HHS Public Access

Author manuscript

Mol Immunol. Author manuscript; available in PMC 2022 February 01.

Published in final edited form as:

Mol Immunol. 2021 February ; 130: 14–19. doi:10.1016/j.molimm.2020.12.006.

CD1A FUNCTION IN HUMAN SKIN DISEASE

Annemieke de Jong[1], **Graham Ogg**[2]

[1]Department of Dermatology, Columbia University Irving Medical Center, New York, NY, USA,

[2]Medical Research Council Human Immunology Unit, Radcliffe Department of Medicine, Oxford National Institute for Health Research Biomedical Research Centre, Medical Research Council Weatherall Institute of Molecular Medicine, University of Oxford, Oxford, UK

Abstract

The high expression of CD1a on Langerhans cells in normal human skin suggests a central role for this lipid antigen presenting molecule in skin homeostasis and immunity. Although the lipid antigen presenting function of CD1a has been known for years, the physiological and pathological functions of the CD1a system in human skin remain incompletely understood. This review provides an overview of this active area of investigation, and discusses recent insights into the functions of CD1a, CD1a-restricted T cells, and lipid antigens in inflammatory and allergic skin disease. We include recent publications and work presented at the biennial CD1-MR1 EMBO workshop held in 2019 in Oxford, regarding lipids that increase and those that decrease T cell responses to CD1a.

1. CD1A AND ITS EXPRESSION IN HUMAN SKIN

CD1a is a relatively non-polymorphic β2-microglobulin-associated membrane protein that is structurally related to MHC class I, yet the antigen binding cleft of CD1a is specifically equipped to accommodate lipids rather than peptides. The antigen binding cleft comprises of two pockets (A' and F') lined with hydrophobic amino acids that can accommodate the acyl chains of lipid ligands (Zajonc et al., 2003, Zajonc et al., 2005). Of the four cell-surface expressed CD1 isoforms in humans, CD1a is the only isoform that lacks an adaptor protein binding tyrosine-based cytoplasmic sorting motif in its short cytoplasmic tail, and therefore does not traffic to the late endosomes. Nevertheless, CD1a is internalized and traffics to the early recycling endosomes, and recycles back to the plasma membrane (Salamero et al., 2001, Barral et al., 2008). The capture and exchange of lipid antigens by CD1a occurs at neutral pH, and is thought to take place both at the cell surface and in early endosomes (Cernadas et al., 2010, Manolova et al., 2006). This differs from CD1b, CD1c, and CD1d, which traffic more extensively through the endosomal network, and have pH requirements and accessory mechanisms for antigen loading (reviewed in (Moody and Porcelli, 2003)). The ability of CD1a to more readily exchange lipids at the cell surface and early endosomes

(Manolova et al., 2006, Cernadas et al., 2010), suggests that the lipid repertoire presented by CD1a also reflects that of the extracellular milieu. The biological relevance of this in the context of a skin immunology is not fully understood.

CD1a was first described to be present on the surface of immature thymocytes (Reinherz et al., 1980), expression of which is lost upon T cell maturation. Subsequently, expression of CD1a was detected on the surface of Langerhans cells in the epidermis of the skin (Murphy et al., 1981), and has since commonly been used as a marker for Langerhans cells in combination with Langerin expression. The constitutively high expression of CD1a on Langerhans cell in normal skin suggests an important role for lipid antigen presentation in skin homeostasis. The localization of Langerhans cells at the barrier between skin immune system and skin microbiome makes these CD1a expressing cells ideally positioned to detect barrier breaches and changes in local extracellular milieu (Yoshida et al., 2014). Beyond Langerhans cells, CD1a is expressed at lower levels on a subset of dermal myeloid dendritic cells, and recent insights have shown that upon acute sterile skin inflammation, there is early infiltration of another CD1a+ dendritic cell subset, co-expressing BDCA-2 and CD123 (Chen et al., 2020). These markers are generally associated with plasmacytoid dendritic cells, but may become expressed by other cells during a wound healing response. Furthermore, in inflammatory skin diseases such as atopic dermatitis, and psoriasis, the frequency of CD1a-expressing dendritic cell subsets is increased, and migratory patterns of Langerhans cells are altered (Wollenberg et al., 1996, Langeveld-Wildschut et al., 2000, He et al., 2020). Specifically, it has been observed that psoriatic lesional Langerhans cells show reduced mobilization in response to TNFα and IL-1β, which was subsequently shown to be related to an IL-17A-induced component of the keratinocyte secretome (Cumberbatch et al., 2006, Eaton et al., 2018). Retained populations of CD1a-expressing antigen presenting cells may promote maintenance of cutaneous inflammation. Besides dendritic cells, CD1a can be expressed and upregulated on a subset of skin innate lymphoid cells (ILCs), in particular ILC2 cells by TSLP, released in the context of skin inflammation. This CD1a expression has been shown to be functionally capable of activating CD1a-restricted T cells (Hardman et al., 2017).

Overall, the baseline high expression of CD1a on skin resident Langerhans cells, as well as on dermal dendritic cells, supports the notion that CD1a-dependent T cell activation plays a normal physiological role in human skin. Also, the increase in CD1a expressing DC subsets in inflammation, and upregulation of CD1a on ILC2 in atopic dermatitis skin may underlie the increased activation of CD1a-reactive T cell populations in inflammatory skin disease.

2. CD1A-RESTRICTED T CELLS, LIPIDS ANTIGENS, AND MODES OF ANTIGEN RECOGNITION

2.1. CD1a-autoreactive T cells

The first described CD1a-restricted T cell clone (BK6) was a $CD4^{-}/CD8^{-}$ double negative T cell clone isolated from a patient with systemic lupus erythematosus, which responded to CD1a in the absence of exogenous lipid antigen (Porcelli et al., 1989). Later studies revealed that these so-called CD1a-autoreactive T cells are common in blood of healthy individuals,

suggesting they have a normal physiological function (de Jong et al., 2010, de Lalla et al., 2011). Their expression of skin-homing chemokine receptors CCR4, CCR10, and cutaneous lymphocyte antigen (CLA) were the first indication that these T cells commonly home to the skin. Indeed, CD1a-autoreactive responses were also detected among T cells isolated from non-diseased skin tissue (de Jong et al., 2010). Based on their chemokine receptor expression, CD4 expression, as well as their dominant production of IL-22 in the absence of IL-17A, many of these CD1a-autoreactive T cells appeared to represent Th22 cells, a human skin homing T cell subset (Eyerich et al., 2009, Trifari et al., 2009, Duhen et al., 2009).

Initial studies of CD1a-autoreactive T cells were performed using functional readouts such as IL-22 and IFN-γ release in response to CD1a transfectants. Recently, tetramer staining has been used to detect CD1a-restricted T cells more broadly, independent of their activation status or cytokine profiles. A study from the Moody laboratory, presented at the CD1/MR1 workshop, showed staining of human skin T cells using fluorescently-labeled CD1a tetramers (Cotton et al., 2020). “Unloaded” CD1a tetramers stained on average 1% of skin T cells, which were bona fide CD1a-reactive T cells, since they produced cytokines in a CD1a-dependent manner. The production of IL-22 by the tetramer^{+} T cells confirmed the previously suggested Th22 phenotype of CD1a-autoreactive T cells and directly demonstrated the presence of such cells in skin (de Jong et al., 2010). The tetramer staining did not require exogenous lipids, but instead relied on the endogenous lipids present in the CD1a molecules purified from human cells. This observation supports the notion that activation of CD1a-autoreactive T cells must be tightly regulated in normal uninflamed skin. Overall, the availability of “unloaded” CD1a tetramers as a tool for the identification and quantification of CD1a-reactive T cells will likely fuel new studies into their functions in normal skin immunity and in inflammatory skin disease.

2.2. Interactions between TCR and CD1a – The role of lipid antigens

Whereas the recognition of peptide antigens by MHC-restricted T cells is generally highly specific for the peptide motif, for CD1-restricted T cells the specificity of the TCR for CD1-lipid complexes has varied from highly specific (Moody et al., 1997), to cross-reactive or even seemingly independent of the lipid antigen (Wun et al., 2018, Mallevaey et al., 2011, Gapin et al., 2013). The latter appears to hold true for CD1a-autoreactive T cells, where lipid antigen recognition appears to play less of a role in T cell activation. Increasing evidence suggests that small hydrophobic lipids that nest inside the CD1a protein and do not protrude, allow the TCR to interact with the CD1a protein itself, rather than with the lipid. Indeed, the activation of CD1a-autoreactive T cells by sebaceous gland lipids that lacked hydrophilic headgroups (de Jong et al., 2014), prompted the ‘Absence of Interference model’. In this model, small lipids nesting inside the CD1a protein allow the TCR to contact the surface of CD1a, whereas certain lipids with large or charged headgroups prevent the interaction between TCR and CD1a and thereby prevent T cell activation (de Jong, 2015, Layre et al., 2014). Structural work is consistent with this model; the trimolecular structure of a CD1a-autoreactive TCR (BK6) bound with CD1a loaded with lysoPC showed that the TCR bound to the A’ roof of CD1a and did not interact with the lipid, which did not protrude from the CD1a protein (Birkinshaw et al., 2015). Also, Rossjohn’s group showed that mutation of the outer surface of the A’ roof of can more generally block T cell responses,

supporting the idea of TCR specificity for CD1a itself (Cotton et al., 2020). Sulfatide as well as long chain sphingomyelin were capable of disrupting the roof over the A' tunnel, leading to a loss of the CD1a-TCR binding plane, indirectly preventing TCR binding (Birkinshaw et al., 2015).

An important implication of this mode of T cell activation is that it is not dependent on the absence or presence of a particular lipid antigen, but rather on the ratio of permissive lipids (allowing TCR to interact with CD1a) and non-permissive or inhibitory lipids (preventing TCR from interacting with CD1a). This mode of activation may have consequences for CD1a-dependent T cell activation in inflammatory skin disease, where the composition of extracellular lipids in stratum corneum is often altered (van Smeden et al., 2014, van Smeden et al., 2013, Imokawa et al., 1991, Di Nardo et al., 1998), and lipid modifying enzymes, such as phospholipase A2 (PLA2) increase levels of known permissive lipids, including small, single chain lysolipids that resemble lysoPC (Bourgeois et al., 2015, Murakami et al., 2016).

2.3. Inhibitory lipids for CD1a-autoreactive T cells.

The abundance of permissive lipids, CD1a-expressing APCs, as well as CD1a-reactive T cells in normal skin suggests that, under non-inflammatory conditions, regulatory mechanisms are in place to prevent constant T cell activation. Prior studies have provided preliminary indications that certain non-permissive lipids could prevent CD1a-dependent T cell activation by preventing CD1a/TCR interactions (Birkinshaw et al., 2015, de Jong et al., 2014). Studies presented at the 2019 Oxford CD1-MR1 conference looked at this phenomenon in more detail, and showed the effects of individual lipids on the binding of CD1a tetramers to CD1a-reactive T cells isolated from human skin. "Unloaded" CD1a tetramers containing endogenous lipids were able to stain CD1a-reactive T cells, likely because the CD1a molecules contained abundance of permissive lipids. Elution of the lipid from CD1a monomers and analysis by HPLC-MS, detected multiple families of lipids including diacylglycerols, phosphatidylcholines, and sphingomyelins. Testing of the individual lipids loaded onto CD1a, and tetramerized for staining of the CD1a-reactive T cell lines, showed that whereas many self lipids permitted tetramer binding, certain molecular species of sphingomyelin strongly inhibited CD1a tetramer binding. This was observed for all the CD1a-reactive T cell lines tested, suggesting broad blocking/inhibitory effects when this sphingomyelin is bound to CD1a (Cotton et al., 2020). This finding confirms the ability of certain lipids with charged headgroups to disrupt the binding of the TCR to CD1a, and putatively block T cell activation, which raises many follow up questions with potentially broad clinical applications. The abundance of sphingomyelins in all cells further prompts the questions whether under normal homeostatic conditions these lipids render CD1a non-antigenic to T cells. In terms of clinical implications, such inhibitory lipids may provide a means to halt CD1a-dependent T cell activation in the skin in the context of inflammatory skin disease and/or allergic contact dermatitis. It is of relevance that CD1d reactivity was also found to be enhanced in the presence of acid sphingomyelinase suggesting that the pathway may be more widely applicable (Melum et al., 2019). Future clinical and translational work will reveal the clinical relevance of these molecular findings.

2.4. Bacterial lipid recognition by CD1a-restricted T cells

Although cumulative evidence points to a CD1a-reactive T cell population representing a significant population in human skin, it is currently unclear if these 'self-reactive' T cells are the main population of CD1a-restricted T cells in humans. Prior studies have identified CD1a-restricted T cells specific for the mycobacterial lipopeptide antigen dideoxymycobactin (DDM) from *Mycobacterium tuberculosis*, and DDM loaded dextramers identified the presence of low-frequency DDM-reactive CD1a-restricted T cells in the peripheral blood of *M. tuberculosis* exposed individuals (Kasmar et al., 2013). In another study, CD1a-restricted T cells responding to *M. leprae* lipids were isolated from lesional skin of an *M. leprae* patient (Hunger et al., 2004). These studies indicate that foreign antigen-specific CD1a-restricted T cell responses are also part of the T cell repertoire, but it is not yet known if the response is caused by antigen-exposure. Recognition of other, more common bacterial lipids by CD1a-restricted T cells has not been investigated, yet the abundance of CD1a molecules at the interface between skin microbiome and skin immune system suggests that lipids from resident commensal and pathogenic bacteria could be bound by CD1a and presented to T cells.

A preliminary study investigating this was presented at the EMBO CD1-MR1 workshop. The laboratory of Annemieke de Jong developed CD1a tetramers loaded with a common bacterial membrane phospholipid, and detected a population of CD1a-restricted T cells in skin and blood, that specifically bound the bacterial lipid antigen-loaded tetramer (Monnot et al., 2019). In the peripheral blood, these T cells were predominantly detected in the $CD4^+$ αβ T cell fraction, and were readily isolated and expanded in vitro. The T cells responded specifically to bacterial phospholipid antigen in a dose-dependent manner, both in a plate-bound CD1a assay as well as an antigen presenting cell-based assay. This newly identified subset of CD1a restricted T cells specifically bound the bacterial lipid loaded tetramers, but not the unloaded tetramers. By separately sorting CD1a-autoreactive and CD1a bacterial lipid reactive T cells and performing single cell RNAseq, preliminary results showed that these two CD1a-restricted $CD4^+$ T cell subsets have distinct transcriptional profiles. Whereas the bacterial lipid reactive T cells were overrepresented in a Th2-like cluster, the CD1a-autoreactive T cells more frequently clustered with regulatory T cells (Treg) (Monnot et al., 2019). This suggests the CD1a-autoreactive and bacterial lipid-reactive T cells represent different T cell subsets with likely distinct functions. Ongoing studies aim to understand the role of CD1a-dependent recognition of bacterial phospholipids in the T cell response to commensals and pathogens that colonize our skin in health and disease.

Another transcriptional study of CD1-restricted T cell subsets, including CD1a-restricted T cells, was presented at the CD1-MR1 meeting by Daniel Pellicci. His group identified CD1a-endo and CD1a-DDM tetramer binding T cells in peripheral blood of donors, and determined by single cell RNAseq that these T cells express diverse TCRs and that the gene expression profiles of this population differed from those of NKT cells, as well as from CD1b-restricted T cell populations (Nguyen-Robertson et al., 2019). The ex vivo analysis of gene expression profiles of CD1a-restricted T cell populations will help us better understand the phenotypes, diversity and functional properties of these T cells.

3. CD1A-RESTRICTED T CELLS IN INFLAMMATORY SKIN DISEASE

3.1. PLA2-dependent augmentation of CD1a-autoreactive T cell responses

PLA2 enzymes, both from exogenous and endogenous sources, are increased in some inflammatory skin diseases, and are a hallmark of chronic inflammation (Murakami et al., 2016, Chiba et al., 2004, Cheung et al., 2016, Mahil et al., 2017). PLA2 enzymes cleave phospholipids at the sn-2 position, yielding a lysophospholipid and a fatty acid, both of which have been shown to be permissive lipids for CD1a-autoreactive T cells (Bourgeois et al., 2015, Birkinshaw et al., 2015). The generation of these 'neolipid' antigens by PLA2 has been shown to play a role in the activation and expansion of CD1a-restricted T cells in skin and blood of patients with atopic dermatitis (Jarrett et al., 2016), psoriasis (Cheung et al., 2016), and wasp and bee venom allergy (Bourgeois et al., 2015). In these three patient populations, the source of PLA2 differed; PLA2 came from wasp or bee venom (Bourgeois et al., 2015), house dust mite (Jarrett et al., 2016), and an endogenous source such as cytoplasmic PLA2G4D present in mast cell derived exosomes (Cheung et al., 2016). Irrespective of the source, PLA2-dependent augmentation of CD1a-autoreactive T cell activation was observed in T cell lines, polyclonal T cell cultures, and ex vivo in T cell populations isolated from human skin or blood. This provides a link between inflammation and CD1a-restricted T cell activation.

In addition to promoting CD1a neolipid antigen generation (Bourgeois et al., 2015, Subramaniam et al., 2016), wasp venom phospholipase represents a dominant target for IgE in the setting of wasp venom-induced anaphylaxis. Challenge of human skin with bee venom led to the production of lysophosphatidylcholine in the skin, consistent with PLA2 activity *in vivo* (Bourgeois et al., 2015). An analogous mechanism was noted for PLA2 activity within house dust mite extracts (Jarrett et al., 2016), which are known to be a source of IgE reactivity in at least 70% of individuals with atopic disease including atopic dermatitis, and some subtypes of asthma and rhinitis. Individuals with moderate-to-severe atopic dermatitis have impaired skin barrier, which can associate with mutations in the gene encoding filaggrin, a key component of the stratum corneum barrier. Filaggrin was found to inhibit the HDM-derived PLA2 activity, suggesting a role of filaggrin beyond that of a pure structural function to an additional anti-inflammatory role (Jarrett et al., 2016).

It is also noteworthy that langerin is thought to support CD1a loading (Hunger et al., 2004) and polymorphisms within its corresponding gene *CD207* are strongly associated with atopic dermatitis (Paternoster et al., 2015, Hunger et al., 2004). CD1a-reactive T cells rapidly infiltrated the skin after house dust mite challenge and were capable of producing IFNγ and IL-13 in these settings. Type 2-inducing cytokines and lipid mediators were found to induce CD1a-expression by innate lymphoid cells (ILC); and *Staphylococcus aureus* induced expression of PLA2G4A by ILC leading to amplification of a CD1a-dependent T cell response (Hardman et al., 2017). It is of interest that many known allergens are lipid-binding proteins and it is postulated that these may aid the transport or loading of lipids into the CD1 pathways, which promote a subsequent inflammatory response and concurrent peptide-specific T cell and IgE reactivity, analogous to the known mechanisms of saposins (Zhou et al., 2004).

Endogenous PLA2 activity has also been implicated in the pathogenesis of psoriasis. The gene encoding PLA2G4D is an enriched transcript in lesional skin (Chiba et al., 2004, Mahil et al., 2017) and was recently shown to promote a CD1a-autoreactive T cell response which is elevated in the blood and tissue of patients with psoriasis (Cheung et al., 2016, Kim et al., 2016). Furthermore, in the imiquimod model of psoriasis in human CD1a transgenic mice, anti-CD1a antibody administration was associated with reduction in clinical score, implicating potential therapeutic relevance for the pathway (Kim et al., 2016). PLA2 enzymes associate with a diverse family of non-inflammatory and inflammatory mediators, and it remains to be fully investigated whether distinct substrates, products or conditions will promote a net generation of pro-inflammatory or homeostatic signals.

3.2. CD1a dependent T cell responses to contact allergens

Allergic contact dermatitis is a common delayed type hypersensitivity reaction, generally thought to be caused by T cells recognizing small chemicals. For many known skin contact allergens, the exact mechanism by which T cells react to the allergenic chemicals has remained unclear. Since most common skin allergens are non-peptidic in nature, they were thought to require binding to a large protein to be recognized, in a process referred to as haptenation. Although there is evidence that certain drugs, such as sulfamethoxazole, lidocaine, and penicillins, can initiate T cell mediated hypersensitivity through haptenation of peptides, MHC or TCR (reviewed in (Bharadwaj et al., 2012, Adam et al., 2011)), it remains unclear to which extent this mechanism accounts for the larger spectrum of contact allergens. Many known contact allergens lack reactive groups to covalently bind to proteins and form haptens, and therefore T cell reactivity to these compounds is likely mediated through other mechanisms. In recent years, CD1a has been implicated in the activation of T cells in response to contact allergens. In a human CD1a transgenic mouse model, the response to urushiols, the oily allergenic compounds in poison ivy, was shown to be at least partially mediated by CD1a (Kim et al., 2016). Both ear thickness as well as $CD4^+$ IL-17 and IL-22 producing T cells were increased after urushiol sensitization and challenge in CD1a transgenic as compared to wild type mice. In poison ivy sensitized individuals, increased CD1a-restricted responses to urushiol were observed (Kim et al., 2016). Another study provided evidence for the augmentation of CD1a and CD1d-autoreactive responses by several small contact allergens (Betts et al., 2017). In this study, the activation of CD1-restricted T cell lines appeared to be dependent on endogenous lipids, yet the mechanism by which the response was augmented remained incompletely understood.

A more recent study investigated the role of CD1a in allergic T cell responses to chemical compounds found in cosmetics and other personal care skin products, including creams and fragrances (Nicolai et al., 2020). Allergic contact dermatitis to personal care products is highly prevalent, but in most cases the mechanism by which these small molecules are seen by T cells has remained unclear. In this study, balsam of Peru, a tree oil widely used in cosmetics and toothpaste, was found to activate CD1a-autoreactive T cells in a dose dependent manner (Nicolai et al., 2020). Within balsam of Peru, benzyl benzoate and benzyl cinnamate appeared to be the compounds stimulating the T cell response. A broad screening of compounds with similar ring structures and/or double bonds, including other known contact allergens, identified a variety of structures capable of eliciting a CD1a-dependent

T cell response. These compounds included farnesol, a contact allergen commonly found in fragrances. X-ray crystallography of the crystal structure of the CD1a-farnesol binary complex showed that farnesol was positioned centrally, deep inside the CD1a antigen binding cleft. This positioning inside the CD1a cleft clearly indicated that the farnesol antigen was inaccessible to the T cell receptor. The structural data further indicated that the binding of farnesol did not involve haptenation. HPLC-MS analysis of eluents from untreated and farnesol treated CD1a protein, indicated that farnesol displaced endogenous lipids from the CD1a protein. This suggested a mechanism by which the contact allergens activated CD1a-autoreactive T cells through the displacement of endogenous non-permissive lipids from the CD1a binding cleft, making the CD1a surface accessible to the TCR. This mechanism fits with the Absence of Interference model, and further broadens the observation of lipid-independent interactions between TCRs and CD1a. Overall, this recent study (Nicolai et al., 2020) provided a missing molecular link between common allergenic chemical compounds found in fragrances and personal care products and a mechanism by which they can directly initiate a T cell response. Further patient investigations will determine whether this mechanism commonly underlies the process of allergic contact dermatitis.

Acknowledgements

A.de Jong's work is currently supported by National Institute of Health / National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS R01 AR074037, K01 AR068475). Support has been received from UK Medical Research Council, NIHR Clinical Research Network, British Association of Dermatologists, British Skin Foundation, Misses Barrie Charitable Trust, Wellcome Trust, NIHR Oxford Biomedical Research Centre (BRC). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, the Department of Health or the NIH. Relevant competing interests: G. Ogg has served on advisory boards or has received research grants with Eli Lilly, Pfizer, Novartis, Janssen, Sanofi/Genzyme and UCB Pharma. We would like to thank Gwennaëlle Monnot for critical reading of the manuscript.

References

Adam J, Pichler WJ & Yerly D 2011. Delayed Drug Hypersensitivity: Models Of T-Cell Stimulation. Br J Clin Pharmacol, 71, 701–7. [PubMed: 21480949]

Barral DC, Cavallari M, Mccormick PJ, Garg S, Magee AI, Bonifacino JS, De Libero G & Brenner MB 2008. Cd1a And Mhc Class I Follow A Similar Endocytic Recycling Pathway. Traffic, 9, 1446–57. [PubMed: 18564371]

Betts RJ, Perkovic A, Mahapatra S, Del Bufalo A, Camara K, Howell AR, Martinozzi Teissier S, De Libero G & Mori L 2017. Contact Sensitizers Trigger Human Cd1-Autoreactive T-Cell Responses. Eur J Immunol, 47, 1171–1180. [PubMed: 28440548]

Bharadwaj M, Illing P, Theodossis A, Purcell AW, Rossjohn J & Mccluskey J 2012. Drug Hypersensitivity And Human Leukocyte Antigens Of The Major Histocompatibility Complex. Annu Rev Pharmacol Toxicol, 52, 401–31. [PubMed: 22017685]

Birkinshaw RW, Pellicci DG, Cheng TY, Keller AN, Sandoval-Romero M, Gras S, De Jong A, Uldrich AP, Moody DB, Godfrey DI & Rossjohn J 2015. Alphabeta T Cell Antigen Receptor Recognition Of Cd1a Presenting Self Lipid Ligands. Nat Immunol, 16, 258–66. [PubMed: 25642819]

Bourgeois EA, Subramaniam S, Cheng TY, De Jong A, Layre E, Ly D, Salimi M, Legaspi A, Modlin RL, Salio M, Cerundolo V, Moody DB & Ogg G 2015. Bee Venom Processes Human Skin Lipids For Presentation By Cd1a. J Exp Med, 212, 149–63. [PubMed: 25584012]

Cernadas M, Cavallari M, Watts G, Mori L, De Libero G & Brenner MB 2010. Early Recycling Compartment Trafficking Of Cd1a Is Essential For Its Intersection And Presentation Of Lipid Antigens. J Immunol, 184, 1235–41. [PubMed: 20026739]

Chen YL, Gomes T, Hardman CS, Vieira Braga FA, Gutowska-Owsiak D, Salimi M, Gray N, Duncan DA, Reynolds G, Johnson D, Salio M, Cerundolo V, Barlow JL, Mckenzie ANJ, Teichmann SA, Haniffa M & Ogg G 2020. Re-Evaluation Of Human Bdca-2+ Dc During Acute Sterile Skin Inflammation. J Exp Med, 217.

Cheung KL, Jarrett R, Subramaniam S, Salimi M, Gutowska-Owsiak D, Chen YL, Hardman C, Xue L, Cerundolo V & Ogg G 2016. Psoriatic T Cells Recognize Neolipid Antigens Generated By Mast Cell Phospholipase Delivered By Exosomes And Presented By Cd1a. J Exp Med, 213, 2399–2412. [PubMed: 27670592]

Chiba H, Michibata H, Wakimoto K, Seishima M, Kawasaki S, Okubo K, Mitsui H, Torii H & Imai Y 2004. Cloning Of A Gene For A Novel Epithelium-Specific Cytosolic Phospholipase A2, Cpla2delta, Induced In Psoriatic Skin. J Biol Chem, 279, 12890–7. [PubMed: 14709560]

Cotton RN, Cheng TY, Wegrecki M, Le Nours J, Orgill DP, Pomahac B, Talbot SG, Willis RA, Altman JD, De Jong A, Ogg G, Van Rhijn I, Rossjohn J, Clark RA & Moody DB 2020. Human Skin Is Colonized By T Cells That Recognize Cd1a Independently Of Lipid Journal Of Clinical Investigation, In Press.

Cumberbatch M, Singh M, Dearman RJ, Young HS, Kimber I & Griffiths CE 2006. Impaired Langerhans Cell Migration In Psoriasis. J Exp Med, 203, 953–60. [PubMed: 16567387]

De Jong A 2015. Activation Of Human T Cells By Cd1 And Self-Lipids. Immunol Rev, 267, 16–29. [PubMed: 26284469]

De Jong A, Cheng TY, Huang S, Gras S, Birkinshaw RW, Kasmar AG, Van Rhijn I, Pena-Cruz V, Ruan DT, Altman JD, Rossjohn J & Moody DB 2014. Cd1a-Autoreactive T Cells Recognize Natural Skin Oils That Function As Headless Antigens. Nat Immunol, 15, 177–85. [PubMed: 24362891]

De Jong A, Pena-Cruz V, Cheng TY, Clark RA, Van Rhijn I & Moody DB 2010. Cd1a-Autoreactive T Cells Are A Normal Component Of The Human Alphabeta T Cell Repertoire. Nat Immunol, 11, 1102–9. [PubMed: 21037579]

De Lalla C, Lepore M, Piccolo FM, Rinaldi A, Scelfo A, Garavaglia C, Mori L, De Libero G, Dellabona P & Casorati G 2011. High-Frequency And Adaptive-Like Dynamics Of Human Cd1 Self-Reactive T Cells. Eur J Immunol, 41, 602–10. [PubMed: 21246542]

Di Nardo A, Wertz P, Giannetti A & Seidenari S 1998. Ceramide And Cholesterol Composition Of The Skin Of Patients With Atopic Dermatitis. Acta Derm Venereol, 78, 27–30. [PubMed: 9498022]

Duhen T, Geiger R, Jarrossay D, Lanzavecchia A & Sallusto F 2009. Production Of Interleukin 22 But Not Interleukin 17 By A Subset Of Human Skin-Homing Memory T Cells. Nat Immunol, 10, 857–63. [PubMed: 19578369]

Eaton LH, Mellody KT, Pilkington SM, Dearman RJ, Kimber I & Griffiths CEM 2018. Impaired Langerhans Cell Migration In Psoriasis Is Due To An Altered Keratinocyte Phenotype Induced By Interleukin-17. Br J Dermatol, 178, 1364–1372. [PubMed: 29194565]

Eyerich S, Eyerich K, Pennino D, Carbone T, Nasorri F, Pallotta S, Cianfarani F, Odorisio T, Traidl-Hoffmann C, Behrendt H, Durham SR, Schmidt-Weber CB & Cavani A 2009. Th22 Cells Represent A Distinct Human T Cell Subset Involved In Epidermal Immunity And Remodeling. J Clin Invest, 119, 3573–85. [PubMed: 19920355]

Gapin L, Godfrey DI & Rossjohn J 2013. Natural Killer T Cell Obsession With Self-Antigens. Curr Opin Immunol, 25, 168–73. [PubMed: 23384972]

Hardman CS, Chen YL, Salimi M, Jarrett R, Johnson D, Jarvinen VJ, Owens RJ, Repapi E, Cousins DJ, Barlow JL, Mckenzie ANJ & Ogg G 2017. Cd1a Presentation Of Endogenous Antigens By Group 2 Innate Lymphoid Cells. Sci Immunol, 2.

He H, Bissonnette R, Wu J, Diaz A, Saint-Cyr Proulx E, Maari C, Jack C, Louis M, Estrada Y, Krueger JG, Zhang N, Pavel AB & Guttman-Yassky E 2020. Tape Strips Detect Distinct Immune And Barrier Profiles In Atopic Dermatitis And Psoriasis. J Allergy Clin Immunol.

Hunger RE, Sieling PA, Ochoa MT, Sugaya M, Burdick AE, Rea TH, Brennan PJ, Belisle JT, Blauvelt A, Porcelli SA & Modlin RL 2004. Langerhans Cells Utilize Cd1a And Langerin To Efficiently Present Nonpeptide Antigens To T Cells. J Clin Invest, 113, 701–8. [PubMed: 14991068]

Imokawa G, Abe A, Jin K, Higaki Y, Kawashima M & Hidano A 1991. Decreased Level Of Ceramides In Stratum Corneum Of Atopic Dermatitis: An Etiologic Factor In Atopic Dry Skin? J Invest Dermatol, 96, 523–6. [PubMed: 2007790]

Jarrett R, Salio M, Lloyd-Lavery A, Subramaniam S, Bourgeois E, Archer C, Cheung KL, Hardman C, Chandler D, Salimi M, Gutowska-Owsiak D, De La Serna JB, Fallon PG, Jolin H, Mckenzie A, Dziembowski A, Podobas EI, Bal W, Johnson D, Moody DB, Cerundolo V & Ogg G 2016. Filaggrin Inhibits Generation Of Cd1a Neolipid Antigens By House Dust Mite-Derived Phospholipase. Sci Transl Med, 8, 325ra18.

Kasmar AG, Van Rhijn I, Magalhaes KG, Young DC, Cheng TY, Turner MT, Schiefner A, Kalathur RC, Wilson IA, Bhati M, Gras S, Birkinshaw RW, Tan LL, Rossjohn J, Shires J, Jakobsen S, Altman JD & Moody DB 2013. Cutting Edge: Cd1a Tetramers And Dextramers Identify Human Lipopeptide-Specific T Cells Ex Vivo. J Immunol, 191, 4499–503. [PubMed: 24089190]

Kim JH, Hu Y, Yongqing T, Kim J, Hughes VA, Le Nours J, Marquez EA, Purcell AW, Wan Q, Sugita M, Rossjohn J & Winau F 2016. Cd1a On Langerhans Cells Controls Inflammatory Skin Disease. Nat Immunol, 17, 1159–66. [PubMed: 27548435]

Langeveld-Wildschut EG, Bruijnzeel PL, Mudde GC, Versluis C, Van Ieperen-Van Dijk AG, Bihari IC, Knol EF, Thepen T, Bruijnzeel-Koomen CA & Van Reijsen FC 2000. Clinical And Immunologic Variables In Skin Of Patients With Atopic Eczema And Either Positive Or Negative Atopy Patch Test Reactions. J Allergy Clin Immunol, 105, 1008–16. [PubMed: 10808184]

Layre E, De Jong A & Moody DB 2014. Human T Cells Use Cd1 And Mr1 To Recognize Lipids And Small Molecules. Curr Opin Chem Biol, 23, 31–8. [PubMed: 25271021]

Mahil SK, Catapano M, Di Meglio P, Dand N, Ahlfors H, Carr IM, Smith CH, Trembath RC, Peakman M, Wright J, Ciccarelli FD, Barker JN & Capon F 2017. An Analysis Of Il-36 Signature Genes And Individuals With Il1rl2 Knockout Mutations Validates Il-36 As A Psoriasis Therapeutic Target. Sci Transl Med, 9.

Mallevaey T, Clarke AJ, Scott-Browne JP, Young MH, Roisman LC, Pellicci DG, Patel O, Vivian JP, Matsuda JL, Mccluskey J, Godfrey DI, Marrack P, Rossjohn J & Gapin L 2011. A Molecular Basis For Nkt Cell Recognition Of Cd1d-Self-Antigen. Immunity, 34, 315–26. [PubMed: 21376640]

Manolova V, Kistowska M, Paoletti S, Baltariu GM, Bausinger H, Hanau D, Mori L & De Libero G 2006. Functional Cd1a Is Stabilized By Exogenous Lipids. Eur J Immunol, 36, 1083–92. [PubMed: 16598820]

Melum E, Jiang X, Baker KD, Macedo MF, Fritsch J, Dowds CM, Wang J, Pharo A, Kaser A, Tan C, Pereira CS, Kelly SL, Duan J, Karlsen TH, Exley MA, Schutze S, Zajonc DM, Merrill AH, Schuchman EH, Zeissig S & Blumberg RS 2019. Control Of Cd1d-Restricted Antigen Presentation And Inflammation By Sphingomyelin. Nat Immunol, 20, 1644–1655. [PubMed: 31636468]

Monnot GC, Wegrecki M, Sallee B, Bordone L, Rohde C, Rossjohn J & De Jong A 2019. Recognition Of Bacterial Membrane Phosphatidylglycerols By Human Cd1a-Restricted T Cells. Abstract, Embo Cd1/Mr1 Workshop 2019.

Moody DB & Porcelli SA 2003. Intracellular Pathways Of Cd1 Antigen Presentation. Nat Rev Immunol, 3, 11–22. [PubMed: 12511872]

Moody DB, Reinhold BB, Guy MR, Beckman EM, Frederique DE, Furlong ST, Ye S, Reinhold VN, Sieling PA, Modlin RL, Besra GS & Porcelli SA 1997. Structural Requirements For Glycolipid Antigen Recognition By Cd1b-Restricted T Cells. Science, 278, 283–6. [PubMed: 9323206]

Murakami M, Yamamoto K, Miki Y, Murase R, Sato H & Taketomi Y 2016. The Roles Of The Secreted Phospholipase A2 Gene Family In Immunology. Adv Immunol, 132, 91–134. [PubMed: 27769509]

Murphy GF, Bhan AK, Sato S, Mihm MC Jr. & Harrist TJ 1981. A New Immunologic Marker For Human Langerhans Cells. N Engl J Med, 304, 791–2.

Nguyen-Robertson C, Souter MNT, Eltahla AA, Reddiex SJJ, Cheng JMH, Rossjohn J, Cheng TY, Van Rhijn I, Williams SJ, Uldrich AP, Luciani F, Moody DB, Godfrey DI & Pellicci D 2019. Transcriptomic Analysis Of Group 1 Cd1-Restricted T Cells. Abstract, Embo Cd1/Mr1 Workshop 2019.

Nicolai S, Wegrecki M, Cheng TY, Bourgeois EA, Cotton RN, Mayfield JA, Monnot GC, Le Nours J, Van Rhijn I, Rossjohn J, Moody DB & De Jong A 2020. Human T Cell Response To Cd1a And Contact Dermatitis Allergens In Botanical Extracts And Commercial Skin Care Products. Sci Immunol, 5.

Paternoster L, Standl M, Waage J, Baurecht H, Hotze M, Strachan DP, Curtin JA, Bonnelykke K, Tian C, Takahashi A, Esparza-Gordillo J, Alves AC, Thyssen JP, Den Dekker HT, Ferreira MA, Altmaier E, Sleiman PM, Xiao FL, Gonzalez JR, Marenholz I, Kalb B, Yanes MP, Xu CJ, Carstensen L, Groen-Blokhuis MM, Venturini C, Pennell CE, Barton SJ, Levin AM, Curjuric I, Bustamante M, Kreiner-Moller E, Lockett GA, Bacelis J, Bunyavanich S, Myers RA, Matanovic A, Kumar A, Tung JY, Hirota T, Kubo M, Mcardle WL, Henderson AJ, Kemp JP, Zheng J, Smith GD, Ruschendorf F, Bauerfeind A, Lee-Kirsch MA, Arnold A, Homuth G, Schmidt CO, Mangold E, Cichon S, Keil T, Rodriguez E, Peters A, Franke A, Lieb W, Novak N, Folster-Holst R, Horikoshi M, Pekkanen J, Sebert S, Husemoen LL, Grarup N, De Jongste JC, Rivadeneira F, Hofman A, Jaddoe VW, Pasmans SG, Elbert NJ, Uitterlinden AG, Marks GB, Thompson PJ, Matheson MC, Robertson CF, Australian Asthma Genetics C., Ried JS, Li J, Zuo XB, Zheng XD, Yin XY, Sun LD, Mcaleer MA, O'regan GM, Fahy CM, Campbell LE, Macek M, Kurek M, Hu D, Eng C, Postma DS, Feenstra B, Geller F, Hottenga JJ, Middeldorp CM, Hysi P, Bataille V, Spector T, et al. 2015. Multi-Ancestry Genome-Wide Association Study Of 21,000 Cases And 95,000 Controls Identifies New Risk Loci For Atopic Dermatitis. Nat Genet, 47, 1449–1456. [PubMed: 26482879]

Porcelli S, Brenner MB, Greenstein JL, Balk SP, Terhorst C & Bleicher PA 1989. Recognition Of Cluster Of Differentiation 1 Antigens By Human Cd4-Cd8-Cytolytic T Lymphocytes. Nature, 341, 447–50. [PubMed: 2477705]

Reinherz EL, Kung PC, Goldstein G, Levey RH & Schlossman SF 1980. Discrete Stages Of Human Intrathymic Differentiation: Analysis Of Normal Thymocytes And Leukemic Lymphoblasts Of T-Cell Lineage. Proc Natl Acad Sci U S A, 77, 1588–92. [PubMed: 6966400]

Salamero J, Bausinger H, Mommaas AM, Lipsker D, Proamer F, Cazenave JP, Goud B, De La Salle H & Hanau D 2001. Cd1a Molecules Traffic Through The Early Recycling Endosomal Pathway In Human Langerhans Cells. J Invest Dermatol, 116, 401–8. [PubMed: 11231314]

Subramaniam S, Aslam A, Misbah SA, Salio M, Cerundolo V, Moody DB & Ogg G 2016. Elevated And Cross-Responsive Cd1a-Reactive T Cells In Bee And Wasp Venom Allergic Individuals. Eur J Immunol, 46, 242–52. [PubMed: 26518614]

Trifari S, Kaplan CD, Tran EH, Crellin NK & Spits H 2009. Identification Of A Human Helper T Cell Population That Has Abundant Production Of Interleukin 22 And Is Distinct From T(H)-17, T(H)1 And T(H)2 Cells. Nat Immunol, 10, 864–71. [PubMed: 19578368]

Van Smeden J, Janssens M, Kaye EC, Caspers PJ, Lavrijsen AP, Vreeken RJ & Bouwstra JA 2014. The Importance Of Free Fatty Acid Chain Length For The Skin Barrier Function In Atopic Eczema Patients. Exp Dermatol, 23, 45–52. [PubMed: 24299153]

Van Smeden J, Janssens M, Lavrijsen AP, Kezic S, Vreeken RJ & Bouwstra JA 2013. Skin Barrier Dysfunction In Non-Lesional Atopic Eczema: The Role Of Stratum Corneum Lipids. Eur J Dermatol.

Wollenberg A, Kraft S, Hanau D & Bieber T 1996. Immunomorphological And Ultrastructural Characterization Of Langerhans Cells And A Novel, Inflammatory Dendritic Epidermal Cell (Idec) Population In Lesional Skin Of Atopic Eczema. J Invest Dermatol, 106, 446–53. [PubMed: 8648175]

Wun KS, Reijneveld JF, Cheng TY, Ladell K, Uldrich AP, Le Nours J, Miners KL, Mclaren JE, Grant EJ, Haigh OL, Watkins TS, Suliman S, Iwany S, Jimenez J, Calderon R, Tamara KL, Leon SR, Murray MB, Mayfield JA, Altman JD, Purcell AW, Miles JJ, Godfrey DI, Gras S, Price DA, Van Rhijn I, Moody DB & Rossjohn J 2018. T Cell Autoreactivity Directed Toward Cd1c Itself Rather Than Toward Carried Self Lipids. Nat Immunol, 19, 397–406. [PubMed: 29531339]

Yoshida K, Kubo A, Fujita H, Yokouchi M, Ishii K, Kawasaki H, Nomura T, Shimizu H, Kouyama K, Ebihara T, Nagao K & Amagai M 2014. Distinct Behavior Of Human Langerhans Cells And Inflammatory Dendritic Epidermal Cells At Tight Junctions In Patients With Atopic Dermatitis. J Allergy Clin Immunol, 134, 856–64. [PubMed: 25282566]

Zajonc DM, Crispin MD, Bowden TA, Young DC, Cheng TY, Hu J, Costello CE, Rudd PM, Dwek RA, Miller MJ, Brenner MB, Moody DB & Wilson IA 2005. Molecular Mechanism Of Lipopeptide Presentation By Cd1a. Immunity, 22, 209–19. [PubMed: 15723809]

Zajonc DM, Elsliger MA, Teyton L & Wilson IA 2003. Crystal Structure Of Cd1a In Complex With A Sulfatide Self Antigen At A Resolution Of 2.15 A. Nat Immunol, 4, 808–15. [PubMed: 12833155]

Zhou D, Cantu C 3rd, Sagiv Y, Schrantz N, Kulkarni AB, Qi X, Mahuran DJ, Morales CR, Grabowski GA, Benlagha K, Savage P, Bendelac A & Teyton L 2004. Editing Of Cd1d-Bound Lipid Antigens By Endosomal Lipid Transfer Proteins. Science, 303, 523–7. [PubMed: 14684827]

Highlights

- Normal human skin contains CD1a-expressing antigen presenting cells, in particular Langerhans cells, as well as CD1a-restricted T cells
- Expression of CD1a and retention of CD1a expressing antigen presenting cells are increased in forms of skin inflammation, which may underlie the observed increase in CD1a-dependent T cell responses
- A proportion of CD1a-autoreactive T cells interacts primarily with the CD1a protein itself rather than with the lipid bound
- The binding of CD1a-autoreactive T cell receptors to CD1a can be prevented by certain classes of lipids, which may function as inhibitors of CD1a-dependent T cell responses
- CD1a tetramers containing endogenous lipids and those loaded with specific lipid antigens can be used to distinguish different subsets of CD1a-restricted T cells

Concluding remarks

In summary, in recent years there has been significant progress in understanding the extent and nature of CD1a reactivity and the potential implications for disease. The abundance of CD1a-restricted T cells in skin and their proposed role in inflammatory skin disease underscores the need for investigating the mechanisms that regulate their activation. Important areas of translational research include the further identification of classes of lipids that block TCR-CD1a interactions, as well as increased understanding of the link between PLA2 activity, permissive lipids and CD1a dependent T cell activation. Last, the identification of CD1a-restricted T cells that respond to common bacterial phospholipids, using CD1a tetramers, enables future studies into the connection between skin microbiome and activation of these lipid-specific T cells. Overall, understanding the interplay between lipids, CD1a molecules and T cells in human skin is an active area of research that will provide important insights for patients, with relevance to therapeutic intervention.

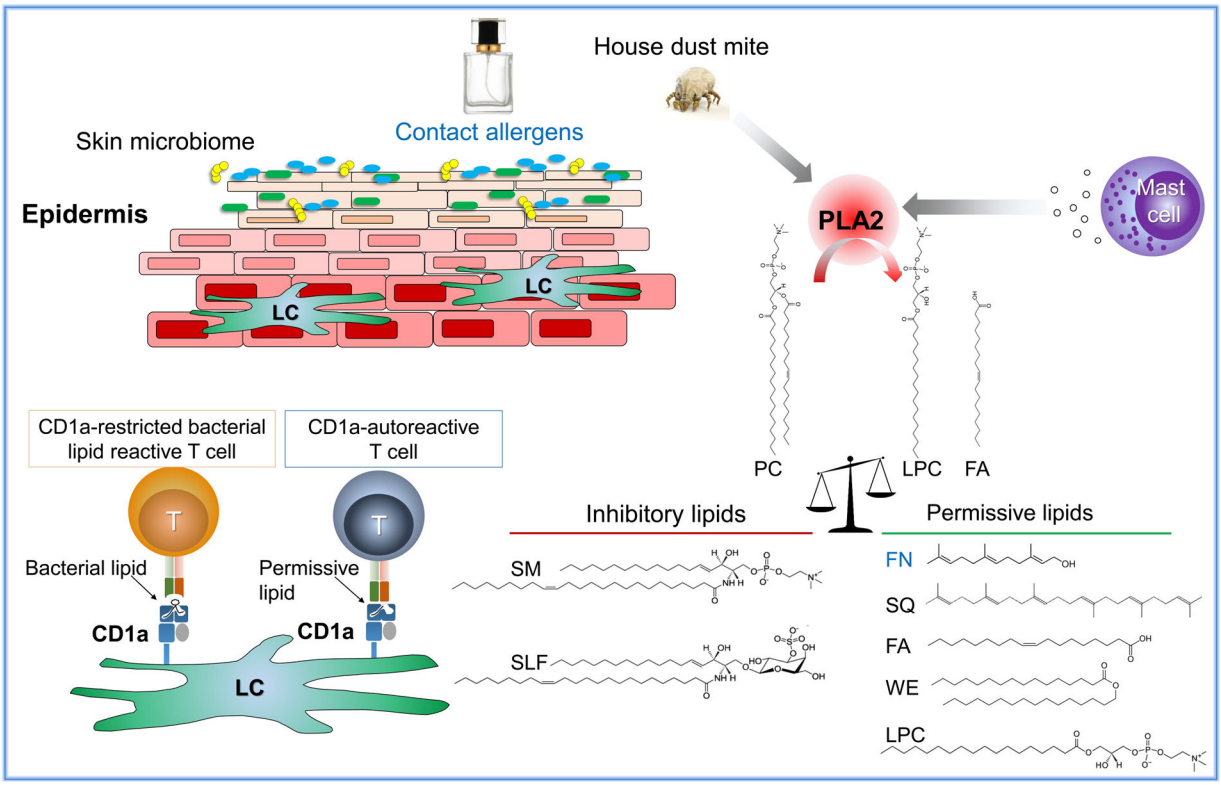

Figure 1. CD1a and lipid recognition in human skin.

Langerhans cells (LC) are in close proximity to the skin microbiome. A subset of human T cells recognizes a bacterial phospholipid in the context of CD1a. Another subset of skin T cells is CD1a-autoreactive and primarily interacts with CD1a, rather than the lipid bound. Permissive lipids allow the interaction between autoreactive TCR and CD1a, whereas inhibitor lipids prevent this interaction. PLA2 from exogenous or endogenous sources, such as house dust mite, mast cells, respectively, cleaves membrane phospholipids, yielding permissive lipids and augmenting CD1a-autoreactive T cell responses. Certain contact allergens such as farnesol have been shown to displace resident lipids, enabling TCR-CD1a interactions (Nicolai et al., 2020).

LC Langerhans cell, PLA2 Phospholipase A2, SM Sphingomyelin, SLF Sulfatide, FN Farnesol (contact allergen), WE Wax ester, FA Fatty acid, LPC Lysophosphatidylcholine, SQ Squalene.