T cells from SLE patients, but not healthy controls, can provide help for IgG production and therefore might promote autoantibody responses in SLE.[59] Group 1 CD1-expressing DCs were found in thyroid biopsy samples from autoimmune thyroiditis. Autoreactive cytotoxic CD1a and CD1c-restricted T cells were likewise identified in biopsy samples, suggesting that they may play a pathogenic role.[100] The role of CD1a-restricted T cells was indirectly suggested in ulcerative colitis (UC) in which patients with UC were found to have $CD14^+$ $CD1a^+$ monocytes with higher expression of inflammatory markers.[101] Additionally, anti-CD1a treatment of NOD/SCID IL2Rγ null (NSG) mice reconstituted with PBMC from UC patients, a model of UC, showed an improved histological score.[101]

While the expression of CD1 molecules in other inflammatory conditions does not directly implicate CD1-restricted T cells in their pathogenesis, it nonetheless supports further research. CD1b was found to be expressed in perivascular inflammatory cells in multiple sclerosis (MS) lesions, but not in non-MS controls.[102] The presence of greater than 2 $CD1a^+$ Langerhans cells in a given bile duct in liver biopsies can serve as a specific marker in the diagnosis of patients with primary biliary cirrhosis.[103] Recently, CD1b was shown to be upregulated on alveolar macrophages of smokers and correlated with disease severity.[92] Cigarette smoke was found to induce the oxidation of lipids in bronchial epithelial cells, and oxidized lipids could potentially serve as neoantigens for CD1b-restricted T cells.[92] Thus, group 1 CD1-restricted T cells may play a role in several autoimmune and inflammatory conditions.

VII. GROUP 1 CD1-RESTRICTED T CELLS IN MALIGNANT CONDITIONS

A. CD1 molecule expression in malignancies

Many tumor-specific glycolipids are known to be immunogenic, suggesting a role of group 1 CD1-restricted T cells in tumor immunity. Indeed, the expression of group 1 CD1 in tumor tissues has been shown to be associated with clinical outcomes of various cancers. Tumor infiltration by CD1a-positive DCs is associated with favorable prognosis in various types of malignancy including skin,[104] oral,[105] tongue,[106] thyroid,[107] ovarian,[108] and gallbladder cancer.[97] CD1b expression was detectable in tumor-bearing human livers but not in healthy livers.[109] Patients with gastric cancer have increased number of circulating $CD1c^+$ DCs.[110] However, some cancer types may downregulate CD1 expression to escape from immune surveillance. IL-10 produced by metastatic melanoma down-regulates CD1a, CD1b and CD1c expression on DCs.[111] Alpha fetoprotein produced by hepatocellular carcinoma can also reduce CD1a, CD1b, and CD1c expression by human monocyte-derived DCs.[112] In addition, low CD1b expression was reported to associate with poor overall survival in patients with prostate cancer[113] and advanced lung adenocarcinoma.[114]

B. Anti-tumor immunity by group 1 CD1-restricted T cells

To determine the potential role of group 1 CD1-restricted T cells in cancer treatment, Lepore et al. identified a novel class of self-lipids, methyl-lysophosphatidic acids (mLPAs), which are enriched in leukemia cells and recognized by CD1c-restricted T cells.[7] They found that mLPA-specific T cells efficiently killed $CD1c^+$ leukemia cells *in vitro* and delayed the leukemia progression in NSG mice xenografted with primary $CD1c^+$ acute myeloid leukemia blasts.[7] The preferential accumulation of mLPAs in different types of leukemias and the broad expression of CD1c by a large number of primary acute leukemias, raising the possibility of using mLPA-specific CD1c-restricted T cells as novel immunotherapy for patients with CD1c-expressing acute leukemias.[7]

CD1b-restricted T cells were also shown to provide protection in malignancy using a double transgenic mouse model (hCD1Tg/HJ1Tg), expressing human group 1 CD1 molecules and CD1b-autoreactive HJ1 TCR.[9] This study showed that CD1b autoreactive HJ1 T cells recognized a panel of phospholipids and responded more potently to tumor-derived lipids than lipids from normal cells. Treatment with CpG oligodeoxynucleotides (ODN), a potent anti-tumor agent, was found to enhance HJ1 autoreactivity.[9] *In vivo* adoptive transfer of HJ1 T cells resulted in protection against CD1b-expressing RMA-S tumors, but not the parental RMA-S cells. Additionally, the co-administration of HJ1 T cells and CpG ODN resulted in the greatest reduction of tumors.[9] Mechanistically, HJ1 T cells, and thus CD1b-autoreactive T cells may contribute to anti-tumor immunity by directly lysing tumor cells in the initial stages and later by activating other $CD8^+$ T cells. Thus, both CD1b and CD1c-restricted T cells have an anti-tumor effect. These group 1 CD1-restricted T cells provide a new treatment strategy for leukemias and more research should be performed for the application of adoptive immunotherapy targeting tumor-associated lipid antigens.

C. CD1a-specific chimeric antigen receptors (CAR) T cells

Since CD1a is not expressed on mature T cells, CD1a-specific CAR T cells have been generated to selectively target $CD1a^+$ cortical T-cell acute lymphoblastic leukemia (coT-ALL).[115] CD1a-specific CAR T cells showed robust cytotoxicity against CD1a-expressing T-ALL cells both *in vitro* and in a coT-ALL xenograft NSG mouse model. In addition, CD1a-specific CAR T cells harbored the long-term protection, which was confirmed by re-challenging with the CD1a-expressing T-ALL cells. These findings support the therapeutic use of CD1a-specific CARTs for coT-ALL. However, it is unclear whether CD1a-specific CARTs can kill CD1a-expressing APCs *in vivo* and affect the overall CD1a-restricted T cell responses in recipients.

VIII. CONCLUSION

Despite their abundance in humans, 0.3-10% of circulating T cells in the PBMC and 1% of skin T cells,[42, 49] more prevalent than iNKT or MAIT cells, group 1 CD1-restricted T cells remain an understudied area in immunology. The recent use of group CD1 tetramers has allowed for better understanding of group 1 CD1-restricted T cells at the polyclonal setting.[6] This technology is only beginning to extend the phenotypic and functional characterization established by *in vitro* expanded T clones and cell lines. Large scale CD1 tetramers studies allowed to determine the frequency of Mtb lipid-specific T cells among diverse human populations,[57] as well as the likely phenotype and thus role that these cells may be playing in infection.[55] Future work using CD1 tetramer sorting paired with single cell sequencing will allow for in-depth profiling of group 1 CD1-restricted T cell phenotype and will therefore be key for growth in the field. Previously, much of the work focused on PBMC-derived T cells, but further understanding of the role of group 1 CD1-restricted T cell in diseases requires the use of disease relevant human tissues, such as was recently accomplished through TCR sequencing of cells from resected Mtb-infected human lungs.[50]

Using the hCD1Tg mouse models, group 1 CD1-restricted T cells were found to have an inflammatory and cytotoxic functionality, offer protection in Mtb and SA infections, lead to inflammation, and have anti-tumor capacity.[5, 8-10, 31, 44] Mouse systems allow for the probing of mechanisms by which group 1 CD1-restricted T cells mediate protection and pathophysiology. Thus, work in model animals will likely continue playing an essential role in the field.

The abundance of autoreactive group 1 CD1-restricted T cells in healthy humans is still a puzzle. Autoreactive T cells can play a pathogenic role in inflammatory conditions such as psoriasis, AD, and contact dermatitis through the recognition of self-lipid antigens and allergens.[11, 93, 95, 96, 98] Regulation of self-reactivity appears to occur through modulation of group 1 CD1 expression as well as preferential presentation of non-permissive self-lipids.[43, 91, 92] Research is needed on additional immunological players that may contribute to this regulatory framework.

Our understanding of protection against specific diseases afforded by group 1 CD1-restricted T cells pushes closer to the development of relevant vaccines and treatments. Lipid nanoparticle vaccine were shown to induce group 1 CD1-restricted T cell activation and

expansion.[56] Recently a CD1a-specific CART cell treatment was created targeting CD1a^{+} cortical T-ALL.[115] Several papers have shown that CD1a presentation plays a role in various skin inflammatory conditions for which treatments targeting T cell activation pathways or CD1a could be developed.[8, 11] Group 1 CD1-restricted T cells are important players in human immunology and could be the target of vaccines and treatments for a variety of human diseases.

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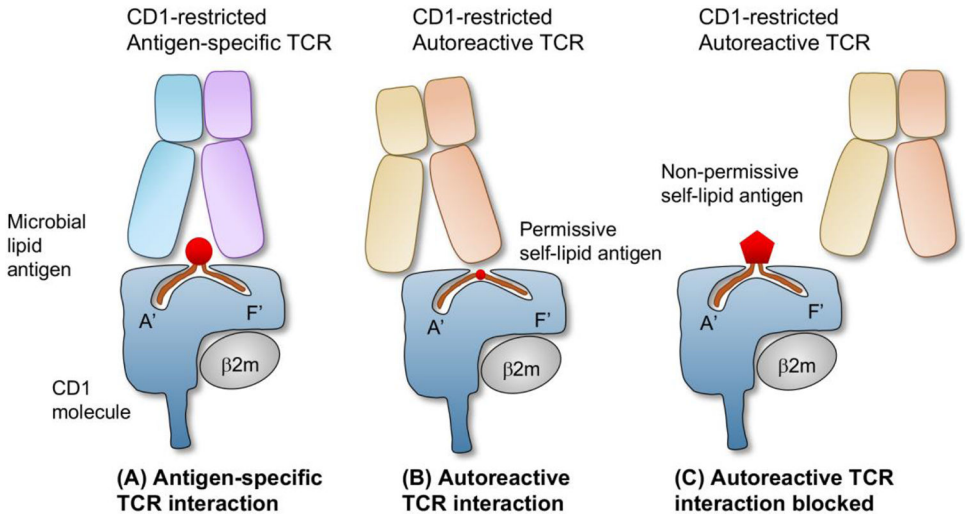

FIG. 1: Lipid antigens modulate binding of group 1 CD1-restricted TCR.

(A) Antigen-specific TCR interaction requires the recognition of both lipid antigen and CD1 molecule. (B) CD1-restricted autoreactive T cells bind to CD1 molecules loaded with permissive self-lipid antigens. (C) Non-permissive self-lipid antigens disrupt the recognition of CD1-restricted autoreactive T cells.

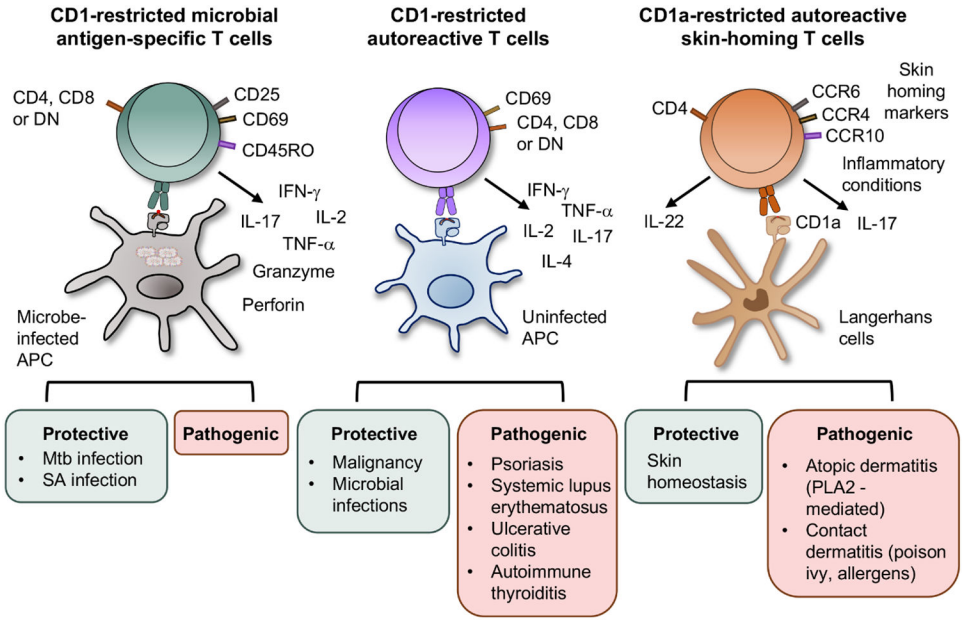

Figure 2. The protective and pathogenic roles of group 1 CD1-restricted T cells in various conditions.

Microbial antigen-specific T cells have been shown to play a protective role in Mtb and SA infections through the production of inflammatory cytokines, inducing cytotoxicity in infected APCs, and inflammation (left panel). Autoreactive group 1 CD1-restricted T cells have potentially both pathogenic (in autoimmune and inflammatory conditions) and protective (in malignancy and infection) roles (middle panel). CD1a-restricted skin-homing T cells uniquely express IL-22 and which is thought to play an important role in skin homeostasis. They can also play a pathogenic role in atopic dermatitis and contact dermatitis through the recognition of allergens and self-lipids (right panel).

Table 1.
Lipid antigens recognized by group 1 CD1-restricted T cells.

Self, microbial, or allergenic lipid antigens which bind to group 1 CD1 molecules allowing for direct or permissive binding to group 1 CD1-restricted T cells.

	Endogenous lipids	Microbial lipids		Lipids in allergic or inflammatory conditions
		Mtb	Others	
CD1a	squalene, wax esters, fatty acids, TAG 94, DAG, ceramide, PC, PI, LPC 42, SM 43, sulfatide 18	DDM [45, 78], MAP [29]	MAP 29	Lysophospholipids 98, urushiol 8, 1,4-benzoquinone, resorcinol, isoeugenol, cinnamaldehyde, DNCB 99, benzyl cinnamate, benzyl benzoate, farnesol, coenzyme Q2 11
CD1b	DAG 85, phospholipids 47, PG , PA, LPA, PG, PE, PS, PC, PI, PIM, GM1, GM2, SM, DAT 2, PE 90	DAT 80, GMM 66, MA 65 , SGL 116, LAM, PIM 70, Ac2SGL 117, GroMM 67	BbGL-II 85, cardiolipin, PG 10	Phospholipid 93, oxidized self-lipids 92
CD1c	MAG 89, LPC, LPA, sulfides 1, CE, mLPA 7	MPM, PM [74, 118]; GMM [54, 55]	ASG39	

ASG, acylated steryl glycosides; Ac2SGL, diacylated sulfoglycolipids; CE, cholesteryl esters; DAG, diacylglycerol; DAT, diacyltrehalose; DDM, dideoxymycobactin; DNCB, 2,4-dinitrochlorobenzene; GM1, monosialoganglioside GM1; GM2, monosialoganglioside GM2; GMM, glucose monomycolate; GroMM, glycerol monomycolate; LAM, lipoarabinomannan; LPA, oleoyl lysophosphatidic acid; LPC, lysophosphatidylcholine; MA, mycolic acid; MAG, monoacylglycerol; MAP, mycolyl arabinogalactin peptidoglycan; mLPA, methyl-lysophosphatidic acid; MPM, mannosyl-b-1-phosphomycoketide; PA, phosphatidic acid; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PG, phosphatidylglycerol; PI, phosphatidylinositol; PIM, phosphatidyl inositol mannan; PM, phosphomycoketide; PS, phosphatidylserine; SM, sphingomyelin; TAG , triglycerides fatty acids

Table 2.

Properties of group 1 CD1-restricted T cells identified with human CD1 tetramers

	Antigen	Species source	Characteristics of identified T cells			Ref.
			Co-receptor and TCR usage	Activation markers	Cytokine production	
CD1a	Endo	Mammalian	$CD4^+$		IL-22, IFN-γ	42, 43
	DDM	Mtb			IFN-γ, TNF-α	78
CD1b	Endo	Mammalian	TRDV1 or variable	CD25, CD69		2
	GMM	Mtb	**GEM**: $CD4^+$, TRAV1-2/ TRAJ9; **LND5-like**: $CD4^+$, $CD8^+$, or DN, TRAV17, TRBV4-1; or variable	$CD45RO^-$ or $CD45RO^+$	IL-2, IFN-γ, TNF-α, IL-6, IL-13, IL-17, IL-25, IFN-α, IFN-β, IL-1Rα, TNF-β, MIF, MIP1β, CCL17, CCL1, CXCL1	6, 46, 51, 57, 77, 119
	MA	Mtb	$CD4^+$ or $CD4^-$	$CD45RO^-$ or $CD45RO^+$	IFN-γ, TNF-α	57, 79
	SGL	Mtb	$CD4^+$			116
	DAT	Mtb	$CD8^+$, TRBV6-2		IFN-γ	80
	BbGL-II	*Borrelia burgdorferi*	$CD8^+$		IFN-γ	85
	Total microbial lipid extract	Staph, Salmonella, Brucella		CD25	TNF, IFN-γ, IL-8, IL-13, MIP-1α, MIP-1β, oncostatin M, CXCL13, GM-CSF, sTNF-RII, IL-4	47
CD1c	Endo	Mammalian	$CD4^+$ or $CD4^-$, TRBV5-1 or variable	CD69		89
	PM	Mtb	$CD4^-$ TRDV1 or variable $CD4^+$	TRDV1 NKG2D	IFN-γ	1, 74
	GMM	Mtb		CD45RA, CCR7, CD69, CD103		55

Mtb, *Mycobacterium tuberculosis*; Staph, *Staphylococcus aureus*; Salmonella, *Salmonella typhimurium*; Brucella, *Brucella melitensis*; Endo, endogenous lipids; DDM, dideoxymycobactin; GMM, glucose monomycolate; MA, mycolic acid; SGL, sulfoglycolipid; DAT, diacyltrehalose; BbGL-II, *B. burgdorferi* glycolipid II; PM, phosphomycoketide