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CD1a and bound lipids drive T cell responses in human skin disease

Graham S. Ogg[1], **Jamie Rossjohn**[2,3], **Rachael A. Clark**[4], **D. Branch Moody**[5]

[1]Medical Research Council Human Immunology Unit, MRC Weatherall Institute of Molecular Medicine, University of Oxford

[2]Infection and Immunity Program and Department of Biochemistry and Molecular Biology, Biomedicine Discovery Institute, Monash University, Clayton, Victoria, Australia

[3]Institute of Infection and Immunity, Cardiff University, School of Medicine, Heath Park, Cardiff, UK

[4]Department of Dermatology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA.

[5]Division of Rheumatology, Inflammation and Immunity, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School,

Abstract

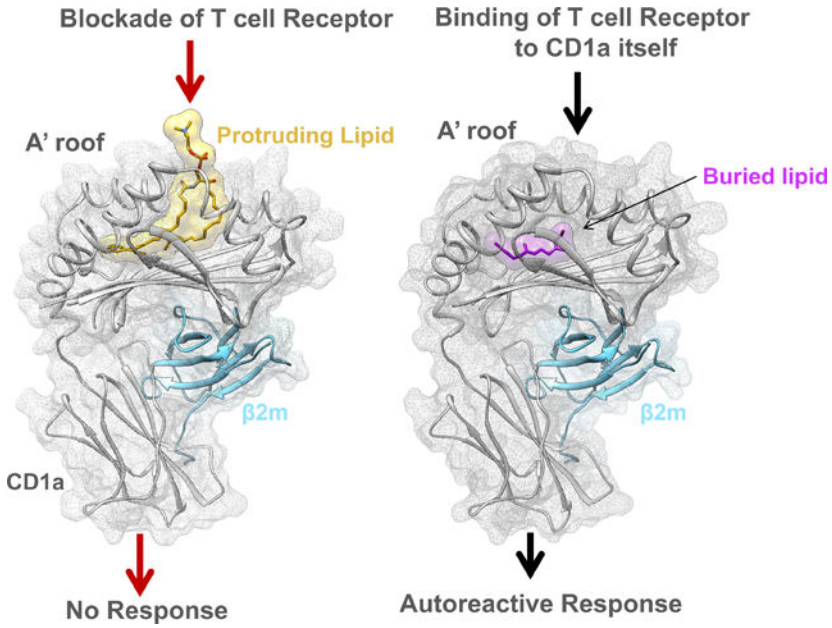
In addition to serving as the main physical barrier with the outside world, human skin is abundantly infiltrated with resident α T cells that respond differently to self, infectious, microbiome and noxious stimuli. To study skin T cells during infection and inflammation, experimental biologists track T cell surface phenotypes and effector functions, which are often interpreted with the untested assumption that MHC proteins and peptide antigens drive measured responses. However, a broader perspective is that CD1 proteins also activate human T cells, and in skin, Langerhans cells (LC) are abundant antigen presenting cells that express extremely high levels of CD1a. The emergence of new experimental tools, including CD1a tetramers carrying endogenous lipids, now show that CD1a-reactive T cells comprise a large population of resident T cells in human skin. Here we review studies showing that skin-derived αβ T cells directly recognize CD1a proteins, and certain bound lipids, such as contact dermatitis allergens, trigger T cell responses. Other natural skin lipids inhibit CD1a-mediated T cell responses, providing an entry point for the development of therapeutic lipids that block T cell responses. Increasing evidence points to a distinct role of CD1a in type 2 and 22 T cell responses, providing new insights into psoriasis, contact dermatitis and other T cell-mediated skin diseases.

Graphical Abstract Text.

Correspondence: D. Branch Moody bmoody@bwh.harvard.edu.

Conflict of interest

GO, BM, JR are co-inventors of patents related to CD1a. GO has relevant research collaborations with UCB and Janssen.



New studies show how small buried ligands hide inside CD1a to allow direct TCR contact with the outer surface of CD1a on the A' roof. Most recently, CD1a has been shown to capture sphingomyelins with long alkyl chains and bulky choline groups, which protrude from CD1a to cause dominant negative blockade of TCRs that approach the surface of CD1a, which can inhibit inflammatory responses. In these two new models, small or large lipids turn on or off T cell response without precise recognition of the lipid epitopes.

Keywords

αβ T cells; CD1a; Langerhans cells; contact dermatitis; psoriasis

Skin resident memory T cells in humans

The skin of a healthy adult human contains approximately 20 billion memory T cells, twice as many T cells as are present in the entire circulation. Approximately 10–30% of these T cells recirculate between the blood and skin, including a population of skin tropic central memory T cells (T_{CM}). The majority are nonrecirculating resident memory T cells (T_{RM}) [1] accumulate in skin as a result of immunologic challenges, including exposure to infectious agents, allergens and haptens. Metabolically, T_{RM} live off the fat of the land, importing exogenous fatty acids from the tissue microenvironment. Thus, memory T cells accumulate in epithelial barrier tissues that are specific for the antigens encountered at that site and produce the cytokines that are effective in eliminating the immunologic challenge. Once in place, pathogenic T_{RM} are long-lived, remain anatomically localized, where they are difficult to eliminate in diseases like psoriasis, vitiligo, contact dermatitis, and rheumatoid arthritis.

A better understanding of the biology and antigen recognition of skin resident T cells could lead to new therapies that selectively inactivate or deplete these cells, instead of globally

suppressing T cell activation with corticosteroids and other broadly acting agents. Many published studies of tissue-resident memory T cells assume without experimental evidence that the target of response is classical MHC I and II proteins presenting peptide antigens. This review emphasizes new insights into the molecular and disease-related functions of CD1a, an MHC I-like protein that is expressed at extremely high density on Langerhans cells (LC) located throughout human skin. Because CD1a is not expressed in mice, most knowledge comes from human experimental systems. CD1a proteins normally present lipid antigens, and CD1a can be directly recognized by TCRs [2, 3]. These data raise new questions about whether skin resident T cells respond to CD1a itself [3], clinically relevant skin microbiome lipids [4], CD1a-presented contact allergens [5] or all of the above. In this new view, both MHC and CD1a, presenting either peptides or lipids, can drive physiological and skin disease-related T cell responses.

Two mechanisms of CD1a mediated T cell recognition

McMichael and Milstein started the molecular investigation of human CD1a with early work showing that its heavy chain is nearly the same size as MHC I, and both proteins bind β2 microglobulin [6]. However, CD1a and MHC I were recognized by different antibodies and showed markedly distinct patterns of expression in the thymus. After early studies demonstrated CD1b presentation of lipid antigens [7], CD1a was shown to activate αβ T cells by presenting self sulfatides and foreign lipopeptides [8–10]. The presentation mechanism involved anchoring the fatty acyl chains of amphipathic antigens into a hydrophobic cleft in CD1a, with the sulfosugar or peptide moiety presented to on the outer surface of CD1a for T cell receptor recognition [11, 12].

Whereas these molecular studies were carried out on individual T cell clones, larger populations of CD1a autoreactive T cells were later identified among genetically unrelated human donors [13, 14]. Although initially detected in the blood, human CD1a-autoreactive T cells express skin addressins such as cutaneous lymphocyte associated antigen, CCR4, CCR6 and CCR 10, implying possible migration to the skin [13], where CD1a is expressed at high density on LCs [15]. Further lipid autoantigens were detected in skin at higher levels than other tissues, and De Jong and Cheng showed that CD1a autoreactive cells were activated by small hydrophobic skin lipids: squalene, free fatty acids and wax esters [16].

These stimulatory molecules were comprised almost solely of aliphatic hydrocarbons. They lacked rigid and hydrophilic sugar, phosphate or peptide head groups, which were previously thought to be needed to form epitopes that protrude from CD1a for TCR binding. One theoretical possibility was that these small and hydrophobic lipids actually lacked TCR epitopes and that the epitopes were on CD1a itself, such that the mechanism of activation might be direct recognition of CD1a, rather than carried lipid [16]. This mystery was solved by Birkinshaw and colleagues, who showed that lysophosphatidylcholine or other small lipids can bind fully inside the cleft of CD1a, and TCRs can recognize solely the outer surface of CD1a, via contact with a structure known as the A’-roof [2]. Thus, by 2015 the molecular basis of CD1a-mediated activation was established to occur by two mechanisms: TCR discrimination of the hydrophilic head groups of carried lipids and direct autoreactivity to the outer surface of CD1a proteins.

CD1a function in Allergic Skin Disease

Early experiments that addressed the functional role of human CD1a in disease focused on exogenous allergens as candidate antigens for T cells. For example, bee and wasp venom were able to drive human CD1a-reactive skin T cell responses. However, the stimulatory materials extracted in to protein rather than lipid fractions of venom, which allowed identification of a new mechanism: the exogenous phospholipase A component of the venoms acted to cleave phosphodiacylglycerols to generate lysophospholipid neoantigens [17, 18]. In turn, the lysophospholipid products matched those that were shown to bind CD1a and promote autoreactive T cell responses [2, 17]. House dust mites are a major source of allergens in allergic disease, and dust mite-derived phospholipase A2 was subsequently found to contribute to skin and blood CD1a-autoreactive T cell responses after antigen challenge in humans [19].

It is of interest that many clinically relevant atopic allergens contain lipid binding proteins, which may suggest a broader underlying contribution of phospholipases for CD1a-presented lysolipids in allergic disease. Furthermore, filaggrin inhibited house dust mite-derived phospholipase A2 activity, consistent with an immunoregulatory role in addition to its well-known role in skin barrier function [19]. Such human skin challenge experiments also informed the nature of cells co-opted into CD1a antigen presentation in inflammatory tissue environments, including BDCA-2+ myeloid cells [20] and innate lymphoid cell subsets [21].

In a second proposed mechanism involving skin integrity and microbiome lipids, Monnot and colleagues recently discovered phosphatidylglycerol-based CD1a antigens produced by skin commensal organisms including *Staphylococcus aureus* and *S. epidermidis*. Further, they showed elevated frequencies of lysyl-phosphatidylglycerol-specific CD1a-reactive T cells in individuals with atopic dermatitis [4]. Subsets of the lysyl-phosphatidylglycerol-reactive T cells could also respond to endogenous phosphatidylglycerol, defining potential mechanisms of bacterial-induced molecular mimicry in the CD1a system, leading to a type 2 inflammation.

Effector mechanisms of CD1a autoreactive T cells

The earliest studies of CD1a autoreactive T cells found a Th22 effector function profile [13], which was seen in subsequent studies [22–24]. IL-22 is notable because it activates epithelia rather than other immune cells. Also T cells with a pure Th22 phenotype, as contrasted with those producing IL-22 combined with IL-17A, has been more clearly demonstrated in human versus mouse skin [25]. Therefore it is notable that the CD1a system is present in humans but not mice, so CD1a is emerging as a candidate determinant of the unique type 22 response seen in humans.

In more recent work, the interplay of bacteria-responsive CD1a-reactive T cells and autoreactivity was investigated in the setting of psoriasis, where streptococcal infection could promote the generation of polyfunctional CD1a-autoreactive T cells that produce type 1, 2 and 17 cytokines [26]. The data are consistent with earlier work showing that individuals with psoriasis have elevated frequencies of CD1a-autoreactive and cytokine

producing T cells in the blood and skin, explained at least in part through activity of endogenous phospholipase A2 [22–24]. These studies implicate a role for CD1a-reactivity in atopic dermatitis and psoriasis; and begin to define underlying pathways of antigen generation and key effector functions.

CD1a in contact dermatitis

In contrast, most common contact dermatitis allergens are non-proteinaceous, yet in some unknown way activate T cells. Certain models of generalized atopy and contact dermatitis predict that non-peptidic antigens activate immune response through ‘haptenization,’ whereby small molecules form covalent or non-covalent interactions with peptides to generate neoepitopes. There is clinical evidence for the haptenization hypothesis [27], which potentially resolves the chemical dichotomy between non-peptidic contact allergens and the peptidic nature of MHC ligands that are most well-known to activate T cells. The CD1a system provides a second answer that potentially bypasses the peptide-lipid dichotomy altogether by changing the expectations about the chemical nature of antigens for T cells, such that lipids and small molecules are more widely viewed as common antigens for T cells.

A key question now arises: does CD1a present known contact allergens to T cells? Betts et al. found that benzoquinone, cinnamaldehyde and related non-peptidic molecules augmented the response of CD1a- and CD1d-restricted T cells [28]. Mechanistically-oriented studies by Kim et al. showed that CD1a mediates response to urushiol, the potent poison ivy contact allergen [24]. Like the natural skin antigens discussed above [16], the predominant urushiol congener, diunsaturated pentadecylcatechol (C15:2), was buried within the antigen-binding cleft of CD1a. This reaction displaces larger endogenous lipids with head groups, exposing the A’ roof of CD1a for direct TCR contact (Figure 1). Similarly, Nicolai et al. showed that farnesol, as well as benzyl benzoate and benzyl cinnamate, which are small hydrophobic components in the noxious fragrance allergen, balsam of Peru, activate T cells in a similar mechanism (Figure 1) [5]. These examples support a new concept of contact dermatitis pathogenesis: hydrophobic molecules buried in CD1a displace larger lipids whose head groups normally lie on the surface of CD1a. This exchange can unmask the CD1a surface and promote disease in susceptible individuals.

New Tool: CD1a-endo tetramer

Whereas these studies moved beyond clonal response to measure polyclonal responses ex vivo: enumeration of CD1a autoreactive T cells, as well as the study of effector functions on a single cell basis, was missing. Because CD1a is non-polymorphic, fluorescent CD1a tetramers or higher order multimers, known as ‘dextramers,’ do not require genetic matching to the donor. CD1a tetramers and dextramers were first validated by loading them with mycobacterial lipopeptides and detecting responses in tuberculosis patients [29]. However, immunodominant autoantigens were unknown, which raised a barrier to clinical studies of autoreactive T cell response.

Tetramer use normally requires loading with one chemically defined antigen that is needed to gain adequate avidity to mediate MHC-TCR or CD1-TCR response [30]. However, the basic immunology studies showing how TCRs can directly bind to CD1a, as long as the carried lipid does not interfere, suggested a new approach. If this were a general mode of CD1a recognition by TCRs, then perhaps CD1a tetramers carrying endogenous lipids (CD1a-endo tetramers), rather than those loaded with a defined antigen, could bind to polyclonal populations of CD1a autoreactive T cells (Figure 2). In a group of 8 patients, Cotton used CD1a-endo tetramers to stain polyclonal T cells, measuring tetramer positivity of 1–12 percent of all skin T cells in the ex vivo state [3]. Further, CD1a-endo tetramer-stained T cells respond with cytokines in a CD1a-dependent manner, demonstrating functional CD1a-TCR interaction, rather than simply binding to a non-TCR ligand on cells [31].

Naive T cells recognizing a single epitope have been measured at rates below 10^{-4} [32], so these measurements represent a high precursor frequency in absolute terms. These data even raise the hypothesis that CD1a and MHC reactivity might occur at similar rates in skin. Because CD1a is non-polymorphic patient samples do not need to be genetically typed or matched, and the CD1a-endo tetramer reagents overcomes certain difficulties for choosing autoantigens. Thus, the CD1a-endo tetramer can now be used to measure direct CD1a autoreactivity in any patient from any disease site, and recent studies show that CD1c-endo tetramers can also detect [33] or enumerate CD1c autoreactive T cells [31], when alternate CD1c ligands are blocked with antibodies.

The leading hypothesis for small hydrophobic ligand induced autoreactivity is that carried lipids activate T cells by absence of interference with CD1a-TCR interactions, which is supported by many crystal structures showing ligands fully buried in the cleft (Figure 1). A related hypothesis, that is not exclusive of absence of interference, is that lipids could alter the structure of CD1a itself without contacting TCRs. CD1a-lipid crystal structures solved to date show that small ligands clearly act to free up access to the surface of CD1a, but there are also small ligand-induced changes in CD1a structure that could contibute to recognition [2, 5, 24]. For CD1c, ligand binding can notably alter its conformation [34–36].

A second tool: human CD1a transgenesis in mice

Evidence for a non-redundant role of CD1a in human skin disease comes from CD1a transgenic mice developed in Kyoto and subsequently in Oxford. Kobayashi et al. showed relevant cell-type specific expression of the human CD1a transgene, including constitutive expression by LC in the presence or absence of GM-CSF [37]. The model demonstrated enhanced TLR7 agonist effects after skin challenge in the hCD1a transgenic mouse and that response could be inhibited in vivo with anti-CD1a antibodies [24]. Hardman et al. developed a second ‘Oxford’ mouse with higher breeding capacity that allowed confirmation and extension of the ‘Kyoto’ mouse.

CD1a amplified a type 17-dependent inflammation induced by topical TLR7 agonism, and also amplified a type 2-dependent MC903-induced skin inflammation [38]. Furthermore, CD1a promoted a cascade of systemic inflammation suggesting that responses to CD1a

might contribute to some of the known systemic associations with human skin disease. Lastly, both mouse models showed that anti-CD1a antibodies ameliorate both skin and systemic inflammation, supporting the potential for anti-CD1a therapeutics development for autoimmune skin disease. These and related model systems will be of utility in further studies to progress in vivo mechanism and translation of CD1a autoreactive T cells.

A surprise: natural skin lipids can inhibit autoreactivity

CD1a is thought of as an antigen presenting molecule, and antigens have activating functions. In the many studies reviewed above, identification of CD1a and lipids as targets was undertaken using T cell activation assays, an approach that precludes the discovery of blockers of T cell function. However, using CD1-lipid binding assays whereby natural cellular ligands of CD1a are eluted and studied by mass spectrometry, Cotton, Cheng and colleagues identified sphingomyelins as abundant CD1a ligands. Cellular CD1a proteins specifically bound to long chain (>C42) and dually unsaturated lipids in preference to short chain (<C36) lipids [39]. Further, loading such long chain sphingomyelins onto CD1a tetramers leads to potent blockade of CD1a-endo tetramer staining, a finding that held up for polyclonal T cells and across genetically unrelated donors. These studies parallel the independent discovery of lipid blockers of CD1d-mediate activation of NKT cells [40, 41].

The identification of natural lipid blockers of CD1a-mediated T cell responses studies raise two new ideas for cutaneous immunity. CD1a autoreactivity may be up- or down-regulated by the range of lipids present in cells, bringing into consideration natural mechanisms of dominant negative regulation through cellular generation or cleavage of sphingomyelins and related lipids, whose levels are linked to cell stress states [42]. Second, natural CD1a ligands, or synthetic molecules that exaggerate or extend the chemical features that lead to CD1a binding (polyunsaturation and chain length), might be used as therapeutics to specifically downregulate T cell responses in human skin. This approach is supported by structural immunology studies from Wegrecki and colleagues showing how long chain sphingomyelins block TCR response: long chain length causes the choline head group to seat in the superior portion of the cleft to that it is located ~7 angstroms above CD1a platform, blocking access of TCRs to the membrane-distal surface of CD1a [39] (Figure 1). In contrast, common self sphingomyelins seat deeply and the head group does not protrude structurally or block T cell response.

Conclusion

Human CD1a transgenic mice and CD1a-endo tetramers now represent effective experimental tools to more incisively enquire about the disease-specific roles of CD1a-autoreactive T cells. In considering new directions, previously, there was no clear unifying hypothesis for immunological basis of the role of non-peptide antigens in triggering what are clearly T cell mediated hypersensitivity reactions. Recent studies show that urushiol (the poison ivy antigen) [24], balsam of Peru (a common skin contact allergen) [5], as well as dust mite and bee venom-generated lysophospholipids [17–19] mediate CD1a autoreactive T cell responses. Bypassing the need to hypothesize complex B cell-T cell interactions or haptenization of peptides, these data suggest that contact or other allergens can simply be

presented to subsets of T cells that mediate disease responses in contact dermatitis and allergic dermatitis. Further, with new evidence for increased CD1a autoreactive T cells in human blood and psoriatic skin [22, 23], along with the ability of the CD1a-transgene to promote T cell inflammation that mimics certain aspects of psoriatic skin disease, suggest the further use of CD1a-endo tetramers to dissect pathogenetic mechanisms (Figure 2). Last, with good evidence for anti-CD1a antibodies [24, 38] and CD1a-specific lipid blockers [39], CD1a blockade is already being tried in therapies for human CD1a-mediated aspects of human skin disease.

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Data availability statement:

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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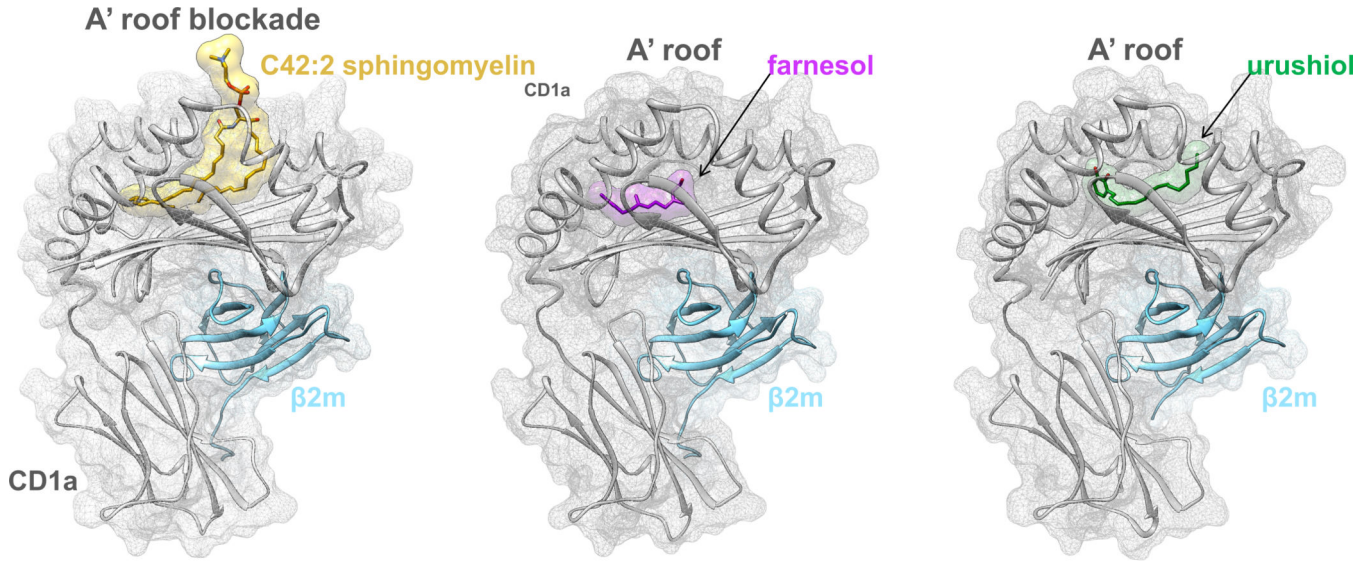

Figure 1. Lipid blockers and activators of CD1a.

The crystal structures of CD1a-β2m dimer carrying various lipid ligands in the binding cleft. Sphingomyelin C42:2 (yellow) protrudes (Cotton, JEM, 2021) broadly from the membrane distal surface of CD1a, so that it can block the approach of TCRs. Farnesol (purple) (Nicolai, Science Immunology, 2020) and urushiol (green) (Kim, Nature Immunology, 2016) are smaller molecules that lack a choline or carbohydrate head group. When such small molecules occupy the inner surface of the CD1a cleft, the loss of larger ligands frees up the outer surface of the CD1a roof for access by TCRs. If the term 'antigen' is restricted to molecules that contact TCRs, then such small urushiol and farnesol are not antigens, strictly speaking. Instead they are activators that act through absence of interference with TCR approach.

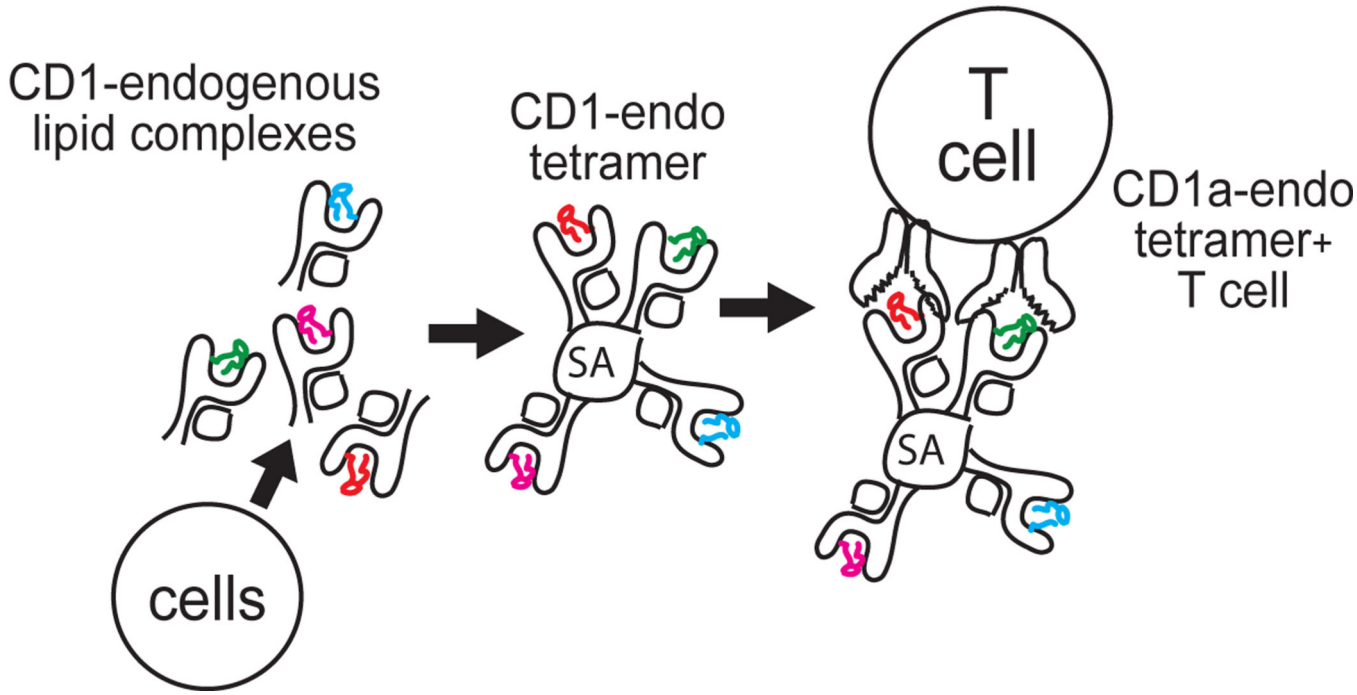

Figure 2. CD1a-endo tetramers are a new tool for T cell detection.

Cells release transmembrane truncated CD1a carrying diverse endogenous lipids from the expresion system. CD1 proteins are multimerized with fluorescent streptavidin molecules to make CD1a endo tetramers that bind to T cells expressing TCRs with intrinsic affinity for CD1a. For CD1a-TCR interactions that do not require lipid, CD1-endo tetramers represent a one-step staining reagent to detect or sort CD1a autoreactive cells from any tissue. Further, since CD1a proteins are non-polymorphic, one kind of CD1a tetramer can be used for any human donor, regardless of genetic background.