Molecules and Cells

Minireview

Current Understanding of the Roles of CD1a-Restricted T Cells in the Immune System

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Cluster of differentiation 1 (CD1) is a family of cell-surface glycoproteins that present lipid antigens to T cells. Humans have five CD1 isoforms. CD1a is distinguished by the small volume of its antigen-binding groove and its stunted A′ pocket, its high and exclusive expression on Langerhans cells, and its localization in the early endosomal and recycling intracellular trafficking compartments. Its ligands originate from self or foreign sources. There are three modes by which the T-cell receptors of CD1a-restricted T cells interact with the CD1a:lipid complex: they bind to both the CD1a surface and the antigen or to only CD1a itself, which activates the T cell, or they are unable to bind because of bulky motifs protruding from the antigen-binding groove, which might inhibit autoreactive T-cell activation. Recently, several studies have shown that by producing T_H2 or T_H17 cytokines, CD1a-restricted T cells contribute to inflammatory skin disorders, including atopic dermatitis, psoriasis, allergic contact dermatitis, and wasp/bee venom allergy. They may also participate in other diseases, including pulmonary disorders and cancer, because CD1a-expressing dendritic cells are also located in non-skin tissues. In this mini-review, we discuss the current knowledge regarding the biology of CD1a-reactive T cells and their potential roles in disease.

Keywords: CD1 molecules, CD1a, inflammatory skin diseases, lipid antigens, lipid-reactive T cells

INTRODUCTION

Research over the last few decades has greatly advanced our knowledge about major histocompatibility complex (MHC)-restricted T cells. The widely held notion that T cells recognize MHC molecules complexed with peptide antigens has now been supplanted by the understanding that T cells can recognize a much broader range of antigens, including carbohydrates (Carbone and Gleeson, 1997), metals (Gamerdinger et al., 2003), small metabolites (Corbett et al., 2014; Kjer-Nielsen et al., 2012), and lipids (Beckman et al., 1994; Kawano et al., 1997). With regard to the latter, multiple studies have shown that T cells can recognize lipid antigens that are complexed to MHC-like proteins called cluster of differentiation 1 (CD1) (Porcelli et al., 1989). The human CD1 family contains five isoforms designated CD1a to CD1e that differ in their antigen-binding groove properties, intracellular-trafficking routes, and cell/tissue expression; consequently, they present different lipid-antigen repertoires. Since mice bear only CD1d (Park et al., 2001), CD1d-restricted T cells are well understood. However, the immunological roles of the other human isoforms are less well understood, including CD1a, the focus of this review.

Lipid-reactive T cells play crucial roles in the pathogenesis of certain diseases, including autoimmune (Akbari et al., 2003; Kim et al., 2016) and infectious diseases (Kinjo et al., 2006; Raftery et al., 2008) and cancer (Lepore et al., 2014). In particular, CD1a-reactive T cells are the most frequent

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CD1-restricted T cells in the blood and participate in the immune response to bacterial infection (Rosat et al., 1999; Visvabharathy et al., 2020) and might play important roles in asthma (Bertorelli et al., 2000), allergy (Agea et al., 2005), psoriasis (Kim et al., 2016), and allergic contact dermatis (ACD) (Betts et al., 2017) immunopathogenesis.

Here, we summarize the molecular properties of the CD1 isoforms, their lipid antigens, and CD1-restricted T cells, with particular focus on CD1a. We then discuss the roles that CD1a-reactive T cells play in several diseases.

THE MOLECULAR PROPERTIES OF CD1a

The CD1 isoforms in human

The CD1 molecules are structurally related to MHC I and like them, present antigen to αβ and γδ T cells (Zeng et al., 1997). However, the antigens originate from lipids, not proteins. All placental mammals have CD1 genes. They are highly conserved and show limited allelic polymorphism (Han et al., 1999; Seshadri et al., 2013), unlike the MHC I and II molecules, which are extremely polymorphic and bear dozens to hundreds of allelic variants (Radwan et al., 2020). The five CD1 isoforms in humans fall into three groups on the basis of sequence homology and immune functions (Angenieux et al., 2000; Calabi et al., 1989). Thus, group 1 contains CD1a, CD1b, and CD1c, which present antigens to clonally diverse T cells. Group 2 contains CD1d, which mostly presents antigens to invariant natural killer T (iNKT) cells. Group 3 contains CD1e, which acts as a lipid chaperone for other CD1 isoforms rather than an antigen presenting molecule (Facciotti et al., 2011).

The CD1a isoform

The structure of CD1a

The CD1a proteins consist of a heavy chain with three extracellular domains (α_1, α_2, and α_3), a transmembrane domain, and a short cytoplasmic tail that is non-covalently associated with the β2-microglobulin light chain (Zeng et al., 1997). The α_1 and α_2 domains form the antigen-binding groove (Fig. 1) (Zajonc et al., 2003). The CD1a antigen-binding groove is narrow and deep and bears non-polar amino acids (Zajonc et al., 2003). These groove characteristics are particularly suited to binding lipids and are evolutionarily conserved (Gadola et al., 2002; Scharf et al., 2010; Zajonc et al., 2003; Zeng et al., 1997). The groove bears two pockets, A′ and F′. A′ is longer and narrower than F′ and is overlaid with a roof-like structure that separates it from the outer protein surface (Fig. 1) (Zajonc et al., 2003). F′ connects A′ to the outer surface and lies close to the T-cell receptor (TCR) recognition region (Zajonc et al., 2003). In more detail, its A′ pocket has a fixed terminus that restricts the length of the inserted alkyl chain (Zajonc

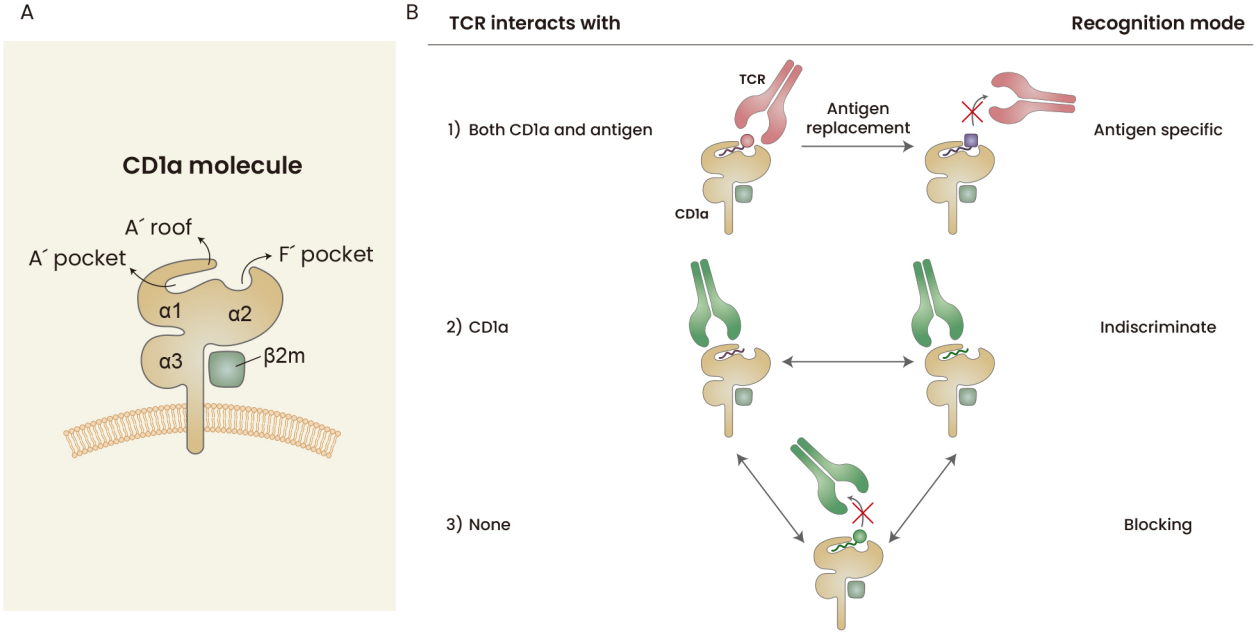

Fig. 1. Schematic representation of CD1a and modes by which T cell receptors interact with the CD1a-lipid complex. (A) The structural feature of CD1a. The heavy chain consists of three domains (α1, α2, α3) with a short cytoplasmic tail, and it is non-covalently associated with a light chain (β2m). The α1 and α2 domains form the lipid antigen-binding groove, which bears two pockets, A′ and F′. (B) TCRs recognize CD1a-lipid complexes by three modes: head-group recognition (upper), absence of interference (middle) and interference (bottom). 1) Some TCRs interact with a specific head-group of lipids protruding out of the CD1a and form a ternary lipid-CD1a-TCR complex. 2) Some headless lipids are completely buried within antigen binding groove and allow TCRs the opportunity to directly bind to the A roof of CD1a. In this case, TCRs do not need interact with antigens, but CD1a itself. 3) Bulky head-groups of some lipids can interfere TCR:CD1a interaction, thereby controlling the activation of CD1a-autoreactive T cells. β2m, β2-microglobulin.

et al., 2003). F′ also bears residues that can form hydrogen bonds with the peptide moiety of an antigen (Zajonc et al., 2005). These A′ and F′ features explain how CD1a bind amphipathic lipid antigens, namely, they bear an aliphatic moiety that is deeply buried in A′ and is sequestered from the surrounding aqueous solvent while the polar head-group of the antigen (e.g., carbohydrate, phosphate, peptidic, or other hydrophilic moieties) can protrude from F′ for TCR recognition (Zajonc et al., 2003; 2005).

CD1a assembly and intracellular trafficking

The antigen repertoires of the CD1 isoforms are further shaped by their disparate intracellular-trafficking routes, which exposes them to different antigen arrays. Thus, newly synthesized CD1 heavy chains in the endoplasmic reticulum lumen assemble with β2-microglobulin light chains and spacer ligands (Sugita et al., 1997). The CD1s then leave the Golgi and travel to the plasma membrane. The route the isoforms then take differs: CD1a goes directly to sorting and recycling endosomes and predominantly localizes at the cell surface (Barral et al., 2008; Sugita et al., 1999), and other CD1 isoforms enter late endosomal or lysosomal compartments (Briken et al., 2000; Sugita et al., 1999; 2000). This is because the cytoplasmic tails of other isoforms bear tyrosine-based motifs to which adaptor protein-2 or -3 binds (Briken et al., 2002; Sugita et al., 2002). However, CD1a lacks known endosomal sorting motifs and is internalized from the plasma membrane into early endosomes by an adaptor protein-independent pathway. The effect of these different intracellular trafficking mechanisms on the antigen repertoires of the CD1 isoforms is exhibited by the case of sulfatide: even though all group 1 CD1s can present this promiscuous glycolipid *in vitro* (Shamshiev et al., 2002), *in vivo* it is very largely presented by CD1a due to its co-localization in early endosomes (Cernadas et al., 2010). Notably, the endogenous ligand in the CD1a antigen-binding groove is easily replaced by exogenous lipids and those that do not require intracellular-antigen processing; this process can happen at the cell surface and may in fact stabilize/upregulate cell-surface CD1a expression (Manolova et al., 2006). This type of antigen loading is also observed with other CD1 isoforms but is more common with CD1a. These CD1a features suggest that its antigen repertoire may better reflect the extracellular lipid milieu than those of the other isoforms (Manolova et al., 2006).

CD1a tissue- and cell-specific expression

CD1a is further distinguished from the other CD1s by being constitutively and highly expressed on Langerhans cells and antigen presenting cell (APC) subsets in the skin (Wollenberg et al., 1996). It is also expressed by DCs in mucosal tissues, including the bronchus (Tazi et al., 1993), conjunctiva (Yoshida et al., 1997), cervix (Miller et al., 1992), and lungs (Baharom et al., 2016; Haniffa et al., 2012).

Antigens of CD1a

CD1a presents a diverse array of self and foreign lipids. Many of its self-lipids are small and very hydrophobic lipids such as wax ester, triacylglyceride, squalene (de Jong et al., 2014), and farnesol (Nicolai et al., 2020). While most CD1a self-antigens are lipid metabolites that bind to CD1a in endosomes, CD1a can also bind free fatty acid neoantigens that are, for example, generated from common cell membrane phosphodiacylglycerides by wasp and bee venom phospholipase A_2 (PLA_2) and then bind to CD1a in the extracellular space (Bourgeois et al., 2015). The CD1a-binding foreign antigens include the lipopeptide didehydroxymycobactin (DDM), which scavenges iron, thereby promoting *Mycobacterium tuberculosis* growth within macrophages (Moody et al., 2004). Thus, CD1a presents a broad array of lipid antigens; this makes it a highly versatile mediator of many different immune responses.

Modes by which T cells interact with CD1a

CD1a-restricted T cells interact with CD1a *via* three modes (Fig. 1). The first is called "head-group recognition", which resembles the highly specific peptide-epitope recognition by MHC-restricted T cells. Thus, the CD1a-restricted TCR specifically recognizes the protruding polar head-group of the lipid antigen and forms a ternary lipid-CD1a-TCR complex (Zajonc et al., 2005). An example of such an antigen is DDM: its alkyl chain is buried in A′ while its peptidic head-group moiety protrudes from F′ and is recognized by the TCR of DDM-specific T cells (Zajonc et al., 2005).

The second and third CD1a:T cell interaction modes are less antigen-specific, sometimes even antigen-independent (de Jong et al., 2014; Sieling et al., 2005). The second mode is called "absence of interference" (de Jong et al., 2014):some CD1a-restricted T cells recognize small highly hydrophobic permissive headless lipids (Birkinshaw et al., 2015; de Jong et al., 2014; Nicolai et al., 2020) that are completely buried inside CD1a and allow the TCR to bind to the roof over A′ (Birkinshaw et al., 2015). Thus, the TCR does not directly contact the antigen or require its specific positioning (de Jong et al., 2014). Mutation of the A′ roof generally blocks "absence of interference" recognition (Cotton et al., 2021). The third mode is mediated by certain non-permissive lipids whose polar head-groups block TCR:CD1a interaction, thereby inhibiting autoreactive T-cell activation (Birkinshaw et al., 2015; de Jong et al., 2014). It may be a regulatory mechanism that blocks autoimmune reactions in non-inflammatory conditions to the abundant lipid antigens being presented by CD1a-expressing APCs.

CD1a-RESTRICTED T CELLS

The αβ TCRs of CD1a-restricted T cells are probably as variable as those of conventional αβ T cells: de Jong et al. (2010) showed that while some CD1a-restricted T cell clones have the same variable or joining regions, most have different CDR3 sequences. This variability was also observed for T cells from the same donor (Cotton et al., 2021; de Lalla et al., 2011).

A cell-surface marker/cytokine phenotype that identifies all CD1a-restricted T cells is not yet available. However, several CD1a-restricted T-cell subset phenotypes have been reported. They include skin-homing T_H22 cells in the blood that express cutaneous lymphocyte antigen, CCR4, CCR6, and CCR10 and secrete interleukin (IL)-22 (de Jong et al., 2010). CD1a-re-

stricted T_H1, T_H2, and T_H17 subsets also participate in various diseases (Jarrett et al., 2016; Kim et al., 2016; Subramaniam et al., 2016). The different cytokine profiles of CD1a-restricted T cells suggest that they may function in multiple different ways in the immune system.

CD1a-restricted T cells are often detected by measuring their production of specific cytokines in the presence and absence of anti-CD1a blocking antibody. This method can overlook inactive CD1a-restricted T cells and T cells that produce non-targeted cytokines. This can be overcome by CD1a-tetramer staining. CD1d-tetramer staining has greatly facilitated the identification/characterization of CD1d-restricted T cells (Benlagha et al., 2000; Matsuda et al., 2000). Studies show that CD1a tetramers can detect CD1a-restricted T cells, including DDM-specific (Kasmar et al., 2013) and Jurkat.BK6 CD1a-restricted T cells (Birkinshaw et al., 2015). Unloaded CD1a-tetramers (i.e., endogenous lipid:CD1a complexes) also identify CD1a-autoreactive T cells in human skin (Cotton et al., 2021). Thus, the tetramer method will provide new insights into CD1a-restricted T cells, including their frequencies in different organs and their cytokine profiles, TCR patterns, and novel markers. This in turn may reveal multiple subsets with different functions and will yield a more fine-tuned classification system for these T cells.

CD1a-RESTRICTED T CELLS IN DISEASES

Skin diseases

CD1a is abundantly expressed in the skin and the blood contains large numbers of skin-homing CD1a-restricted T cells (de Jong et al., 2010). This suggests that CD1a-restricted T cells may participate in skin diseases. Indeed, there are several CD1a-mediated skin diseases, which can be grouped according to whether self-antigens or foreign antigens drive the pathological process.

Skin diseases mediated by self-antigens

ACD is an example of the type IV allergic reactions, which are characterized by delayed T cell-mediated immune responses. Most ACD contact-sensitizers are small and lipophilic and therefore easily penetrate skin barriers (Kaplan et al., 2012; Vocanson et al., 2009). When APCs are treated with contact-sensitizers such as 2,4-dinitrochlorobenzene (DNCB) or 1,4-benzoquinone, they activate CD1a-restricted T cells from human blood, which then produce various cytokines, including IL-2, IL-4, IL-5, IL-6, IL-9, IL-10, IL-22, IL-13, granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon γ (IFN-γ), and tumor necrosis factor α (TNF-α). However, it seems that the CD1a-bound antigen is endogenous lipid, not DNCB (Betts et al., 2017). The endogenous antigen(s) and how DNCB participates remain unclear.

Several CD1a-reactive T cell-mediated skin diseases are driven by neoantigens that are generated by host- or foreign organism-derived enzymes that degrade lipid. An example is PLA_2, which cleaves cell membrane phospholipids, thereby generating inflammatory mediators such as thromboxanes, prostaglandins, and leukotrienes (Vasquez et al., 2018). Along with these inflammatory effects, PLA_2 also promotes inflammation in psoriasis (Cheung et al., 2016), atopic dermatitis (Jarrett et al., 2016), and wasp and bee venom allergy (Bourgeois et al., 2015; Subramaniam et al., 2016) by indirectly triggering CD1a-restricted T cells. In psoriasis, atopic dermatitis, and wasp/bee allergy, the PLA_2 is respectively produced by mast cells (i.e., PLA2G4D), house-dust mite (HDM), or is a wasp/bee venom molecule (Bourgeois et al., 2015; Subramaniam et al., 2016). In all three cases, PLA_2 degrades cell-membrane phospholipids, thus generating CD1a-binding neoantigens that activate CD1a-restricted T cells. Since the neoantigen-recognizing CD1a-restricted T cells crossreact with neoantigens generated by different PLA_2 molecules, the PLA_2 molecules appear to act on similar substrates, thereby producing similar lipid neoantigens (Jarrett et al., 2016; Subramaniam et al., 2016). The neoantigens may be free fatty acids and lysophospholipids since PLA_2 generates them by cleaving the ester bond of membrane phosphodiacylglycerol and these products bind to CD1a (Birkinshaw et al., 2015; Bourgeois et al., 2015; Cheung et al., 2016).

How CD1a-restricted T cells participate in psoriasis, atopic dermatitis, and wasp/bee venom allergy has not been fully determined. With regard to psoriasis, this chronic autoimmune skin disease not only involves mast cells (Balato et al., 2012) but also T_H17 cytokines (IL-22 and IL-17A) (Kagami et al., 2010) and IFN-α (Nestle et al., 2005). Cheung et al. (2016) showed that psoriatic mast cells produce PLA2G4D-containing exosomes that are taken up by APCs; the PLA2G4D activity then generates neoantigens that stimulate human CD1a-restricted T cells in skin lesions to produce IFN-γ, IL-22, and IL-17A. This is supported by our study showing that the lipid self-antigens generated during psoriasis inflammation may be rare self-antigens in the normal environment, and that they may promote CD1a-restricted T_H17 responses, thereby exacerbating psoriasis symptoms. Notably, our experiments with a psoriasis-like mouse model and peripheral blood mononuclear cells from psoriasis patients showed that blocking CD1a decreased cytokine production and reduced inflammation symptoms (Kim et al., 2016).

With regard to atopic dermatitis, which is a chronic inflammatory skin condition with a complex pathogenesis, patients bear CD1a-restricted T cells in the skin and peripheral blood that exhibit elevated T_H1 and T_H2 cytokine production. This activity is further increased when these cells are challenged with HDM, which contains PLA_2. Interestingly, deficiency in filaggrin, a skin barrier protein, associates with atopic dermatitis: atopic dermatitis patients with filaggrin mutations exhibit more PLA_2 activity than healthy humans. Since filaggrin inhibits PLA_2, filaggrin deficiency may promote atopic dermatitis by elevating PLA_2 activity, thereby increasing the neoantigens that activate human T_H2 CD1a-restricted T cells (Jarrett et al., 2016). Interestingly, group 2 innate lymphoid cells (ILC2s) are enriched in atopic dermatitis skin lesions (Salimi et al., 2013) and may serve as a neoantigen-generating APC, thereby promoting the CD1a-restricted T cell responses in atopic dermatitis: when atopic dermatitis skin is challenged with HDM, the epithelial cells become damaged and rapidly secrete thymic stromal lymphopoietin, which induces $CD1a^+$ ILC2s to produce PLA2G4A. This generates CD1a neoantigens and activates human CD1a-restricted T cells that secrete IFN-γ and IL-22 (Hardman et al., 2017).

Wasp/bee venom allergy associates with cutaneous inflammation and in the worst cases with systemic allergic responses such as anaphylactic shock and death. Patients with wasp/bee venom allergy have higher frequencies of T_H2-biased CD1a-restricted T cells that express IL-13 and promote IgE production. Notably, when patients gained clinical tolerance to wasp/bee venom *via* subcutaneous immunotherapy, their peripheral blood CD1a-restricted T cells lost their T_H2 responses (Subramaniam et al., 2016).

Skin diseases mediated by foreign antigens

Foreign antigen-recognizing CD1a-restricted T cells also mediate several skin diseases. Studies with human CD1a-transgenic mice and human patients showed that pentadecylcatechol (C15:2) in urushiol, an oily compound in poison ivy/poison oak leaves, triggers CD1a-restricted T_H17 cells. Treatment with CD1a-blocking antibodies alleviated murine skin inflammation (Kim et al., 2016).

ACD can also be generated by exogenous antigens: human CD1a-restricted T cells can recognize, both *in vitro* and *ex vivo*, balsam of Peru, a common cosmetics ingredient, along with its components, benzyl benzoate and benzyl cinnamate and structurally related compounds to squalene, namely, farnesol, a known contact-sensitizer. These compounds are small and sequester completely within CD1a. They may displace the non-permissive endogenous ligands in CD1a and lay bare the CD1a surface for recognition by CD1-restricted T cells (Nicolai et al., 2020).

Thus, this overview of CD1a-related skin diseases suggests that novel therapeutic targets for treating skin diseases may include CD1a-restricted T cells, PLA_2, and CD1a molecules.

Non-skin diseases

Since CD1a is expressed in tissues other than skin, CD1a-restricted T cells may also play pathological roles in non-skin diseases, including asthma and allergy: thus, human lung DCs express CD1a (Baharom et al., 2016; Haniffa et al., 2012); atopic asthma patients have greater numbers of $CD1a^+$ cells in the airway (Bertorelli et al., 2000); and patients who are allergic to cypress pollens have CD1a-restricted responses to these antigens in their peripheral blood (Agea et al., 2005). Notably, the lipophilic air pollutant benzo[a]pyrene, which associates with cardiovascular, lung, and autoimmune diseases, has been shown to decrease CD1a surface expression,

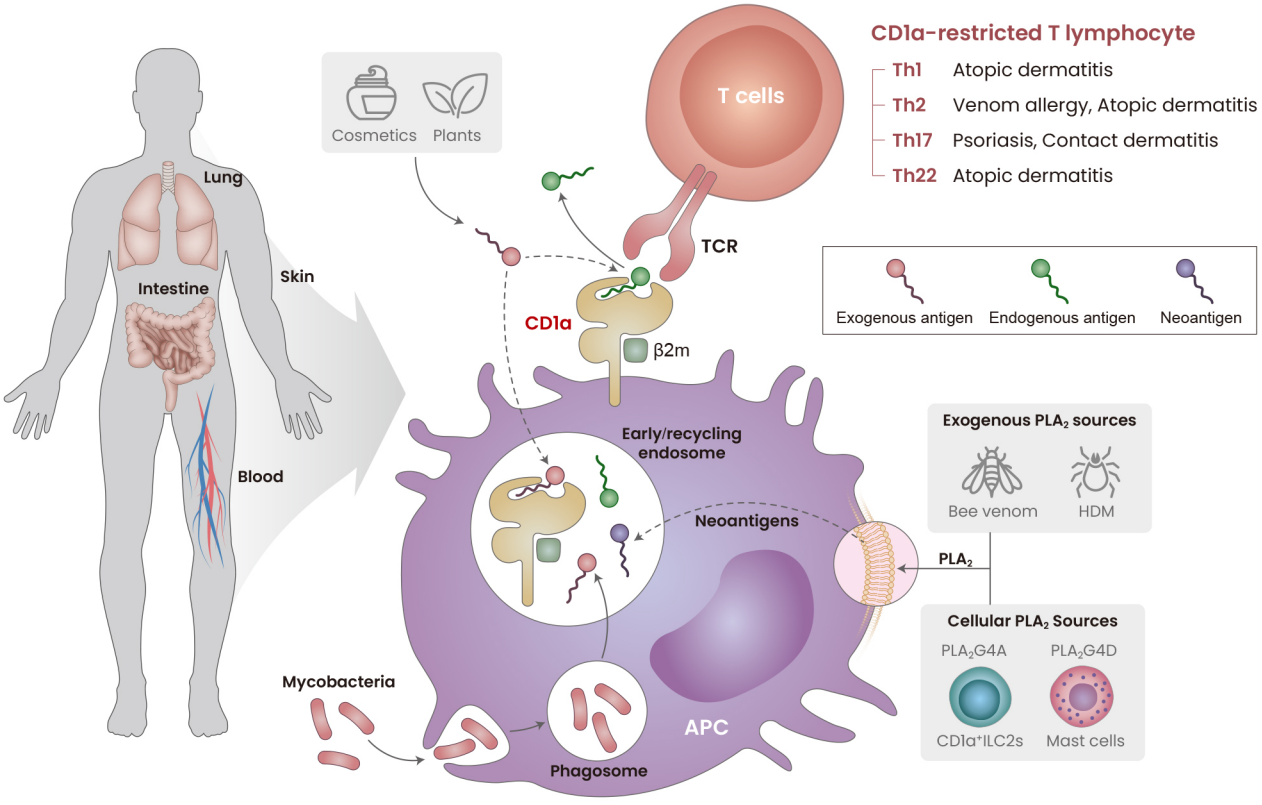

Fig. 2. Overview of antigen presentation by CD1a and roles of CD1a-reactive T cells in diseases. CD1a-expressing APCs are abundant, but not limited, in skin. Antigens of CD1a are derived from self or various foreign sources such as Mycobacteria, plants and cosmetics, and presented on CD1a in early/recycling endosomal compartments or at cell surface. Similar to the origins of antigens, host- or foreign-derived PLA_2 can generate neoantigens of CD1a under certain conditions. CD1a-reactive T cells activated by recognizing the complex of CD1a and antigen or CD1a itself produce various cytokines, thereby controlling immune responses occurred in inflammatory skin diseases such as contact dermatitis, psoriasis and atopic dermatitis.

thereby reducing CD1a-restricted T-cell activation in human (Sharma et al., 2017).

Tumor microenvironments may modulate CD1a expression, thereby shaping CD1a-restricted T cell anti-tumor activities. In gallbladder cancer, patients with marked $CD1a^+$ DC infiltration into the tumor survived longer and were less likely to develop distant metastasis than patients with low $CD1a^+$ DC infiltration (Kai et al., 2021). However, this prognostic relationship was not observed in early breast cancer patients (Schnellhardt et al., 2020) and studies on colorectal cancer patients showed that high $CD1a^+$ DC numbers in advancing tumor margins associated with shorter disease-free survival (Sandel et al., 2005; Suzuki et al., 2002). The clinical relevance of $CD1a^+$ DCs in tumors, the tumor-derived antigens that drive CD1a-restricted T cells, how tumor microenvironments regulate CD1a, and how CD1a-restricted T cells affect tumor growth remain to be clarified.

CONCLUSION

Here, we reviewed current knowledge about CD1a, CD1a-restricted T cells, and their pathological roles (Fig. 2). Through this review, we emphasized mechanisms of antigen-processing by CD1a, activation modes of CD1a-restricted T cells, and their roles in immune disorders such as contact dermatitis, atopic dermatitis, and psoriasis. We also pointed out the limitations of previous studies and questions unsolved, including the development, naïve-to-effector/memory dynamics, and subpopulations of CD1a-restricted T cells and their potential roles in non-skin diseases. Studies using human CD1 transgenic mice or other experimental animal models may help elucidate the CD1a and CD1a-reactive T cells functions in the immune system.

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CONFLICT OF INTEREST

The authors have no potential conflicts of interest to disclose.

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