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A Comparative Review of the C-type lectin receptor Langerin (CD207) in Mice and Humans: Implications for Future Therapeutic Studies

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Zusammenfassung

Im Fokus der fortgeschrittenen Immuntherapie wurden zielgerichtete Zellansätze, bei denen Antigene auf spezialisierte dendritische Zellen (Antigen-präsentierende Zellen) gelenkt werden, eingehend untersucht. Die Ergebnisse deuten auf eine hohe Wirksamkeit hin, zusätzlich zu dem Vorteil einer geringeren Nutzlast aufgrund geringerer “Off-Target-Effekte”, die jedoch noch klinisch nachgewiesen werden müssen. Sowohl bei Mäusestämmen als auch bei Menschen wurden Studien mit Zielzellen durchgeführt, die speziell auf den C-Typ-Lektin-Rezeptor (CLR) Langerin (CD207) auf Langerhans-Zellen (LCs) und anderen dendritischen Zellen (DCs) abzielen. Das Ziel dieser Studien ist es, ein besseres Verständnis der menschlichen Immunreaktionen im Hinblick auf geeignete Therapien zu zeigen. Dennoch gibt es einige Einschränkungen bei der Anwendung der Ergebnisse von Studien an Mäusen und auf den Menschen. Daher ist diese Arbeit von großer Bedeutung, da sie die LCs, dem Langerin-Rezeptor, in Mäusen und Menschen vergleicht. In diesem Kontext muss ebenfalls in Betracht gezogen werden, dass ein besseres Verständnis der wichtigsten Unterschiede zwischen Mäusen und Menschen (unterschiedliche Hautdicke, Nerveninnervation, unterschiedliche Epidermis-Zusammensetzung) notwendig ist. Ebenfalls einzubeziehen ist auch die unterschiedliche Langerinbeschaffenheit in Bezug auf die Struktur, Bindungsaffinität, zelluläre Expression, Lokalisierung und Rolle bei Menschen und Mäusen. Daher trägt diese Übersichtsstudie dazu bei, eine bessere Entwicklung einer DC-gerichteten Immuntherapie zu etablieren. In diesem Feld besteht nämlich eine erhebliche Wissenslücke, da ein Großteil des immunologischen Verständnisses derzeit nur aus Studien an Mäusen stammt. Diese Studien haben zwar wesentlich zur Definition vieler grundlegender Aspekte der Immunologie beigetragen, doch die Anwendung dieser Erkenntnisse auf den Menschen stößt aufgrund der großen Speziesunterschiede an ihre Grenzen. Daher könnte ein optimiertes Modell (z. B. humanisierte Mäuse oder Ex-vivo-Modelle der menschlichen Haut) einen großen Benefit darstellen, um die derzeitigen Einschränkungen in der präklinischen Forschung zu überwinden. Darüber hinaus interagieren Liganden, die auf humanes Langerin abzielen, möglicherweise nicht in ähnlicher Weise mit Langerin in der Maus, was die Verwendung von Mausmodellen für die präklinische Validierung erschwert. Die Ausrichtung auf DCs (insbesondere über Langerin) ist eine vielversprechende immuntherapeutische Strategie. Die Unterschiede zwischen den Spezies in Bezug auf Langerin müssen jedoch gründlich verstanden werden, um eine erfolgreiche Übertragung von Tiermodellen auf den Menschen zu gewährleisten. Diese vergleichende Übersicht spielt eine entscheidende Rolle bei der Überbrückung der Kluft zwischen experimentellen Tiermodellen und der klinischen Anwendung beim Menschen.

Abstract

In advanced immunotherapy, targeted cell approaches by means of directing antigens to specialized dendritic cells (Antigen Presenting Cells) have been thoroughly studied and the results suggested high effectiveness, in addition to the advantage of reduced payload due to less off-target effects, yet not proven clinically. Targeted cell studies in both mice and humans have been carried out, specifically targeting the C-type lectin receptor (CLR) langerin (CD207) on Langerhans cells (LCs) and other dendritic cells (DCs). These studies aim at better understanding of human immune reactions to these targeted therapies. Nevertheless, there are some constraints in applying the findings of murine studies on humans. Thus, this review is of importance as it compares LCs focusing on its hallmark langerin receptor in mice and humans. Apparently, further understanding of the major differences between mice and humans, for instance, variation in skin thickness, nerve innervation & difference in epidermis composition, in addition to other differences between mice & human langerin in terms of its structure, binding affinities, cellular expression and its localizations & role is needed. Thus, this study review is very useful for better design of DC- targeted immune therapies. A significant knowledge gap exists because much of our immunological understanding is derived from murine studies. While these studies have significantly contributed to defining many fundamental aspects of immunology, there are some limitations in applying these findings to humans owing to the fact of major species differences. Therefore, a more refined model or approach (e.g., humanized mice or ex vivo human skin models) may be needed to overcome current limitations in preclinical research. Additionally, ligands that target human langerin may not interact similarly with murine langerin, posing challenges in using mouse models for preclinical validation. Targeting DCs (especially via langerin) is a promising immunotherapeutic strategy. However inter-species differences in langerin must be thoroughly understood to ensure successful translation from animal models to human ones. This comparative review plays a crucial role in bridging the gap between experimental animal models and clinical application in humans.

Introduction

LCs were first discovered by chance, in 1868 by Paul Langerhans at Berlin (Langerhans, 1868); he described some dendritically shaped cells in the human epidermis that were later named after him. Currently, the most advanced hallmark for identifying LCs in both mice and humans is langerin/CD207. The ultrastructural discovery of Birbeck granules (BGs) was also an important piece of identification (Romani, Clausen, et al., 2010).

LCs are antigen-presenting dendritic cells (DCs) residing in the epithelia. The phenotypic hallmark is their expression of the CLR langerin (CD207). Langerin is also expressed on another population of DCs in the dermis and other tissues of the body in mice and humans. These ‘dermal langerin⁺ DCs’ are unrelated to LCs (Bigley et al., 2015; Poulin et al., 2007). Now, models using genetically engineered mice contribute to our understanding of the role of LCs in eliciting adaptive immune responses against pathogens or tumors and in inducing and maintaining tolerance against self-antigens or harmless substances in vivo (Grabbe et al., 1991; Maraee et al., 2020; Stoitzner et al., 2008). It has been recently demonstrated that LCs are multifaceted regarding their phenotype, ontogeny, and function. Moreover, LCs exhibit dual characteristics: of tissue-resident macrophages, while also functioning as antigen-presenting cells (APCs) with (DC)-like features (Doebel et al., 2017; Otsuka et al., 2018).

Most of the current studies have been done on mice, and they have significantly contributed to defining many fundamental aspects of immunology, there is a major constraint in applying these findings to humans owing to the fact of major species differences. In summary, extrapolating data from murine studies to human biology can sometimes be problematic due to differences in immune responses between species. Thus, the role of LCs in regulating immune responses in the skin may vary between humans and mice. Additionally designing drugs using targeted ligands highly specific to human langerin might not necessarily exert similar binding specificity to murine langerin which will unfortunately hinder further in vivo preclinical investigations.

Aiming at better understanding of LCs and other langerin expressing cells in both humans and murine, this review, aims at digging deeper into the comparative aspects between human langerin and murine langerin in order to further enhance immunological and antitumor therapies such as the important langerin targeted liposomal delivery platform which presents a promising tool for novel therapeutic applications (Wamhoff et al., 2019a).

This review covers the following main points: Structural and functional overview of langerin receptor in both humans and mice, its expression in mice versus humans, its role on LCs and on other cell types in mice versus humans and lastly implications and future directions of langerin targeting.

1. Comparative Study / Langerin (CD207) in Mice & Humans

This review will highlight and summarize the most recent findings on langerin receptor covering these main topics: The structure of langerin in murine and humans, the expression patterns of langerin in murine and humans, the role of langerin in murine and humans & the various implications and future directions of this study review topic.

1.1. Langerhans Cells & Langerin Structure

In this section, we provide an introduction to LCs and langerin (CD207) with regard to its structure, binding sites and ligand specificity in both mice & humans.

1.1.1. LCs in Murine and Humans / History & Paradigm

Before the discovery of specific markers, LCs, a specialized subset of DCs in the skin were mainly identified using broad immunological markers. In human skin, two key markers were commonly used: HLA-DR: A molecule of the major histocompatibility complex class II (MHC-II) present on many antigen-presenting cells (APCs) & CD1a: A molecule more specific to LCs in the healthy human epidermis (not found on mice LCs), making it a useful distinguishing marker. In contrast, in mice, identifying LCs was more challenging due to the lack of a specific LC marker. For many years, researchers relied on MHC-II expression (as in humans) to identify these cells. However, MHC-II is expressed on a wide range of dendritic and other immune cells in mice, so it lacked specificity. This changed with the work of Romani, Clausen, et al. (2010) and others, who contributed greatly to the development and use of anti-langerin (CD207) antibodies. Langerin is a CLR specifically expressed by LCs and some other DC subsets. The availability of anti-langerin antibodies allowed for more specific and reliable identification of LCs in both mice and humans. In summary, Romani et al. (2010) study played a crucial role in advancing the immunological tools available to study LCs, especially in mice, by introducing langerin as a hallmark marker, replacing less specific indicators like MHC-II (Romani, Clausen, et al., 2010).

Historically, the stratified squamous epithelium (SSE) was believed to contain a single type of myeloid-derived DCs Mononuclear Phagocytes (MNP) population: (LCs).

In 1973, Silberberg (Silberberg, 1973) demonstrated the role of LCs in immunity on human subjects. By 1985, Steinman and Cohn (Steinman & Cohn, 1973) classified LCs as APCs, similar to DCs after a study done on mice. Now it is clear that not only LCs inhabit the SSE, but also other DC subsets that function differently (Vine et al., 2024).

Today, human LCs are recognized as a distinct class of MNPs in the skin. They are well-defined as a distinct population of DCs in the steady-state epidermis, characterized by the expression of CD45, HLA-DR, CD1a, and langerin (CD207). These markers are essential for identifying LCs and distinguishing them from other cell types in the skin (Romani, Clausen, et al., 2010).

Mechanism of action of LCs

LCs play a critical role in immune surveillance by recognizing and capturing pathogens through Toll-like receptors (TLRs) and CLRs. This process involves the migration of LCs to lymph nodes (LNs), where the pathogen is processed in the endolysosomal system where MHC-II molecules present fragments of the antigen to naïve CD4⁺ T cells, initiating an immune response (Vine et al., 2024). The findings of Vine et al. provide significant insights into the functions of LCs in mice (Vine et al., 2024). In mice, langerin⁺ cells play a critical role in the reactivation of skin tissue-resident memory cells (TRMs) by recognizing keratinocyte-derived antigens. Keratinocytes act as the primary replication site for various viruses, including arboviruses, herpesviruses, papillomaviruses, and vaccinia virus (Chessa et al., 2020). Consequently, the direct recognition of viral antigens presented on MHC-I molecules by keratinocytes offers the fastest mechanism to reactivate TRMs during a viral reinfection.

Mouse LCs, which account for about 3 to 5% of all nucleated cells in the epidermis, are located in the stratum spinosum, where they form a dense network across the skin's entire surface (Romani et al., 2003). Dendrites of LCs extend between keratinocytes and even penetrate tight junctions, reaching into the stratum corneum (Kubo et al., 2009). This enables LCs to sample both antigens expressed in keratinocytes and those on the skin's surface (Kamenjarin et al., 2023). Using a mouse model that allows for selective antigen targeting to keratinocytes in a specific area of the skin, the study of (Kamenjarin et al., 2023) demonstrates that antigen expression in keratinocytes leads to the rapid, antigen-specific reactivation of skin TRM cells. The resulting data showed that epidermal LCs are the APC type essential for early CD8⁺ TRM reactivation in the epidermis. The reactivation of TRM cells has been shown to swiftly trigger innate and adaptive immune responses that protect against tissue reinfection or reactivation of

latent viruses. (Ariotti et al., 2014; Kamenjarin et al., 2023; Rosato et al., 2017; Ryan et al., 2021; Schenkel et al., 2014).

In humans, the conclusion of Fehres et al., 2017 study provided evidence that human LCs are able to cross-present antigens to CD8⁺ T cells after langerin-mediated internalization (Fehres et al., 2017). Another study using autologous human tissues, proved that both in vitro & in vivo, resting human epidermal LCs effectively maintain tolerance in normal skin by activation and proliferation of skin resident regulatory T cells (Tregs) (Seneschal et al., 2012). Also, LCs was proved to have a significant role in priming CD8⁺ T cells into potent cytotoxic T lymphocytes (CTLs) (Banchereau et al., 2012). Other studies highlighted that resting epidermal LCs in human skin selectively activate Tregs, a subset of TRMs, to maintain immune homeostasis. However, upon encountering pathogens, the same LCs shift to activate effector memory T (TEM) cells, demonstrating their ability to modulate immune responses based on environmental conditions (Banchereau et al., 2012; Oka et al., 2025; Romano et al., 2012; Seneschal et al., 2012).

As a conclusion, both murine and human LCs are crucial epidermal surveyors, comparing mechanism of LCs in both humans and mice, we can conclude that while tolerance is a conserved function of LCs across species, the human LC system may be more adaptable, reflecting the complex immunological demands of the human skin environment.

Ontogeny of LCs in humans and mice

In terms of their ontogeny and homeostasis, LCs establish and sustain their network in the epidermis across three distinct phases (Romani, Clausen, et al., 2010). First, during the prenatal and perinatal period, the epidermis must be seeded with LCs or their progenitors. During murine postnatal development, LCs gradually acquire their defining features in the epidermis. A key maturation marker, langerin (CD207), exhibits a delayed onset compared to MHC class II expression. Intracellular langerin becomes detectable in LCs 2–3 days after birth, marking the initial stages of LC differentiation. By day 10 postnatally, nearly all epidermal LCs co-express MHC II and langerin. Langerin expression intensity continues to increase, reaching adult levels by 3 weeks of age (Tripp et al., 2004). Second, under steady-state conditions in adult skin, the existing LC network requires ongoing maintenance. Third, during inflammatory responses, LCs migrate from the epidermis to skin draining lymph nodes (DLNs), necessitating the recruitment or generation of new LCs to replenish the epidermal network. A similar pattern is observed for

dermal langerin⁺ cells (Romani, Clausen, et al., 2010). In mice prenatal epidermis, most LC precursors express ATPase and CD45. Around birth, MHC-II molecules are added, followed a few days later, by the expression of CLRs: first langerin (Tripp et al., 2004), then DEC-205/CD205 (Dewar et al., 2001).

Regarding human LCs ontogeny, recently, Prof. Adelheid Elbe-Bürger's research group investigated human prenatal skin and provided a detailed description of the development of LC network in the epidermis for the first time. Similar to the mouse system, there is a high proliferation rate of CD45⁺ leukocytes in fetal/embryonic skin, which decreases postnatally. During the first to second trimester, markers on epidermal leukocytes appear sequentially: initially HLA-DR, followed by CD1c, then langerin, and finally CD1a (Romani, Clausen, et al., 2010; Schuster et al., 2009).

Analyzing this data, we can conclude that LCs development and homeostasis follow parallel patterns in mice and humans, with both species showing stepwise markers expression and similar responses to inflammation. Key differences lie in marker names and expression timing, but the overall sequence and roles are conserved.

Maintenance of LCs homeostasis in the steady-state epidermis in humans & mice

Regarding the lifespan of LCs in mice skin in steady state, Miriam Merad provided evidence supporting Krueger et al.'s hypothesis from 1983. She demonstrated that LCs or their precursors can either divide within the skin or belong to a very long-lived cell population. Using bone marrow chimeric mice and a model of murine parabiosis, Merad showed that LCs are radio-resistant and remain of host origin for nearly 2 years, which is almost the entire lifespan of the mouse (Merad et al., 2002). LCs in other epithelia might differ, though. For example, vaginal mucosal DCs (probably LCs) (Iijima et al., 2007) or DCs in the airway epithelium differ in that they are not as long-lived and are repopulated by circulating precursor cells (Romani, Clausen, et al., 2010).

In humans, LCs are essential for maintaining skin homeostasis, and their diversity has been recognized for some time. In the study of (Liu et al., 2021) (X. Liu et al., 2021), using single-cell RNA sequencing (scRNA-seq) and mass cytometry, researchers identified four distinct LC subsets in humans: two found in the steady state (LC1 and LC2) and two in an activated state in human epidermis and in LCs generated from CD34⁺ hematopoietic stem cells (HSC-LCs). This study aimed to explore the diversity of human LCs and found that the epidermis contains functionally and phenotypically distinct LC subsets. LC1 cells are more stable under

inflammatory conditions, with strong self-renewal, antigen uptake, and cytokine production linked to innate immunity. In contrast, LC2 cells are more responsive to stimulation, showing faster proliferation with Macrophage Colony-Stimulating Factor (M-CSF), greater migratory ability, and high expression of genes involved in adaptive immune regulation. Upon M-CSF stimulation, LC1 displayed significantly increased cell survival and decreased apoptosis compared with the changes in LC2. These findings map the differentiation pathways of human LCs and provide a valuable foundation for future research into LC biology. The two LC subsets LC1 & LC2 respond differently to inflammatory environments. LC2 has a greater capacity to induce regulatory Tregs compared to LC1. However, their functions are not mutually exclusive, often overlapping or complementary. LC1 primarily acts under steady-state conditions as an effector LC, while LC2 plays a more regulatory role during inflammation. Together, they likely cooperate to balance immune responses and maintain skin homeostasis (X. Liu et al., 2021).

Comparing LCs in humans & mice

In mice, epidermal LCs have unique origins in the steady state. In contrast to other DC populations that are in the spleen and the mucosal epithelium. Epidermal LCs are maintained either through self-renewal or by a local pool of radio-resistant proliferating host hematopoietic precursor cells that reside in the skin. The mice skin contains five different types of DCs: epidermal LCs, migratory LCs, dermal langerin⁺ DCs, dermal langerin⁻ DCs and dermal macrophages. The last 2 populations are similar to dermal langerin⁺ DCs in that they can be found in tissues other than the dermis, whereas LCs are unique to the epidermis (Merad et al., 2008).

In humans, a relatively recent study suggests the role of LCs in replenishment of inflamed epidermis. Human monocytes can become LCs in situ under certain conditions, ensuring the epidermis retains LCs after inflammation, yet there is an additional alternative pathway of LC differentiation from CD1c⁺ DC precursor that may have relevance in vivo. (Milne et al., 2015) Earlier studies noted LCs repopulation in human epidermis following bone marrow transplants, where macrophages morphed into LCs, displaying BGs. Researchers concluded that macrophages transform into LCs in the skin (Murphy et al., 1986).

Lineage of LCs in humans and in mice

Recent studies of the lineage of skin LCs have found that differentiation of LCs is dependent on Transforming Growth Factor (TGF- β 1). This becomes apparent in TGF- β 1 knockout mice that totally lack epidermal LCs (Borkowski et al., 1996, 1997). TGF- β 1 appears to be derived from LCs themselves and act in an autocrine way (Kaplan et al., 2007). TGF- β 1 induces the transcription factor Id2. Therefore, as expected, the Id2 knockout mice did also not have any LCs in their epidermis (Hacker et al., 2003) just like TGF- β 1 knockout mice. Runx3 is another transcription factor that is regarded as a key regulator of cell lineage decisions. It is involved in TGF- β 1 signalling and again, mice that lack this transcription factor are devoid of LCs (Fainaru et al., 2004).

The dependence on TGF- β 1 and its downstream target Id2 was also found for human LCs which are derived from CD34⁺ hematopoietic progenitor cells (Strobl et al., 1997). LCs maintain themselves not only through self-renewal under normal conditions, but are replenished by myeloid precursors following injury in both species. Studies indicated that human monocytes could generate langerin⁺ cells in vitro meaning that they may serve as precursors. More recent studies using lineage-negative cells and CD34⁺ progenitors suggest an alternative differentiation pathway that does not rely on monocytes. Using isolated human LCs (an in vitro study) of (Milne et al., 2015) (Milne et al., 2015), the major finding of this study was that CD1c⁺ DCs differentiate into LCs in response to granulocyte macrophage colony-stimulating factor (GM-CSF), TGF- β 1 and bone morphogenetic protein 7 (BMP7). The data findings highlighted a new potential functional precursor for LCs which is the CD1c⁺ DCs and an alternative pathway for the differentiation of LCs which might have a relevance in vivo (Milne et al., 2015).

To summarize, both species rely on TGF- β 1 and its downstream transcription factor Id2 signalling for LC development. Mice have a more clearly defined lineage from embryonic precursors and rely heavily on Runx3. Humans show more flexibility, with potential monocyte-independent pathways and a newly discovered role for CD1c⁺ DCs as alternative LC precursors.

Heterogeneity of epidermal mononuclear phagocytes in humans & mice

The study of (Zhu et al., 2024) showed that LCs are the key cells that elicit immune activation/tolerance in the epidermis. **(Table 1)** Human and mouse LCs have generally similar phenotypes, with some unique surface markers for each species. Both are easily recognized in the epidermis by their expression of CD45 (LY5), MHC-II, and the CLR langerin (CD207), which is key to BG formation (Figdor et al., 2002; Merad et al., 2008; Takahara et al., 2002; Tripp et al., 2004; Valladeau et al., 2002a). They also express Epithelial Cell Adhesion Molecule (EpCAM) and E-cadherin, a molecule that helps LCs attach to keratinocytes, though the exact role of E-cadherin in LCs is still unclear (Tang et al., 1993). Additionally, human and mouse LCs share the expression of SIRP α (CD172 α), CD11b, and CX3CR1, which are also found on most cDC2 and monocytes (Deckers et al., 2018). However, human LCs differ in that they express low levels of CD11c, lack F4/80, and show higher levels of CD1a and moderate levels of CD1c. These CD1 molecules suggest that human LCs play a role in lipid antigen presentation either microbial lipids or self-lipid antigens (A. De Jong et al., 2010). Upon activation, both human and mouse LCs upregulate MHC-II, CD40, and CCR7, then migrate to skin DLNs (Ohl et al., 2004). See **(Table 1)**

Recent proposals suggest mouse LC may come from a lymphoid-committed progenitor due to CD8 α expression (Anjuère et al., 2000). However, CD8 α has not been seen on human DCs. Also, CD1a, a marker of human LC, is missing in mice. These differences highlight challenges in translating findings between human and mouse LCs which is crucial for refining preclinical models.

LC subsets in humans and mice

Previous studies on murine LCs subsets revealed that “long-term LCs” persist in the mouse epidermis over time and “short-term LCs” are rapidly replenished in response to inflammation in the epidermis (Seré et al., 2012). The “short-term LCs” express high levels of classical LC characteristic molecules such as langerin, EpCAM, CD205, and CD24, while “long-term LCs” express monocyte characteristic molecules such as CX3CR1 and CD11b, but express low levels of langerin (Ferrer et al., 2019; Seré et al., 2012).

In humans, Reynolds et al. (Reynolds et al., 2021) were the pioneers who visually revealed LC subpopulations in human skin using scRNA-seq. They divided LCs in human skin into four

subgroups, namely LC1-LC4, based on their expression of different signature genes (Zhu et al., 2024). See **(Figure 1)**

In humans, hematopoietic stem cells (HSCs) differentiate into pre-LC1 and pre-LC2, which mature into epidermal LC1 and LC2. Under inflammatory conditions, both LC1 and LC2 are activated, and under the influence of the transcription factor IRF4, they migrate to LNs where they drive T-cell polarization promoting the generation of Tregs (Zhu et al., 2024). (Figure 1)

Compared to mouse LCs, our understanding of human LCs remains limited. With the identification of human LC subsets, it is essential to explore their characteristics and distinct functions in both physiological and pathological conditions from a subset-specific perspective. The number and function of LC subsets may differ across various body sites and age groups, requiring further research. Additionally, the vertical distribution of LC subsets in the epidermis and hair follicles should also be examined. Previous studies on LCs in skin diseases have often treated them as a homogeneous population.

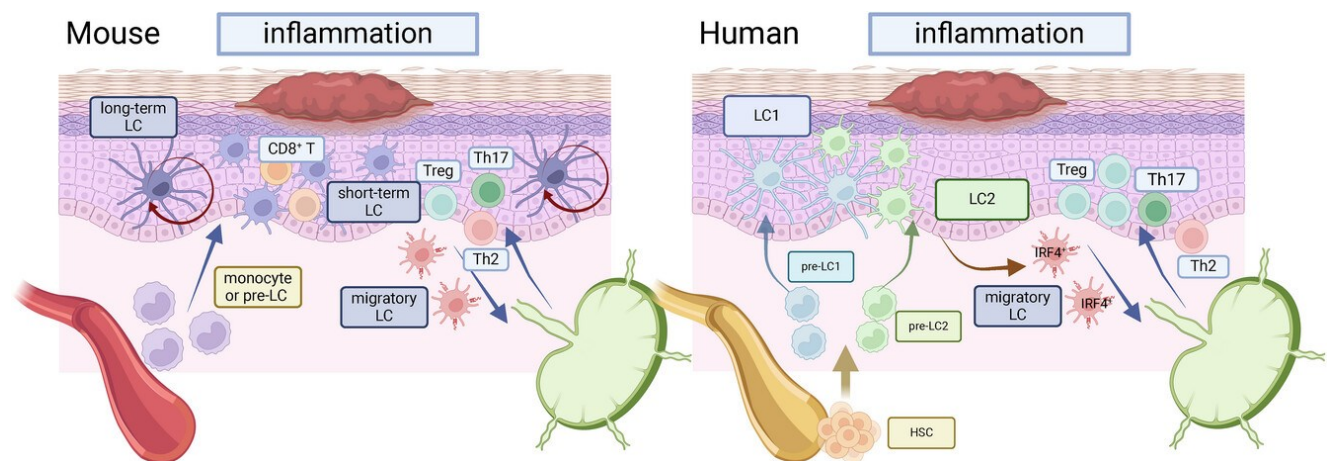


Figure 1 The working models of LC subsets in mice and humans under inflammation (Zhu et al., 2024)

In mice, inflammation triggers the rapid recruitment of peripheral monocytes to the epidermis, where they differentiate into "short-term LCs" after resident LCs are depleted. Meanwhile, LC precursors in the epidermis either self-renew or are replenished by bone marrow-derived cells, which then become "long-term LCs". In response to inflammatory signals, LCs enhance the

function of epidermal effector CD8⁺ T cells or migrate to LNs to activate various T-helper (Th) cells and Tregs (Zhu et al., 2024). (**Figure 1**)

However, in the context of different skin diseases, LC subsets may be affected in distinct ways, leading to variations in their abundance and function. This could help explain the conflicting results observed in earlier studies regarding LCs immunological functions. LCs show considerable heterogeneity in their origin, development, and functions. The roles of LCs in skin immune diseases are complex and variable, likely influenced by differences in the skin microenvironment (e.g., microbes, allergens, autoantigens, stress stimuli) and/or the distinct functions of LC subsets (**Figure 1**). A better understanding of LC subsets could provide valuable insights into developing therapeutic strategies by manipulating LC subsets (Zhu et al., 2024).

Study		Surface markers								Precursor			
		Subsets	Langerin	MHCII/HLA-DR	CD11b	EpCAM(X. Liu et al. 2021)	CD1a	CD24	CD205	CD172a	CD80	CD86	
Mouse	(Seré et al. 2012)	Long-term LCs	High	High	Low	High	No	High	High	Ns	Unknown	Unknown	ID2 ⁺ bone marrow-derived cells
		short-term LCs	Low	High	High	Low	No	Low	Low	Ns	Unknown	Unknown	myeloid cells expressing lysozyme M
		classical LCs	High	Positive	Low	High	No	Unknown	High	High	Low	Low	CX3CR1-expressing cells pre-LC
		Pre-LCs	Negative	Positive	High	Low	No	Unknown	Low	slightly low	slightly high	Slightly high	CD115 Gr-1 ^{hi} cells
Human	(Ferrer et al. 2019)	eLCs	High	Low	Low	High	No	High	High	Unknown	Low	High	EpCAM ⁺ cells and others
		EpCAM ⁺ cells	Low	High	High	Low to high	No	Low	Low	Unknown	High	Low	CD11b ⁺ high
		LC1	High	High	Low	High	High	Ns	Ns	Ns	High	Low	pre-LC1
		LC2	Low	Low	High	Low	Low	Ns	Ns	Ns	Low	High	pre-LC2
		LC	High	High	Low	High	High	High	Unknown	High	Unknown	Unknown	CD33 ^{low} cells ⁴
		CD11c ⁺ DCs	Low	Low	High	Low	Low	Low	Unknown	Low	Unknown	Unknown	Unknown
		CD33 ^{low} cells	High	Low	Unknown	Unknown	Low	Unknown	Low	Unknown	Unknown	Unknown	Unknown

Table 1 Heterogeneity of epidermal mononuclear phagocytes in mouse and human studies (Zhu et al., 2024)

Key: Ns: There was no significant difference in the expression of this protein among subsets; No: this protein is not expressed in the subset; Unknown: there is no evidence to verify the expression of this protein; **a:** This conclusion is only an inference and requires further research for verification.

LCs subsets & their functional heterogeneity

In 2021, Liu et al. performed scRNA-seq on langerin⁺ cells isolated from the human inner foreskin SSE and the four distinct subsets of LCs LC1–LC4 were identified. These subsets were distinguished by their unique expression patterns and functional properties: LC1 (CD207^{hi}, CD1a⁺): This subset represents steady-state LCs, characterized by high levels of CD207/langerin and CD1a, markers associated with antigen presentation. LC2 (CD207^{mid}, CD1c⁺, CD1b⁺): Another steady-state subset with moderate expression of CD207 and co-expression of CD1c and CD1b. LC3 (CD83, CCR7^{lo}): This subset is activated, while their expression of CD83 and low CCR7 levels, suggest early activation without full migratory capacity. LC4 migratory (CCR7^{hi}): The migratory subset, marked by high CCR7 expression, which is involved in guiding DCs to LNs during immune responses. **(Table 1)**

This classification enhances our understanding of the diversity of LCs in human skin, particularly in the foreskin epithelium, and sheds light on their roles in both steady-state conditions and immune activation (X. Liu et al., 2021).

The heterogeneity of LCs was found to have functional significance. LC1s exhibit a greater ability for antigen uptake and self-maintenance, while LC2s are more likely to play an immune-regulatory role and have a higher capacity for migration. Both LC2s and LC3s were present in elevated proportions in the epidermis of psoriasis lesions, suggesting that their immune-regulatory functions may help counterbalance the skin inflammation associated with the disease. Moreover, both LC1s and LC2s were capable of further differentiating into LC3s and LC4s (X. Liu et al., 2021).

In mice, it is now known that langerin⁺ dermal cells are classified as DC1s. Several human studies have also described CD207/langerin⁺ cells in the gut lamina propria, which lacks SSE, ruling out the possibility that these cells are migrating LCs (S. Chang & Kweon, 2010; Flores-Langarica et al., 2005). Bertram et al. (2019) (Bertram et al., 2019) demonstrated that epidermal CD11c⁺ DCs express CD207/langerin, particularly in genital skin and type II epithelium, where up to 80% of these cells expressed the marker.

Additionally, Pena-Cruz et al., 2018 (Pena-Cruz et al., 2018) found that Vaginal Epithelial Dendritic Cells (VEDCs) in humans also express CD207/langerin but do not contain the BGs of LCs. Similarly, Liu et al. (X. Liu et al., 2021) observed differences in BGs between the LC1s and LC2s in the inner foreskin. LC1s had long, sparsely scattered dendrites and well-organized BGs, while LC2s displayed abundant cytoplasm, short, densely packed dendrites, and poorly organized BGs. It is important to note that Liu et al. (2021) assumed that the expression of CD207/langerin was sufficient to define LC, but this assumption is not entirely accurate. As shown by Bertram et al., 2019, the human inner foreskin contains roughly equal proportions of LCs and DCs, with most of the DCs also expressing langerin. This indicates that CD207/langerin expression alone is not definitive for identifying LCs (Bertram et al., 2019). Therefore, relying solely on langerin can misidentify other langerin⁺ DCs as LCs unless anatomical and phenotypic context is considered (Poulin et al., 2007).

Understanding how inflammatory signals influence the migration of DCs from deeper tissues into the skin and mucosa is key for improving vaccine delivery by guiding DCs to the vaccination sites. As highlighted in previous studies on both mice & humans, VEDCs or CD11c⁺ DCs in the SSE can be distinguished from LCs by their expression of markers such as CD11c, CD11b, CD1c, and CD206. This differentiation is important for identifying specific subsets of DCs (Bertram et al., 2019; Vine et al., 2024).

Origin and phenotype of langerin⁺ DCs in mice & humans

In mice, a relatively old study by Larregina et al. 2001 study, could not clearly distinguish between LCs and dermal DCs (dDCs) that migrate from murine whole skin explants (Larregina et al., 2001; Lenz et al., 1993).

Historically, the hallmark of mouse LCs was the tennis-racket-shaped BG, which could only be visualized by transmission electron microscopy (Birbeck et al., 1961; Hashimoto, 1971; Wolff, 1967). Langerin/CD207, a type II transmembrane protein belonging to the family of Ca²⁺-dependent CLRs, was identified as a major molecular component of BG, first in humans (Valladeau et al., 1999, 2000) and later in mice (Valladeau et al., 2002a).

In mice, LCs continue to express langerin throughout their migration process from the epidermis through lymphatic vessels to the LNs. As langerin is expressed intracellularly in LCs for an extended period, Henry et al. study group were able to track their migration to lymphoid organs (Henri et al., 2001). It was also observed that migratory skin DCs continue to express

langerin in skin DLNs. The findings of this study (Stoitzner et al., 2003) show that langerin⁺ cells were found in the T cell areas of the LNs of mice, but were almost always absent from B cell follicles. Moreover, no langerin expression was detected in CD11c cells in the LNs, further supporting the hypothesis that langerin is an exclusive marker for DCs.

Additionally, substantial numbers of langerin⁺ cells were only found in skin DLNs, with only a few scattered cells present in the MLNs. This highlights the reliability of langerin as a marker for epidermis-derived LCs. Weak langerin staining in the mice MLNs was previously shown by Valladeau et al., 2002 (Valladeau et al., 2002a).

Also an earlier study of Valladeau et al., 1999, reported some langerin⁺ cells in the epithelia of the lungs and tonsils in humans (Valladeau et al., 1999). Similar langerin-expressing cells in the epithelium of the gut (A. Kaser, personal communication) may account for the langerin⁺ cells observed in the mesenteric lymphoid tissue.

Larregina et al., Martínez-Cingolani et al. and Hoshino et al. demonstrated in their studies that human hematopoietic stem cells, monocytes, and CD11c⁺ dendritic cells can be induced to differentiate into LCs in vitro upon stimulation with various signalling molecules, indicating their potentiality as precursors for LCs. Moreover, the maturation and development of human LCs and mouse LCs share similar signal pathways, such as the TGF- β signalling (N. Hoshino et al., 2005; Larregina et al., 2001; Martínez-Cingolani et al., 2014).

1.1.2. Langerin Structure

Langerin has a relatively short intracellular cytoplasmic domain (**Figure 2**), which includes a proline-rich domain (PRD), the black small rectangles. The extracellular domain of langerin features a neck region composed of alpha-helices, followed by the carbohydrate recognition domain (CRD). Stable langerin homo-trimers are formed on the cell surface through a coiled-coil interaction in the neck region. Like other CLRs, ligand avidity is enhanced by oligomerization, which may also influence carbohydrate specificity (Van Der Vlist & Geijtenbeek, 2010). In conclusion, while langerin serves as a marker for LCs in both species, its expression and functional roles differ between mice and humans. These differences underscore the importance of cautious interpretation when extrapolating murine LC studies to human contexts (Bigley et al., 2015).

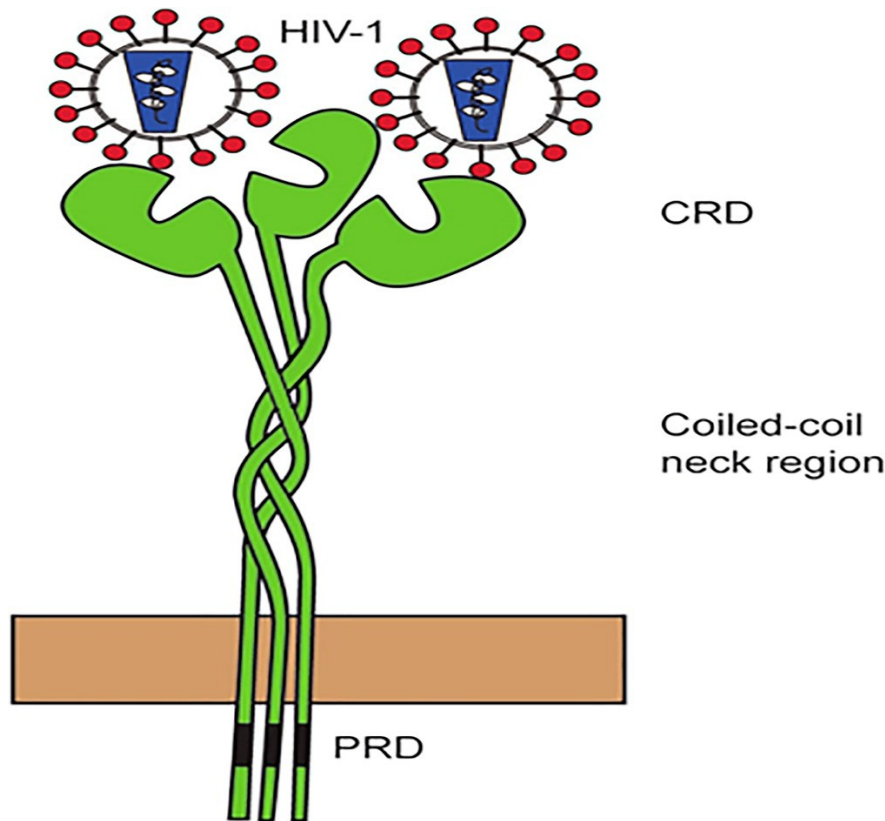


Figure 2 The Trimeric structure of Langerin (Van Der Vlist & Geijtenbeek, 2010)(Van Der Vlist & Geijtenbeek, 2010)

Langerin & Birbeck granules (BG)

The expression of langerin triggers the formation of BG in cell lines (Van Der Vlist & Geijtenbeek, 2010). Langerin/CD207, a type II transmembrane protein belonging to the family of Ca^{2+} -dependent CLRs, was identified as a major molecular component of BGs, first in humans (Valladeau et al., 1999, 2000) and later in mice (Valladeau et al., 2002a). BGs are organelles specifically induced by langerin. When langerin binds to antigens, they are internalized and directed to a unique organelle found in LCs, known as the BGs. First described by Birbeck in 1961 (Birbeck et al., 1961), these granules are penta-laminar, rod-shaped structures exclusive to LCs. Albeit it is not certain whether dermal langerin⁺ DCs possess BGs. Obviously, the expression of langerin in a given cell does not necessarily mean that the cell contains BGs. For example, murine-cultured LCs have lost virtually all BGs (Schuler & Steinman, 1985), yet they express substantial levels of langerin (Stoitzner et al., 2003). As per

Miriam Merad review (Merad et al., 2008), targeting the cell-surface of langerin receptor on human LCs by a langerin-specific monoclonal antibody induces internalization and trafficking of langerin to BGs. Similarly in mice, the homologue of human langerin has been identified and is homogeneously expressed on the surface of mouse epidermal LCs and its engagement induces the formation of BGs (Takahara et al., 2002; Valladeau et al., 2002a). The formation of BGs is a result of the antigen-capture function of langerin, promoting the routing of antigen into these organelles and providing access to a non-classical antigen-processing pathway (Kissenpfennig, Aït-Yahia, et al., 2005; Verdijk et al., 2005).

Mouse and human langerin both induce the formation of pentalamellar membranes typical of BG, a molecule of potential importance in LCs functionality. Although langerin cDNA introduction does not produce the “tennis racket” structures seen in LCs, these structures likely represent a minority of BGs caused by fusion with endocytic vesicles, which doesn't occur in transfected fibroblasts as most langerin molecules superimpose before reaching the cytomembrane (Valladeau et al., 2002a).

As a conclusion, although both human and murine LCs form BGs through langerin expression, their structural features and functional roles differ between species. In humans, BGs exhibit more distinct structural organization and appear to play a significant role in antigen processing. In contrast, murine LCs can function effectively even in the absence of BGs, suggesting these organelles are less critical in mice (Kissenpfennig, Aït-Yahia, et al., 2005; Mc Dermott et al., 2002).

Mouse & human langerin gene structure homology

The gene for mlangerin maps to chromosome 6D, in a region syntenic to the hlangerin gene located on chromosome 2p13 (Soilleux et al., 2000). Notably, hlangerin genes do not belong to any of the known CLR gene clusters, such as the human DC-SIGN and CD23 genes on chromosome 19p13 (Sanford et al., 1991) or the human ASGPR on chromosome 17p11-13, or the human NKR complex on chromosome 12p13-p12 (Lanier, 1998).

In a study that involved cloning a cDNA encoding mlangerin, it was found that the predicted protein shares 66% homology with hlangerin, preserving its unique characteristics. The human and mouse langerin genes have a similar structure, consisting of six exons, three of which encode the CRD. The mlangerin gene maps to chromosome 6D, syntenic to the human gene on chromosome 2p13 (Valladeau et al., 2002a). See **(Figure 3)**.

It was found that mlangerin has an intracellular domain of 46 amino acids with a proline-rich motif (PREPPP) that may function as a signal-transduction site. See (Figure 3). Amino acid sequence comparison in the European Molecular Biology Laboratory database indicated significant homology between mlangerin and several type-II lectins, particularly in their CRD. The mlangerin CRD shows the highest amino acid homology with hlangerin at 75.8% (Valladeau et al., 2002a).



Figure 3 Alignments of mouse and human langerin

Key: Conserved amino acids are shaded and the boxed sequence indicated by the blue arrows forms a signal anchor expected to represent the transmembrane domain according to the European Molecular Biology Laboratory database (Valladeau et al., 2002b).

1.1.3. Langerin Binding Sites & Ligand Specificity

Langerin antigen recognition

In humans, Fungi such as *Candida* and *Malassezia* species are recognized by hlangerin through mannose structures on their outer cell walls (M. A. W. P. De Jong et al., 2010; Tateno et al., 2010), as well as β -glucans exposed at budding scars (upon cell division). Langerin may also play a role in tumor recognition, as glioblastomas are identified by langerin through Gal-6-sulfated lactosamine, a protein expressed in brain tissue (Tateno et al., 2010). In mice, mlangerin

can recognize *Candida albicans* and viruses like HSV & Vaccinia virus, in addition to some bacteria (De Witte et al., 2007; Valladeau et al., 2000).

Langerin binding sites

Langerin, being an endocytic PRR on LCs, binds pathogens like human immunodeficiency virus (HIV) by recognizing surface glycoconjugates, leading to their internalization into BGs. Like many other CLRs, oligomerization is necessary for high-affinity binding to glycan ligands and likely plays a key role in determining its specificity (Feinberg et al., 2010).

The study of (Hanske et al., 2017a) explores the ligand specificities of the human and mouse versions of langerin for both simple and complex glycan ligands. While the two homologs share the same three-dimensional structure and bind simple ligands in the same way, screening over 300 bacterial polysaccharides revealed significant differences in their affinity and selectivity for larger, more complex glycans. Specifically, the study identified considerable variation on the surface near the standard binding site on the receptor, which may serve as a secondary interaction site for larger glycans. The pronounced interspecies differences in this secondary interaction site also highlight how these receptors quickly adapt to recognize complex pathogen glycans while maintaining their overall structure and even preserving the primary binding site. (Hanske et al., 2017a).

Ligand binding specificity of mlangerin & hlangerin

A study determining the structure of human langerin (Chatwell et al., 2008; Galustian, 2004) indicates that langerin does not bind to galactose, so interactions with the sulfate group must contribute significantly to binding of sulfated galactose. There is a conserved specificity to these interactions because both mouse and human langerin bind to ligands with terminal 6-sulfated galactose but not to those with galactose sulfated at the 3-position. It is possible that 6-sulfated galactose binds to langerin in the secondary binding site identified in the CRD (Chatwell et al., 2008; Galustian, 2004).

As per the structural analysis of the hlangerin trimer, glycan array screening with the trimeric fragment revealed that high-mannose oligosaccharides are the best ligands for human langerin. The review by Feinberg et al. (2010) also discusses a challenge in ligand binding to langerin, which is the fixed orientation of the sugar-binding sites in the trimer, likely limiting the types of ligands that langerin can bind (Feinberg et al., 2010). Oligomerization enhances the binding

affinity of CLRs. In some cases, such as with mannose-binding protein, the CRDs are positioned in fixed arrangements, enabling binding only to dense, repetitive sugar structures on target cells, while showing weaker binding to more closely spaced terminal sugars on host glycans. The fixed orientation of the sugar-binding sites in the trimer is likely to place limitations on the ligands that can be bound by langerin. In contrast, for CLRs like DC-SIGN, the CRDs are flexibly connected to the oligomerization domain, allowing them to adapt and bind strongly to a wider variety of glycans with different spacing patterns (Feinberg et al., 2005). This structural characteristic likely contributes to the specificity of langerin for particular pathogens which is considered a big advantage in targeted drug delivery (Feinberg et al., 2010).

The study of Hanske et al. 2017 also concluded that unlike other CLRs, such as DC-SIGN, which lack true homologs across species, langerin is highly conserved across the mammalian lineage. To determine if carbohydrate recognition is also conserved, the researchers compared human and murine langerin side by side. They found that while simple ligands were bound with nearly identical affinities and binding modes, there were substantial differences between the two homologs when it came to complex polysaccharides, both in terms of affinity and specificity. As a result, future studies should carefully reconsider the assumption that polysaccharide specificities can be predicted based on binding data from simpler glycans. In summary, they concluded that there is an indicator of adaptive evolutionary behavior in langerin between mice and humans. In humans, langerin⁺ APCs are predominantly found in the skin and mucosa, suggesting an evolutionary adaptation to target opportunistic fungi, mycobacteria such as *Mycobacterium leprae*, and viruses that invade via the mucosa, like HIV. In contrast, in mice, langerin is present in APC subsets of the blood, lungs and gut, where it encounters different pathogens, including *S. pneumoniae*, *Providencia*, *Proteus* species, HSV, etc.. (Hanske et al., 2017b).

Hanske et al. found that langerin in both species exhibits structural plasticity in its CRD. This allows it to accommodate diverse glycan structures, but with slightly different binding preferences and mechanisms between species which represents a challenge for translational research (Hanske et al., 2017b).

Ligands targeting human LCs and murine LCs

In mice, DCs express various endocytic receptors, including chemokine receptors, scavenger receptors, and CLRs, which facilitate the internalization and cross-presentation of antigens

(Bonifaz et al., 2002; Burgdorf et al., 2007). The precise targeting of individual DC subsets is crucial, as off-target antigen and adjuvant delivery can cause adverse effects or compromise cytotoxic T cell immunity (Flacher et al., 2014).

In healthy humans, DC specific CLR receptors, such as langerin, DNNGR-1 and the chemokine receptor XCR1, are pivotal in developing novel immunotherapies (Fischer et al., 1994; Tullett et al., 2016). Langerin (CD207) on LCs has been shown to facilitate endocytosis and cross-presentation of antigens to prime cytotoxic T cells in humans (Fehres et al., 2017) & in mice (Clausen & Stoitzner, 2015). As such, langerin represents an attractive target receptor for transcutaneous vaccination strategies. The main finding of the Wamhoff et al. study is that human epidermal LCs efficiently internalize targeted liposomes (Wamhoff et al., 2019b).

The study by Wamhoff et al. reports the discovery of the first specific, glycomimetic langerin ligand utilizing a heparin-inspired design strategy, with structural characterization conducted through NMR spectroscopy and molecular docking. The conjugation of this glycomimetic ligand to liposomes enabled targeted delivery specifically to LCs in human skin.

Additionally, liposomes (Fehres et al., 2017) with targeting ligand (Dhodapkar et al., 2014) were efficiently internalized by model cells expressing langerin in skin suspensions, showing no cytotoxicity in other cells even after several days. Also, endocytosis was fast, with most LCs addressed within 20 minutes and minimal off-target cell internalization.

Therefore, liposomes are superior to antibody–antigen conjugates because they allow coformulation of antigens and adjuvants. Targeted delivery to LCs reduces adverse effects and improves immune responses by lowering adjuvant doses.

The fast internalization and prolonged colocalization of targeted liposomes with early endosomal markers indicate that targeted liposomal delivery is effective (Schulze et al., 2019). Unlike antibodies, which recycle back to the plasma membrane, liposomes ensure a higher dose of internalized and processed antigens which was shown in Tacke et al., 2011 clinical trial (Tacke et al., 2011).

Human and murine langerin differentially recognize bacterial glycans

Murine langerin bound 56 out of 313 glycan structures, whereas the human version bound only 10, with only four unique to the human form (Hanske et al., 2017a).

To gather more evidence of the species-specific binding differences of langerin, Hanske et al. study used heat-killed *E. coli* O106 and conducted direct binding assays via flow cytometry.

The results showed that fluorescently labelled murine langerin strongly bound to the bacterial cells, while the human version exhibited almost no binding. This finding further supports the notion that interspecies differences are significant and can affect direct microbial recognition (Hanske et al., 2017b).

The study also concluded that unlike other CLR, such as DC-SIGN, which lack true homologs across species, langerin is highly conserved across the mammalian lineage. To determine if carbohydrate recognition is also conserved, the researchers compared human and murine langerin side by side. They found that while simple ligands were bound with nearly identical affinities and binding modes, there were substantial differences between the two homologs when it came to complex polysaccharides, both in terms of affinity and specificity. As a result, future studies should carefully reconsider the assumption that polysaccharide specificities can be predicted based on binding data from simpler glycans. In summary, they concluded that there is an indicator of adaptive evolutionary behavior in langerin between mice and humans. In humans, langerin⁺ APCs are predominantly found in the skin and mucosa, suggesting an evolutionary adaptation to target opportunistic fungi, mycobacteria such as *Mycobacterium leprae*, and viruses that invade via the mucosa, like HIV. In contrast, in mice, langerin is present in APC subsets of the blood, lungs and gut, where it encounters different pathogens, including *S. pneumoniae*, *Providencia*, *Proteus* species, HSV, etc.. (Hanske et al., 2017b).

Hanske et al. found that langerin in both species exhibits structural plasticity in its CRD. This allows it to accommodate diverse glycan structures, but with slightly different binding preferences and mechanisms between species which represents a challenge for translational research (Hanske et al., 2017b).

In summary, a drug that is designed to bind murine langerin with high affinity might not bind human langerin in the same way, and vice versa, that is why any therapeutic strategy (e.g., vaccine delivery or immune modulation) targeting langerin must account for these differences to ensure it works effectively across species.

Immuno-biological differences between humans & mice

Although various aspects of LC biology and functionality are comparable between mice and humans (Griffiths et al., 2005), major differences in anatomical and immunological features exist regarding murine and human skin (Kanitakis, 2002). The role of LCs in regulating immune

responses in the skin may vary between humans and mice, potentially due to differences in immune cell composition, such as the types of T cells present in the epidermis.

In humans, there are diverse T cell subsets in the skin, including epidermal TRMs, which could affect how LCs interact with these cells and influence the overall immune response. In contrast, murine models feature different immune cell populations that are present in the skin of mice and absent in humans like the epidermal $\gamma\delta$ T cells, which may lead to discrepancies in the way LCs function across species. **(Table 2)**

These variations in immune cell responses could impact the effectiveness of antitumor & immunotherapies given the findings of these three studies (Griffiths et al., 2005; Kanitakis, 2002; Klechevsky et al., 2008).

The CLR langerin (CD207) is highly expressed by LCs in both humans and mice, however, in humans, it is also expressed by a subset of conventional DC2s (cDC2s), while in mice, it is expressed by a subset of cDC1s. Additionally, as indicated in **(Table 2)**, mouse and human skin vary considerably in thickness, number of hair follicles, nerve innervation, and immune composition (Vine et al., 2024). All these differences should be carefully considered when translating data from mice studies to human studies and vice versa.

The thickness of mouse skin, particularly the ears, is generally considered consistent, but human skin can vary significantly in thickness depending on factors such as donor, location, age, and the surgical method used to prepare split-thickness skin (0.2–0.3 mm), which would contribute differently to study results. Although most dDCs are found in the upper, papillary dermis, which is relatively close to the basement membrane, the overall thickness of the skin can still impact the yield and composition of the dermal DC subsets that can be isolated (Romani, Thurnher, et al., 2010).

Area of Comparison	Humans	Mice
CD207/langerin Expression	LCs, subset of cDC2s	LCs, subset of cDC1s
Skin Thickness	Varies per species	Varies per species
Hair Follicles	Varies per species	Varies per species
Nerve Innervation	Varies per species	Varies per species
Immune Composition	Varies per species	Varies per species
Gamma delta ($\gamma\delta$) T cells in epidermis	Not found	Found

Table 2 Key Differences between Humans and Mice

Key: In resting human skin, LCs are the only haematopoietic cells present in the epidermis. In mice, there is an additional population of epidermal $\gamma\delta$ T cells (Merad et al., 2008).

1.2. Expression of Langerin in Murine versus in Humans

Mouse langerin shares 65% and 74% homology in total amino acid and lectin domains, respectively, with h langerin (Takahara et al., 2002).

In mice, langerin is not only expressed in the epidermis, but also is expressed by another subset of DCs found in the stratified epithelial surfaces and by a subset of DCs that is present in most connective tissues, including the dermis, lung, kidney and liver. Also langerin was also spotted in other mice organs including the spleen, LNs, thymus and even the heart (Merad et al., 2008). Interestingly, it is not expressed in gut-associated lymphoid tissues (Takahara et al., 2002). Also, the expression of langerin in mice is regulated at multiple levels. These include the influence of TGF- β 1, the specific subsets of DCs, DC maturation, and the tissue environment. This suggests that langerin expression is tightly dependant on both the immune context and the tissue microenvironment (Takahara et al., 2002).

As for humans, a relatively recent study by Bigley et al., 2015 found that langerin expression in humans is restricted to the CD1c+ "DC2" subset, which corresponds to the CD11b+ DCs population in mice. In mice, langerin is expressed by the XCR1+ "DC1" population which are CD103+ in tissues or CD8+ in lymphoid organs. However, the CD141^{high} XCR1+ DC1 subset in humans does not express langerin (Bigley et al., 2015; Takahara et al., 2002). Also few spotting was observed for langerin in some human tissues like lungs (Valladeau et al., 1999; Xuan et al., 2022), intestinal lamina propria (S. Chang et al., 2010; S. Chang & Kweon, 2010; S.-Y. Chang et al., 2008) & vaginal epithelia (Pena-Cruz et al., 2018).

1.2.1. Langerin⁺ DC Populations in Mice & Humans

In addition to classical LCs and dDCs [i.e. langerin-negative], a triplet of papers in 2007 (Bursch et al., 2007; Ginhoux et al., 2007; Poulin et al., 2007) has identified another population of langerin⁺ DCs that reside in the steady-state dermis of both humans and murine that have often been overlooked or not been paid much attention to. If ever they were spotted, they were regarded as LCs that were just in transit through their journey from epidermis through the dermis on their way to the LNs (Romani et al., 2001).

On a study done on mice, unlike epidermal LCs, dermal langerin⁺ DCs are radiosensitive and exhibit a unique surface phenotype. These DCs migrate from the skin to the LNs both under inflammatory conditions and in normal circumstances, where they constitute the majority of langerin⁺ DCs in skin DLNs. This novel population is derived from the bone marrow, as demonstrated in hematopoietic chimeras. Anatomically, this population is distinct from LCs, as it resides in the dermis of the skin rather than the epidermis. Phenotypically, the dermal langerin⁺ DCs differ from epidermal LCs in their expression of CD11b, Ep-CAM, Dectin-1, CD103, and E-7 integrin (Bursch et al., 2007). **(Table 3)**

In mice, currently, the most useful marker to identify and sort dermal langerin⁺ DCs from murine skin and skin-draining LNs is 'langerin⁺/CD103⁺/CD8^{negative}'. CD8⁺ DCs need to be excluded, because it has been shown repeatedly that lymph node-resident CD8⁺ DCs also express langerin. Langerin⁺ DCs can be distinguished from LCs by their expression of the integrin CD103 and the low expression of CD11b (Merad et al., 2008).

Concerning this relatively newly discovered subset of langerin⁺ DC in humans, unfortunately, till the current date, there is no sufficient data on in humans. All published descriptions of dermal langerin⁺ DCs have so far been in mice. This is due to the rarity of these dermal cells and the logistic (and ethical) difficulties in obtaining large amounts of human skin. Thus, it is comprehensible that knowledge on human skin lags behind. However, It is highly important to remark that, dermal langerin⁺ DCs have recently been identified in human skin and their phenotype is currently under studies (C. Nagao, M.M. and M.C. Udey, unpublished observations; M.C., F. G. and M.M., unpublished observations), (Bigley et al., 2015; Merad et al., 2008). Recently, a highly likely candidate was identified in human dermis, namely a langerin⁺/EpCAM^{negative} DCs. CD103 seems to be no reliable marker for these cells in human skin. The dermal langerin⁺ DCs equivalent was also even found in human bone marrow transplant patients. Like in mice, this cell type turned out to be of donor origin (Romani, Clausen, et al., 2010). It is not certain whether dermal langerin⁺ DCs possess BGs (Stoitzner et al., 2003). **(Table 4)**

Dermal langerin⁺ DCs in humans and mice

Ginhoux et al. study shows that circulating langerin⁺ DCs patrol the dermis in the steady state and migrate to the skin DLNs carrying skin antigens which is sometimes considered a neglected element of immunosurveillance beside LCs that needs to be considered in the design of novel vaccine strategies (Ginhoux et al., 2007). In the steady state of mouse skin DLNs, three subsets of langerin⁺ DCs are found with different proportions: epidermal LCs, dermal langerin⁺ DCs, and blood-derived CD8 α ⁺ DCs which are likely to vary from mouse strain to another (S. Chang & Kweon, 2010). In mice, LCs & langerin⁺ dDCs are unrelated and exhibit distinct functions, this new subset of dDCs expressing langerin (langerin⁺ dDC) was identified in mice (Nagao et al., 2009). In an earlier study, it was shown that EpCAM is selectively expressed by LCs and their derivatives (Borkowski et al., 1996). Bursch et al. reported that this feature can distinguish LCs from langerin⁺ dDC (Bursch et al., 2007). The selective expression of the EpCAM by mouse LC enables the clear differentiation of viable LCs from langerin⁺ dDC in both skin and lymphoid tissue, including ex vivo environments. The differential expressions of EpCAM and langerin indicate the existence of at least three distinct subsets of skin DCs in mice. In fact, currently, five distinct DC populations were found in mice with some functional differences (Henri et al., 2010).

In Nagao et al. study, they found that LCs and langerin⁺ dDCs migrate differently in vitro and repopulate skin compartments at varying rates after depletion. Unlike LCs, langerin⁺ dDCs do not need TGF β 1 for development. Nagao et al. (2009) reported that while langerin⁺ dDCs can develop and localize in the skin without TGF β 1, LCs in both species depend on this cytokine for their development, localization, and/or survival.

Also, the findings of this study suggest that LCs and langerin⁺ dDCs are distinct DC subsets with specialized roles in immune regulation. Identifying these unique skin DC subsets is very important for the development of subcutaneous vaccines (Nagao et al., 2009).

In humans, few scattered langerin⁺ cells have been observed in healthy human skin ever since the availability of antibodies against langerin/CD207 (Valladeau et al., 1999). Though, langerin expression in human dermis is minimal (~1%) (Artyomov et al., 2015; Romani, Clausen, et al., 2010) and is mainly associated with migrating epidermal LCs .

It is important to highlight that in mice, the frequency of occurrence of langerin⁺ dDCs is higher than that in humans, yet much lower than that of langerin^{neg} dDCs: i.e. less than 5% (Nagao et al., 2009; Romani, Clausen, et al., 2010; Yamazaki et al., 2018) of total dDCs. The human equivalent of this rare population is still being studied, with some evidence suggesting that a similar subset may exist in the human dermis, as reported by Romani et al. (2010) (Romani, Clausen, et al., 2010) and discussed in a related article by Teunissen et al. (2010) (Teunissen et al., 2011).

Langerin^{neg} dDCs in humans and mice

Healthy human and mouse skin contains dDCs that do not express langerin/CD207 (Romani et al., 2011) and which represent the majority of the dDCs in both species. Key studies by Michelle Lowes' group in human skin (Zaba et al., 2007, 2009) and Pieter Leenen's group in mouse skin (Dupasquier et al., 2004) highlighted and emphasized that the healthy dermis typically has a higher number of macrophages than DCs.

DC subsets & their lineage in humans and mice

It is rather difficult to translate functional findings between human and mouse DC subsets. Yet, the DC system is still being redefined in both humans and mice, with various subsets identified. Murine thymic DCs expressing CD8 come from a CD4^{low} lymphoid progenitor, leading to the definition of the lymphoid DC lineage (Ardavin, 1997). Mouse LCs are proposed to originate from a lymphoid-committed progenitor based on CD8 expression, though CD8 has not been observed on human DCs (Anjuère et al., 2000). Additionally, CD1a, a marker of human LCs, is absent in mice. These differences highlight the challenges in translating findings between human and mouse DC subsets which is crucial for optimizing preclinical models. The study of (Valladeau et al., 2002a) identifies m langerin/CD207, which shares a lot of functional and structural features with its human counterpart and is valuable for studying mouse LCs (Valladeau et al. 2002a).

This previous study also shows that mouse LCs from epidermal bulk cultures mature into potent immunostimulatory DCs within 3 days, typically losing BGs, as demonstrated by electron microscopy. Fresh mouse LCs expressed langerin, but 3-day cultured epidermal cells showed reduced levels or became langerin^{neg}, indicating that langerin's expression is restricted to immature DCs.

These findings demonstrate that langerin regulation mirrors its human counterpart that is increased by TGF and decreased during LC maturation (Valladeau et al., 2002a).

LCs & DCs proportions in humans and in mice

In human skin, epidermal LCs constitute approximately 1.86% of epidermal cells, and are primarily located near the basement membrane in the suprabasal layers of the epidermis, especially within the stratum spinosum (Bauer et al., 2001). They form a dense, interconnected network that extends dendritic processes between keratinocytes, facilitating efficient antigen surveillance. DCs can be found in the epidermis during inflammatory conditions, but under steady-state conditions, LC subset is the most abundant in the skin. In mucosal tissues, DCs are the dominant population (Bertram et al., 2023; Vine et al., 2024). In contrast, in anogenital skin (such as the labia, foreskin, glans penis, and perineum), both LCs and DCs are present in roughly equal proportions and are distributed throughout the epithelial layer. However, in anogenital type II epithelium (including areas such as the vagina, ectocervix, fossa navicularis, and anal canal), LCs are almost absent, and DCs are the predominant cell type. This highlights the regional and functional differences in the distribution of LCs and DCs across various tissues and conditions (Bertram et al., 2019).

In mice, the density of epidermal LCs varies according to the anatomical site. For instance, studies have reported LCs densities ranging from 600 to 1,500 cells/mm² in areas such as the ear, back, and footpad. On the other hand, certain regions like the tail exhibit lower densities, as few as 110 cells/mm² observed in C57BL/6J mice. However, a research indicated that the ratio of LCs to epithelial basal cells in mice remains consistent across different skin regions, suggesting a coordinated regulation between epithelial and immune cell population (Bergstresser et al., 1980; Park et al., 2021).

Thus, it is important to highlight that the proportion of LCs within the epidermis varies between humans and mice, reflecting species-specific differences in skin immune architecture.

1.2.2. Langerin Expression in various Tissues in Mice & Humans

Mlangerin is expressed by some cells in the bone marrow cultures with TGF- β . DCs in mice thymic medulla are langerin⁺, while langerin⁺ cells are rare in LNs and spleen. Mlangerin mRNA was found in nonlymphoid tissues like the lung, liver, and heart. The role of TGF- β in expanding the langerin⁺ subset in mice aligns with its effects on up-regulating hlangerin in hLC cultures (Valladeau et al., 1999) and its essential function in mouse LC development (Borkowski et al., 1996). Similar to hlangerin, BGs form on transfection of mlangerin cDNA into fibroblasts (Valladeau et al., 2002a).

Regarding the origin of LCs and DCs in mice and humans, several studies were done which showed that langerin is abundantly expressed by mouse epidermal LCs, both at mRNA and protein levels. Using mAb HD24, langerin could not be detected in other epidermal cells other than LCs and could only be detected in scattered DCs in the dermis. Langerin should thus be a highly useful molecular marker for identification and functional studies of mLCs. Mice lack CD1a, a useful marker of human LCs. Mouse LCs do express DEC205, but this molecule is also widely expressed by mature DCs in lymphoid tissue. These findings raise several questions. First, the possibility that langerin⁺ thymic DCs and LCs have a common origin. Second, the expression of langerin by thymic DCs is consistent with the description of BGs in these cells, in both mice (Ardavi'n, 1997) and humans (T. Hoshino et al., 1970). Third, the presence of langerin on thymic DCs opens the interesting perspective that langerin may play a role in T cell selection, possibly by endocytosis of self-derived mannosylated Ags. As to the expression of langerin in diverse other tissues, in addition to skin, mlangerin mRNA is detected in some nonlymphoid organs. In particular, in lung tissue, consistent to the expression of hlangerin in epithelium lining the human airways (Valladeau et al., 1999; Xuan et al., 2022). The significance of mlangerin mRNA in liver and heart remains to be explored. **(Figure 4)**

Previous (Valladeau et al., 2000) and current findings suggest that langerin has a specific role in endocytosis of foreign antigens (e.g., mannosylated microorganisms) in peripheral tissues, as well as self-antigens in the thymus (Valladeau et al., 2002a). **(Figure 4)**

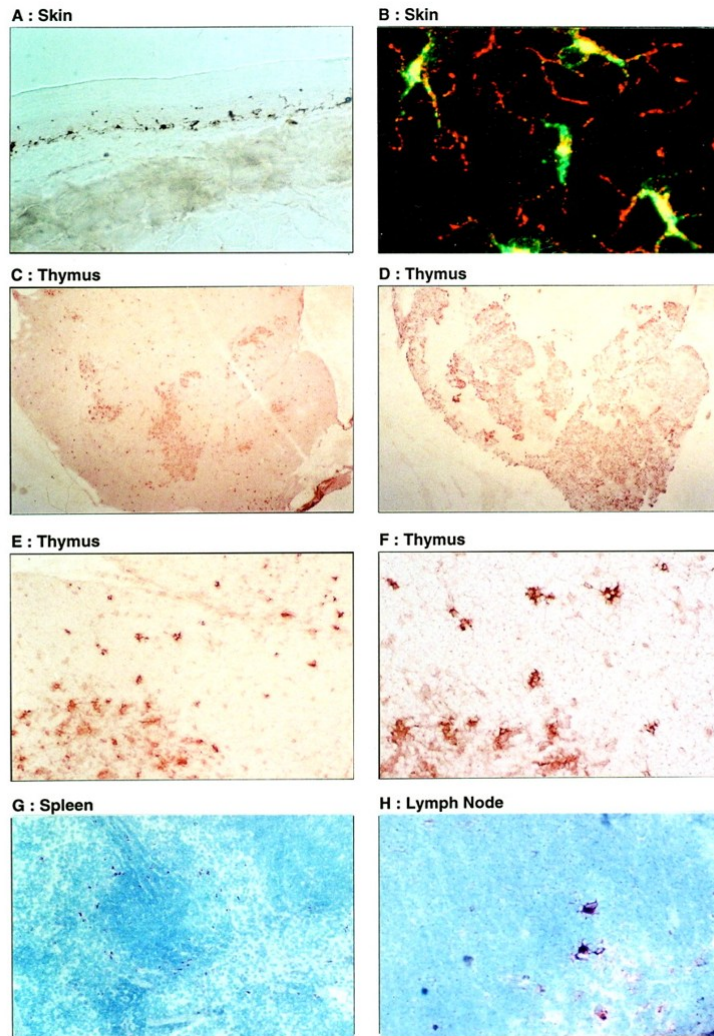


Figure 4 Expression of mlangerin in different mouse tissues in vivo (Valladeau et al., 2002a)

J Immunol. 2002;168(2):782-792. doi:10.4049/jimmunol.168.2.782

Key: mlangerin is expressed by LCs on frozen skin sections with anti-mlangerin polyclonal Ab (A). Double staining with anti-mlangerin mAb HD24 (red) and FITC-anti-MHC-II mAb 2G9 (green) shows expression on the epidermal sheet (B). In thymus, polyclonal anti-mlangerin (red) highlights mlangerin DC in the medulla (C) and cortex (E), as shown by DEC205 serial staining (D). At higher magnification, mlangerin DC display dendritic morphology (F). In spleen, perifollicular areas show some mlangerin cells (G), similarly observed in lymph nodes (H). Control Abs showed no staining (not shown). Magnification: A, 200; B, 1000; C and D, 40; E, 200; F, 400; G, 100; and H, 400.

Langerin expressed in vaginal epithelial DCs (VEDCs) in humans & mice

Recent advances in high-parameter single-cell technologies have significantly changed our understanding of the human SSE myeloid-derived dendritic cells (MNP), particularly the critical role of DCs in type II mucosal tissues. In 2018, Pena-Cruz et al. described a novel subset of DCs in the steady-state human vaginal epithelium, referred to as (VEDCs). Although VEDCs express langerin (CD207), a marker typically associated with LCs, they do not contain the characteristic BGs, which are a distinguishing feature of LCs. This finding indicates that VEDCs are not LCs (Pena-Cruz et al., 2018). Similarly, other DC subsets, such as DC2s, can also express langerin in other human tissues. However, VEDCs differ from LCs in that they do not express the lectin receptor DC-SIGN/CD209, and they can be distinguished from LCs by their expression of CD1c. This distinction was key to understanding that VEDCs represent a unique subset of DCs, separate from the classical LCs (Pena-Cruz et al., 2018).

In mice, although the vaginal epithelium differs in structure from that of the human vaginal epithelium, similar langerin expressing vaginal mucosal APC populations which are distinct from those in other mouse mucosal areas are also found. The functions of these APCs were investigated after intravaginal infection with Herpes Simplex Virus-2 (HSV-2). In mice, epidermal LCs originate from embryonic fetal liver and yolk sac progenitors (J. Z. Zhou et al., 2018), also self-renew locally in the skin under steady state (Merad et al., 2008), additionally they can be replenished from blood monocytes following skin injury (Ginhoux et al., 2007), but whether this is true for mouse cervicovaginal LCs (cvLCs) is unknown. Mouse vaginal DCs were found to comprise at least 3 populations (CD11b⁺F4/80^{hi}, CD11b⁺F4/80^{int} and CD11b⁺–F4/80[–]) with very low langerin expression that are mostly derived from bone marrow non monocytic precursors under steady state but can be replenished by blood Ly-6Chi monocytes after vaginal HSV-2 infection. These cells also contain cup-shaped granules instead of the racquet-shaped BGs found in skin LCs (Iijima et al., 2008). It is unclear which of these vaginal DC populations migrates to the DLNs upon vaginal infection, and their contribution in immunity versus tolerance is also unclear. However, vaginal submucosal CD11b⁺ DCs, but not cvLCs, were found to be capable of inducing vaginal TH1 responses to HSV-2. This echoes previous findings on human studies and suggests tolerogenic functions of cvLCs (Pena-Cruz et al., 2018).

Comparing studies on both humans and mice, we conclude that there are significant differences in langerin expression and cellular characteristics between human and mouse VEDCs. While human VEDCs express langerin and lack BGs, mouse VEDCs exhibit low langerin expression

and possess some structurally different BGs. These distinctions highlight the importance of being cautious in interpretation when extrapolating findings from mouse models to human biology, particularly in the context of mucosal immunity and pathogen interactions.

Langerin in lymph nodes of humans and mice

The utilisation of the anti-langerin antibodies altered the traditional view that all langerin⁺ cells in mice LNs are LCs migrating from the epidermis (Stoitzner et al., 2003; Valladeau et al., 2002a). Now, we can recognise at least three subsets of langerin-expressing DCs in different mice strains in the skin DLNs. **(Table 3)** (i) LCs that have migrated from the epidermis are characterized by high expression levels of MHC-II, CD40, CD205, CD86, CCR7, and the absence of CD8. Moreover, they also express relatively less CD11c. (ii) Migrated dermal langerin⁺ DCs which look similar to the phenotype they had while they were still in the dermis. They express CD103, but largely lack EpCAM, and they are found in the CD11c⁺/CD8^{negative} fraction of DCs. (iii) A resident subset, presumably blood-derived population of langerin⁺ DCs has been described in spleen and LNs. These cells can be distinguished from migratory langerin⁺ cells by their expression of CD8, and high levels of CD11c, and by their lack of CCR7. It is of importance to highlight that the frequency of occurrence of this subset is markedly dependent on the mouse strain. In mostly all other non-skin DLNs, such as the MLNs, this CD8⁺ subset comprises almost all langerin⁺ cells. Similarly, all langerin⁺ DCs in the spleen of mice belong to the CD8⁺ subset. **(Table 3)**

Table 3 Subsets of langerin-expressing DCs in the skin DLNs of mice (Romani, Clausen, et al., 2010)

Subset	MHC-II	CD86	CCR7	CD11c	CD8 α
Langerhans Cells (LCs)	++	++	++	++	—
Dermal langerin ⁺ DCs	+	++	++	++	—
Resident langerin ⁺ DCs	+	+	—	++	+

Key: This table summarizes the expression of key surface markers on different subsets of langerin-expressing DCs in mice (Romani, Clausen, et al., 2010) ++: High expression, +: Moderate expression, —: Not expressed. Resident langerin⁺ DCs are found within tissues and are less migratory compared to LCs or dermal langerin⁺ DCs. They express moderate levels of MHC-II and CD86 and low levels or no expression of CCR7, indicating they play a role in local immune surveillance rather than migration to lymph nodes.

The bulk of langerin⁺ cells in the skin-draining LNs of mice are found in the T-cell areas (Cheong et al., 2007; Stoitzner et al., 2003; Valladeau et al., 2002a). In the spleen, a recent analysis (Idoyaga et al., 2009) revealed that in the steady state most langerin⁺ DCs localize to the marginal zone around white pulp nodules into which blood vessels flow. Meaning that they are ideally placed to take up antigens which are flushed into the spleen by the bloodstream (Idoyaga et al., 2009). This subset elicit extraordinary capacity to cross-present antigens and to promote Th1 responses (Maldonado-López et al., 1999).

A huge gap exists between our knowledge on langerin expression in DCs of murine and human lymphoid organs. All the above-mentioned findings are in mice. Occasional few spottings of BGs in human LNs were reported (Romani, Clausen, et al., 2010; Vernon et al., 1973). Nevertheless, Angel et al. (Angel et al., 2009) recently provided a detailed analysis of normal human LNs. Langerin⁺ cells, all of them coexpressing CD1a, were found in the T-cell area in the paracortex of skin DLNs. About half of these langerin⁺ DCs were phenotypically mature as indicated by their expression of DC-LAMP/CD208. Epidermal LCs and langerin^{neg} dDCs settle in distinct regions in murine LNs (Kissenpfennig, Henri, et al., 2005), while in human LNs, CD1a⁺/langerin⁺ and CD1a⁺/langerin^{neg} DCs are intermingled in the same area (Romani, Clausen, et al., 2010). See **(Table 4)**

To sum up, human and mouse LCs have generally similar phenotypes, with some unique surface markers for each species. Both are easily recognized in the epidermis by their expression of CD45 (LY5), MHC-II, and the CLR langerin (CD207), which is key to BGs formation (Figdor et al., 2002; Merad et al., 2008; Takahara et al., 2002; Tripp et al., 2004; Valladeau et al., 2002a). They also both express EpCAM and E-cadherin (Tang et al., 1993). Human DCs in skin DLNs remain poorly understood owing to the difficulty of obtaining normal human lymphoid tissue. **(Table 4)**

Table 4 DC populations in the skin of mice and humans & skin DLNs in mice (Bigley et al., 2015; Merad et al., 2008)

	Skin				Skin-Draining Lymph Nodes				Skin			
	Mice				Mice				Humans			
Cellular markers	LCs	Migrating LCs	Langerin+ DCs	Langerin- DCs	Migrating LCs	Langerin+ DCs	Langerin- DCs	Langerin+ CD8+ DCs	LCs	Migrating LCs	Langerin- DCs	Langerin+ DCs (DC2)
Langerin	+++	++	++	-	++	++	-	+	+++	++	-	++
Birbeck Granules	++	+	-	-	+	-	-	-	++	+	-	+ or -
CD45	+	+	+	+	+	+	+	+	+	+	+	+
MHC Class II	++	++	++	++	+++	+++	+++	++	++	+++	++ (↑)	ND
CD11c	+	++	++	++	++	++	++	+++	+	+	+	++
CD205	++	+++	-	++	++	-	++	+	-	-	-	ND
CD11b	+	+	Low	++	+	Low	++	-	+ or -	+ or -	++	++
F4/80	+	+	-	+	+	-	+	-	ND	ND	ND	ND
E-cadherin	++	+	ND	ND	+	ND	ND	ND	++	+	-	ND
EpCAM	++	++	-	-	++	+ or -	-	-	+	+	-	-
CD8	-	-	-	-	-	-	-	++	ND	ND	ND	ND
CD103	-	-	++	-	-	++	-	+ [§]	ND	ND	ND	ND
CCR6	+	-	ND	-	-	ND	-	-	+	-	-	ND
CCR7	-	+	↑	↑	+	+	+	+	-	+	↑	ND
CD1a	-	-	-	-	-	-	-	-	+++	+++	++	++
Turnover	Slow	Slow	Fast	Fast	Slow	Fast	Fast	Fast	ND	ND	ND	ND
Origin	Local	Local	Blood	Blood	Local	Blood	Blood	Blood	ND	ND	ND	ND
Response to Radiation	Resistant	Resistant	Sensitive	Sensitive	Resistant	Sensitive	Sensitive	Sensitive	ND	ND	ND	ND

Key: This table shows various markers and characteristics for LCs, migrating LCs, langerin+ and langerin- DCs in both skin and skin-draining lymph nodes in mice and humans, providing insights into their functions, origins, and responses (Bigley et al., 2015; Merad et al., 2008). DCs in the skin can be found in the epidermis (LCs) or the dermis (migrating LCs, langerin+ DCs and langerin- DCs). Expression of the cellular markers is marked by +, where + signifies low levels and +++ signifies high levels; - signifies lack of expression; ↑ signifies upregulation of expression during cell maturation. CCR, CC-chemokine receptor; DC, dendritic cell; EpCAM, epithelial-cell adhesion molecule; LC, Langerhans cell; ND, not defined; §, Heterogeneous expression.

Langerin: A marker for LCs and some DCs. Birbeck Granules: Characteristic of LCs, involved in antigen processing. CD45: A general leukocyte marker. MHC-II : A marker for antigen-presenting cells. CD11c: A marker for dendritic cells. CD205: A receptor involved in antigen uptake. CD11b: A marker for myeloid cells. F4/80: A

macrophage marker. E-cadherin: A marker for epithelial cells. EpCAM: A marker for epithelial cells. CD8: A marker for cytotoxic T cells. CD103: A marker for tissue-resident DCs. CCR6: A chemokine receptor involved in migration. CCR7: A chemokine receptor involved in migration to LNs. CD1a and CD1d: Lipid antigen-presenting molecules

Langerin expression in mesenteric lymph nodes (MLNs) in mice & humans

There have been several reports about langerin expression on DCs in non-skin tissue; however, little is known of the role of langerin⁺ DCs in such tissues, especially the gut. Langerin expression was found on thymic DCs, blood-derived CD8 α ⁺ DCs from secondary lymphoid organs like spleen and LNs, and langerin⁺ CD11b⁻ CD103⁺ DCs in lung and liver. Langerin⁺ DCs have also been noted in spleen and MLNs. In the intestine, langerin⁺ DCs exist in serosal layers, and their expression can increase with systemic lipopolysaccharide (LPS), oral live bacteria, immunization or nutrient deficiency. All langerin⁺ DCs, except epidermal LCs, express CD103 (S. Chang et al., 2010; S. Chang & Kweon, 2010; S.-Y. Chang et al., 2008). The results of Chang & Kweon study on mice also reveal that the generation of langerin⁺ DCs in the gut-associated lymphoid tissue (GALT) is tightly regulated by Retinoic Acid (RA) and that these cells have a suppressive role for maintaining gut homeostasis in the absence of RA. Thus, these findings highlight the importance of dietary and microenvironmental factors in shaping DCs differentiation, distribution and function in mucosal tissues (S. Chang & Kweon, 2010).

Topical transcutaneous immunization can induce langerin⁺ CD8 α ⁻ DCs in MLNs, which accordingly produce antigen-specific immunoglobulin A (IgA) antibodies in the intestine. Additionally, the expression of langerin can be increased in intestine DCs by the use of systemic LPS and oral live bacteria (S. Chang & Kweon, 2010).

The research by Chang & Kweon, 2010, focuses on the role of langerin⁺ DCs in the GALT and their connection to the skin immune system. It highlights several important issues that need further exploration, for instance, the exact origin of langerin⁺ DCs in the MLNs which remains unclear. Additionally, the mechanisms through which these DCs acquire antigens from the skin and the factors driving their migration to the MLNs (most probably by active transport by LCs rather than simple diffusion to LNs) after tissue challenge inflammation (TCI) are still not well understood. Another important aspect to investigate is whether TCI alters RA concentrations in the GALT, potentially creating a favorable environment for langerin expression on DCs. Regarding Vitamin A deficiency (VAD) mice, although RA is known to regulate gut homeostasis, including promoting Tregs and inhibiting Th17 cells, VAD mice do not show

significant gut inflammation despite enlarged MLNs. One possibility is that in the absence of RA, langerin⁺ DCs may play a suppressive role, preventing inflammation in the gut. To address this, further investigation into the role of langerin⁺ DCs and the function of langerin on these cells, as well as the influence of RA deprivation on other gut cell types, is necessary (S. Chang & Kweon, 2010).

In humans, also some studies have identified some langerin⁺ cells in the gut lamina propria which does not contain SSE (S. Chang et al., 2010; S. Chang & Kweon, 2010; S.-Y. Chang et al., 2008). However, this subset is not yet well documented, although langerin expression is prominent and well studied in the skin and mucosal tissues. Further research is needed to elucidate the extent and functional significance of langerin⁺ DCs in human MLNs. MNPs including LCs and DCs, represent a critical and powerful category of phagocytic APCs. These cells fulfil a pivotal function in human skin and mucosa by detecting microbial presence, which they subsequently phagocytose and present to the adaptive immune system, thereby initiating an immune response to pathogenic microbes or promoting immune tolerance to commensal microbes (Vine et al., 2024). Based on the current data, future studies should be carried out targeting implications on mucosal vaccines (S. Chang & Kweon, 2010).

As a conclusion to the findings of this study, the development of langerin⁺ DCs is critically dependent on RA, particularly within the GALT, indicating that VAD can directly influence DC subset composition. These results support the notion that RA plays a pivotal role in shaping intestinal immunity. Consequently, previous *in vivo* studies on VAD should be revisited taking into consideration the role of newly identified langerin⁺ DCs subset, especially within GALT in both mice and humans (S. Chang & Kweon, 2010).

Langerin expressed in epithelial DC population in lungs of mice and humans

Steinman et al., 2003 study on mice (Steinman et al., 2003) showed that the major functional characteristic of DCs is their potent Ag presentation capability. Apparently, DCs have been classified according to their surface markers, phenotype and functions into myeloid, lymphoid, and plasmacytoid DCs (Steinman et al., 2003). In mice, five populations of lymph node DCs have been described (Henri et al., 2001). Among them are the double-negative CD4⁻CD8⁻CD11b⁺ myeloid DCs, the CD4⁺CD11b⁺ myeloid DCs, and the CD8⁺ lymphoid DCs present in both spleen and LNs, plus two additional LN populations that are either CD8⁺DEC-205^{high} or CD8^{low}DEC-205^{low} (Sung et al., 2006).

Although different DC subsets are known to perform distinct functions, their presence in mouse lungs has not been clearly defined. Though in the study of Sung et al., three major DC populations in the lungs were identified. Two of these populations are the myeloid and plasmacytoid DCs, which are well-characterized in other lymphoid organs. The third and largest population is an Integrin E (CD103)⁺ lung mucosal DC & I-A⁺ highCD11c⁺ high DC population. This epithelial DC population was found to express high levels of langerin & resides in both mouse lung mucosa and the vascular wall, where it expresses a wide range of adhesion and costimulatory molecules, avidly endocytoses, and efficiently presents antigens (Sung et al., 2006).

In human airways, a specific DC subset was also identified that expresses surface langerin and to current date, such DC subset does not exist in the blood. Moreover, it was shown that these langerin⁺ lung DCs are distinct from epidermal LCs and express far lower levels of both langerin and CD1a compared to true LCs, and they do not contain BGs. Additionally, they have their counterparts in various human tissues, such as dermis, liver, and tonsils (Bigley et al., 2015; De Monte et al., 2016; Patel & Metcalf, 2018). The study of Patel & Metcalf, 2018, also suggested that these DCs are a subset of the CD1a⁺ CD206⁻ DCs identified by Desch et al. rather than monocyte-derived CD1a⁺ CD206⁺ cells (Desch et al., 2016; Patel & Metcalf, 2018; Xuan et al., 2022).

Future studies could make use of this important DC population and further studies on humans should be conducted to enhance clinical implications making use of the power of antigen presenting functions of these DC subsets.

1.2.3. Langerin expression, proliferation & homeostasis in mice and humans

In mice, according to the study of (Chorro et al., 2009), LCs in the epidermis, despite being of myeloid origin, they have been shown to renew independently of the bone marrow, suggesting the presence of a progenitor source within the dermis or epidermis. The study of (Chorro et al., 2009) found that a single wave of LC precursors is recruited to the epidermis of mice around embryonic day 18 (E18). These precursors then acquire a dendritic morphology, along with expression of MHC-II, CD11c, and langerin shortly after birth. Following birth, langerin⁺ cells undergo a significant increase in proliferation between postnatal day 2 (P2) and postnatal day

7 (P7), expanding their numbers by 10 to 20 times. After the first week of life, langerin⁺ cells in the epidermis continue to proliferate at a lower level. However, in a mouse model of Atopic Dermatitis (AD), a keratinocyte signal was found to trigger an increase in LC proliferation within the epidermis. Similar findings were also reported in the epidermis of human AD patients (Chorro et al., 2009). The findings from the study of (Chorro et al., 2009) on mouse models suggest that while monocytes and classical DCs are continuously renewed from proliferating bone marrow-derived myeloid progenitors (MDPs) (Fogg et al., 2006; K. Liu et al., 2009), LCs in the epidermis are renewed through the proliferation of resident, differentiated LCs. A key discovery from this study is that resident langerin⁺ LCs can be induced to proliferate substantially by signals from keratinocytes in adult mice. This indicates that epidermal LCs are capable of expanding within the epidermis independently of bone marrow input, both under normal conditions and during inflammation (Chorro et al., 2009). However, several questions remain unanswered, including the origin of the epidermal LC precursors and the mechanisms through which these precursors enter the epidermis around E18. One possibility is that the precursors recruited to the epidermis at E18 may come from bone marrow-derived cells, such as MDPs, following the transition of fetal hematopoiesis from the fetal liver to the fetal bone marrow around E15 (Bertrand et al., 2005; Wolber et al., 2002). Alternatively, the epidermal precursors may derive from CX3CR1⁺ cells identified in the dermis of fetuses at E14, which could originate from the fetal liver or yolk sac (Chorro et al., 2009).

In humans, LCs are detected in the fetal epidermis as early as 9 weeks of gestation, expressing markers such as HLA-DR and ATPase (Becerril-García et al., 2020; Romani, Clausen, et al., 2010). During the second trimester, these cells acquire CD1c, followed by langerin and then CD1a (Romani et al., 2012). Regarding their proliferation, high proliferation rates of CD45⁺ leukocytes were observed in fetal skin, which decrease after birth. In adults, LCs are considered long-lived cells that maintain their density in the epidermis through low-level proliferation from local precursors (Becerril-García et al., 2020; Chorro et al., 2009; Romani, Clausen, et al., 2010; Romani & Young, 2015)

To summarise, both species exhibit early recruitment of LC precursors to the epidermis, but vary in timing and sequence of marker expression. Mice show a pronounced postnatal proliferation of langerin⁺ LCs, while in humans, high proliferation occurs during fetal development, decreasing after birth. Additionally, in both species, LCs are maintained in the epidermis through self-renewal, independent of bone marrow-derived precursors under

steady-state conditions. These observations reflect species adaptations to their respective developmental timelines and immune system maturation.

Origin of langerin⁺ DCs in mice & humans

This diagram (**Figure 5**) presents a hypothetical model of cutaneous DCs differentiation pathways in mice under steady-state conditions. Epidermal LCs are maintained by radioresistant hematopoietic progenitors that establish themselves in the skin before birth, while most dermal DCs originate from circulating DC precursors. Studies suggest that circulating blood-derived CCR2⁺ DCs are continuously recruited to the dermis. This recruitment is guided by E and/or P selectins in transplanted animals where E and P selectins are molecules on blood vessels that act like "sticky signals", helping immune cells like CCR2⁺ DCs find their way out of the blood and into the skin, especially during inflammation or transplantation. In response to signals from the skin, CCR2⁺ DCs differentiate into dermal langerin⁺ DCs, though they may also differentiate into dermal langerin^{neg} CX3CR1⁺ DCs. Dermal langerin⁺ DCs transiently capture skin antigens in the dermis before migrating to the skin DLNs, where they present skin-derived peptides in the context of MHC molecules. Both LCs and dDCs require CCR7 for migration to the T cell areas of the skin DLNs (Ginhoux et al., 2007).

In conclusion, LCs are ontogenetically similar in mice and humans, embryonically derived and self-renewing, with monocyte-derived replenishment only during inflammation. However, there is species difference in the lineage of langerin⁺ dDCs which are often CD103⁺ cDC1 in mice, whereas in humans they are usually CD1c⁺ cDC2-like (Becerril-García et al., 2020; Romani, Clausen, et al., 2010; Romani & Young, 2015).

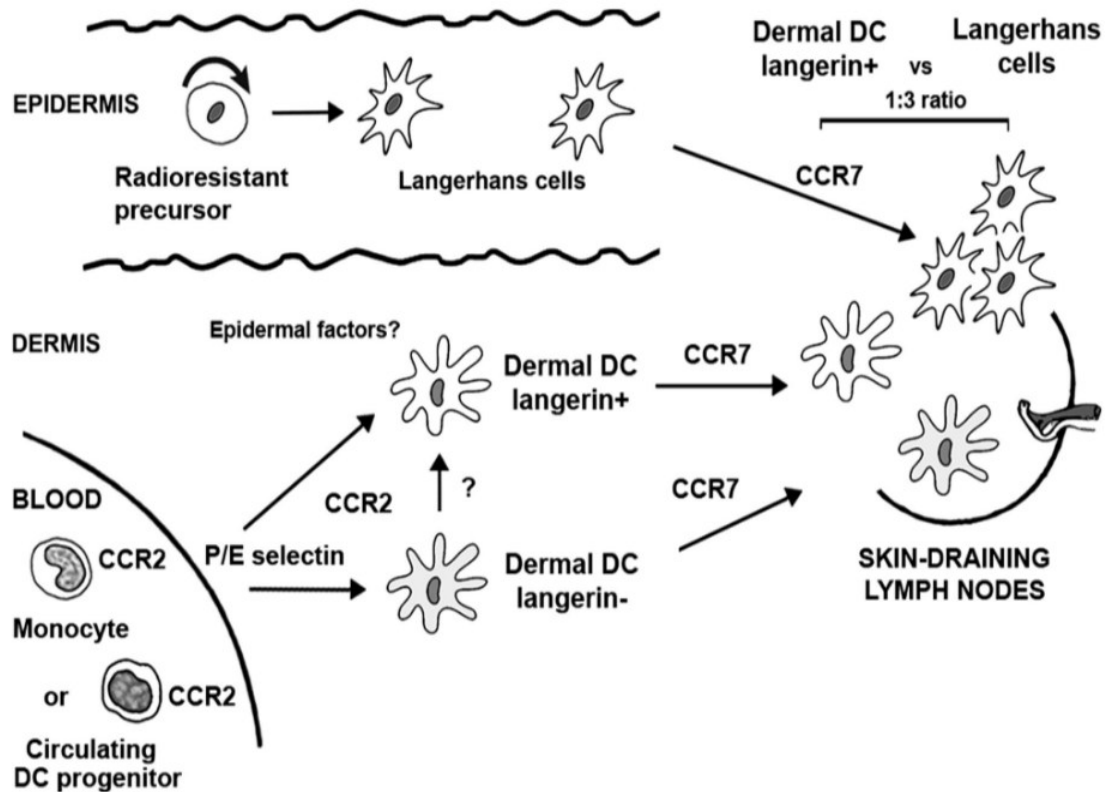


Figure 5 *Origin of langerin⁺ DCs in mice* (Ginhoux et al., 2007)

1.3. Role of Langerin

In mice, it was shown that langerin⁺ dDCs prime CD8⁺ T cells while LCs induce cross-tolerance (Flacher et al., 2014).

Does langerin in mLCs primarily engage in immune activation, or does it also promote immune tolerance? In vivo, the relative involvement of skin DCs versus CD8⁺ DCs in priming effective immune responses is influenced not only by the targeted subset but also by various other factors. These factors include the type, quantity, and formulation of the antigen, the site of immunization, the endocytic pathway and intracellular degradation processes, in addition to the maturation signals received by the DCs (Blander & Medzhitov, 2006; Chatterjee et al., 2012; Delamarre et al., 2003; Flacher et al., 2014; Idoyaga et al., 2011; Spörri & Reis E Sousa, 2005; Tacke et al., 2007).

The conclusion of Flacher et al., 2014 study demonstrates that dDCs play a key role in the activation of CD8⁺ T cells. Cross-tolerance induced by targeting langerin is dependent on LCs,

but not on langerin⁺ dDCs. This was demonstrated by investigating the capacity for cross-presentation among skin DC subsets, focusing on the priming of cytotoxic responses in a murine model. This model involved antigen uptake through langerin/CD207 receptor, which is expressed on both LCs and langerin⁺ dDCs; two crucial cutaneous DC subsets (Flacher et al., 2014).

1.3.1. Role in cross presentation & priming of immune response

In humans, the influence of langerin⁺ dDCs and LCs on immune responses is largely determined by the type of adjuvant used. Understanding the functionality of both DC subsets in both mouse and human skin is crucial, especially now that DC-targeted vaccination conjugating ligands with anti-tumor drugs has now reached clinical trials (Dhodapkar et al., 2014).

In the study done by Flacher et al. (2009) on mice, titled *"Targeting of epidermal Langerhans cells with antigenic proteins: attempts to harness their properties for immunotherapy"*, researchers explored the role of langerin (CD207) in antigen uptake and presentation by epidermal LCs. Langerin, as a CLR receptor is recognized for its ability to bind glycosylated antigens, internalize them, and direct them into antigen-processing pathways for presentation to T cells. The study demonstrated that targeting antigens specifically to LCs via langerin enables efficient antigen internalization and subsequent presentation to T cells. This approach proved effective in eliciting antigen-specific immune responses, underscoring the potential of langerin as a strategic target for antigen delivery in skin-based immunotherapies. However, the authors emphasized that the immune outcome of langerin-mediated antigen targeting is highly context-dependent. In the absence of maturation signals or appropriate adjuvants, this antigen delivery route may promote tolerance rather than immunity. This finding highlights the critical influence of the immunological environment on the direction of the immune response (Flacher et al., 2009).

The aim of a more recent study by Flacher et al. 2014 was to manipulate antigen-specific CD8⁺ T cell killing through DCs in vivo, either to generate robust immunity or immune tolerance. The findings were as follows: First, despite presenting similar antigens to CD8⁺ T cells, langerin⁺ dDCs and LCs, each subset had distinct abilities to prime cytotoxic immune responses. Second, using different adjuvants allows for independent harnessing of the unique potentials of

these simultaneously targeted DC subsets. Third, the study challenges the prevailing idea that DCs activated by danger signals through TLRs are always predisposed to induce strong immune responses (Flacher et al., 2014).

Inflammatory conditions typically trigger the maturation, activation, or migration of LCs. The increased migration of LCs during inflammation can cause partial depletion of epidermal LCs, a process that is often compensated by other LC subsets entering the epidermis in various mouse models. Different LC subsets respond differently to inflammatory stimuli.

Similar to the monocyte-derived LC subset that emerges during inflammation in mice, the number of inflammation-associated hLC subsets also increases under inflammatory conditions. However, hLC subset may additionally have anti-inflammatory effects, unlike their mouse counterparts (Kaplan, 2017; Zhu et al., 2024).

1.3.2. Role in Pathogen Recognition & Uptake

LCs contain specialized organelles, with their dendritic extensions, forming a dense network that serves as the first line of defence against invading pathogens. By extending their dendrites through the tight junctions of the epithelium, LCs actively survey the skin and mucosal surfaces for pathogens and other danger signals (Van Der Vlist & Geijtenbeek, 2010).

The recognition of pathogen surface polysaccharides by glycan-binding receptors is a key component of the innate immune response. Several members of the CLR family such as langerin function as pattern recognition receptors (PRRs), aiding in pathogen uptake, antigen processing, and immune modulation (Hanske et al., 2017b).

Role of LCs against pathogens versus dDCs

Geijtenbeek's group discovered that human LCs can uptake HIV particles and route them into BGs, where instead of transmitting the virus to T cells, the virions are degraded (De Witte et al., 2007). This contrasts with dDCs, which spread HIV to CD4⁺ T cells. This anti-viral function of LCs depends on the langerin molecule, highlighting an innate defence mechanism against HIV (M. A. W. P. De Jong et al., 2010; Hladik & McElrath, 2008). Additionally, LCs have been

found to play a role in regulating dermal blood flow by producing prostanoid synthases that generate vasodilatory prostaglandins E2 and D2 (Van Der Vlist & Geijtenbeek, 2010).

In a mouse model, depletion of LCs abolished flushing induced by nicotinic acid, a common side effect of niacin therapy for dyslipidemia. This suggests that LCs are involved in the regulation of skin vasodilation, which could help manage side effects of niacin treatment. These findings reveal that LCs have both immune and physiological roles, offering new insights into their function and potential future therapeutic applications (Van Der Vlist & Geijtenbeek, 2010).

Langerin in bacterial infection / in viral infection

In both mice and humans, the skin and mucosa are physical barriers that shield the body from pathogens it is exposed to. The two layers: the epidermis or outer mucosa, and the dermis or sub-mucosa separated by the basement membrane contain specialized DCs belonging to the immune system (Steinman & Banchereau, 2007). As professional antigen-presenting cells, these DCs continuously sample their environment for invading pathogens. Upon capturing a pathogen, DCs undergo maturation, during which they upregulate CCR7, signalling the initiation of migration towards the LNs. In addition to CCR7 upregulation, DC maturation involves several other functional and phenotypic changes, including induction of formation of BGs involved in Ag processing, increased expression of MHC-II, co-stimulatory molecules CD86 and CD80, and the production of immune-modulating cytokines (Mellman & Steinman, 2001). Depending on the nature of the antigen, DCs secrete various cytokines that shape the adaptive immune response.

In mice, a direct immunogenic role for LCs was observed in viral infection. Carbone, Heath and colleagues proposed that antigen-transporting LCs are taken up by resident CD8⁺ DCs in the LNs, which then (cross) present the microbial antigens to CD4 and CD8 cells (Carbone et al., 2004; Heath et al., 2004). They also suggested that langerin⁺ dDCs play a significant immunogenic role. This theory, however, may not be applicable to all experimental settings or in vivo situations. Nevertheless, it has served as an interesting hypothesis that has prompted further research.

Additionally, it is currently unclear how the CD8⁺ and CD8-negative subsets of DCs or langerin⁺ cells in murine lymphoid organs correspond to those in human lymphoid organs. Limited studies have characterized such subpopulations (Galibert et al., 2005), with the CLR

Clec9A identified as a potential marker for the putative human counterpart of CD8⁺ DCs (Caminschi et al., 2009).

A recent review about LCs and langerin discusses the role of langerin in protection against viruses, its structure and polymorphisms influence the function of LCs (Van Der Vlist & Geijtenbeek, 2010). LCs express a range of PRRs, including TLRs and CLRs, which appear to be more specific for viral recognition and less for bacterial detection. Unlike dDCs, LCs do not express TLR-4 and exhibit low levels of TLR-2 and TLR-5, which are known to recognize bacteria. This suggests that LCs are less responsive to bacteria, potentially protecting against excessive sensitivity to commensal bacteria that naturally inhabit the skin (Van Der Vlist & Geijtenbeek, 2010)

In humans, Hunger et al., study also suggested an antibacterial role of human langerin on LCs (Hunger et al., 2004). Additionally another study on human skin explants proved that langerin prevents HIV-1 transmission by LCs via internalizing the virus into BGs and degrading it (De Witte et al., 2007).

Role of langerin in HIV-1

LCs, being equipped with PRRs, can detect and respond to a wide range of pathogens. One important PRR is langerin. Immature LCs have been shown to protect against HIV infection through langerin (Van Der Vlist & Geijtenbeek, 2010).

Recent research suggests that langerin interacts with various pathogens such as HIV-1, mycobacteria, and fungi. While CLRs are known to influence adaptive immune responses, the specific role of langerin on LCs in promoting these responses is not yet fully understood (Van Der Vlist & Geijtenbeek, 2010).

It is useful to highlight that in humans, langerin binds HIV-1 gp120 via high mannose glycans leading to viral internalization and degradation preventing its transmission to T cells. As for mice, no known role in HIV-1, yet mostly studied in fungal infections such as *Candida albicans* and viral infections like HSV & Vaccinia virus, in addition to some bacteria (De Witte et al., 2007; Valladeau et al., 2000).

After Kervevan et al. experiments, there was evidence that human LCs, when properly targeted, are capable of efficiently inducing T follicular helper (T_{fh}) cells and B cells responses in the germinal centre (Kervevan et al., 2021). As a result, targeting langerin receptor on human LCs

appears to be a promising strategy for developing an effective HIV-1 vaccine (Kervevan et al., 2021).

In short, the advances in DC biology over the past decade have opened the door to the development of innovative HIV-1 vaccines. Targeting human LCs is a particularly promising approach, given their innate ability to drive the differentiation of Tfh cells and their capacity to transport vaccine antigens directly to the DLNs, specifically to the B cell zones, where humoral responses are initiated. Therefore, targeted approaches to human LCs should be further explored for future clinical studies (Kervevan et al., 2021).

Role of langerin & DC-SIGN in HIV-1

Due to the similarities between the CRD domain of DC-SIGN and langerin, it is tempting to speculate that langerin shares a similar pathogen recognition profile with DC-SIGN. Indeed, both langerin and DC-SIGN bind to HIV-1 (De Witte et al., 2007; Geijtenbeek et al., 2000) and *Mycobacterium tuberculosis* (Hunger et al., 2004; Maeda et al., 2003), and both CLRs are capable of internalizing antigens and processing them for antigen presentation. However, their roles in HIV-1 transmission are quite different; while DC-SIGN facilitates HIV-1 transmission, langerin degrades HIV-1, preventing its transmission. This distinct function of langerin may reflect its antiviral role in LCs (Van Der Vlist & Geijtenbeek, 2010).

1.3.3. Role in Skin Diseases

Murine and human LCs can uptake antigens, migrate, undergo phenotypic maturation, and present antigens to T cells in DLNs, thus shaping the following immune response. LCs demonstrate significant functional flexibility, which is influenced by different microenvironments or their specific identities (Doebel et al., 2017; X. Liu et al., 2021; Romani, Clausen, et al., 2010).

In cutaneous lupus erythematosus (CLE)

In the skin lesions of CLE patients, epidermal LCs exhibit abnormal morphology (Sontheimer & Bergstresser, 1982). Also, the number of LCs is abnormally altered in both the site of lesions and in the DLNs in CLE patients (Kanauchi et al., 1989) and in MRL-Fas (lpr/lpr) (MRL-lpr) mice (Eriksson & Singh, 2008). Eriksson & Singh, 2008 research investigates the behavior of LCs in the skin, in the context of autoimmune dermatitis on mice strains prone to developing lupus-like skin inflammation, a significant reduction in the migration of LCs from the skin to the skin DLNs in these strains compared to healthy controls. This impaired migration leads to an accumulation of activated LCs in the skin. Also, the extent of LC migration impairment correlated with the onset and severity of dermatitis in these mice, indicating that LCs migration dysfunction is highly associated with disease progression. These findings suggest that LCs play a critical role in skin related autoimmune diseases specifically CLE proven in both mice & human (Eriksson & Singh, 2008; King et al., 2015). Yet, further research is necessary to clarify the exact mechanisms through which langerin contributes to the development of autoimmune skin diseases and to investigate potential therapeutic approaches targeting LCs.

Role in atopic dermatitis (AD)

Human epidermal LCs proliferate in the steady state, and proliferation is increased in patients with AD. The exact role of LCs in AD is debated, but increased LC proliferation in human AD patients and in mouse models suggests LCs may be directly related to the disease's pathophysiology (Chorro et al., 2009). This implies the necessity of further studies targeting these cells to enhance AD therapy.

1.3.4. Role in Immune Tolerance and Cancer

Although adult human skin contains 10 to 20 billion resident memory T cells, resting LCs selectively induce the activation and proliferation of skin-resident Tregs, whereas in the presence of foreign pathogen, activated LCs induce the proliferation of effector memory T cells but limit Tregs activation (Seneschal et al., 2012). See **(Figure1)**. The results of (Seneschal et al., 2012) study suggest a specific role for LC in maintaining immune tolerance in normal human skin, as well as enhancing a protective immune response against foreign pathogens. Also, non-activated LC found to be constantly migrating to DLNs to present self-antigens establishing immune tolerance under homeostatic conditions in both mice and humans (Ghigo et al., 2013; L. Zhou et al., 2022).

Similar to LCs in mice, human LCs reside in the basal and supra-basal layers of the epidermis forming a dense first-line defence network against invading pathogens (L. Zhou et al., 2022). A recent study compared LCs occurrence frequencies in human non-melanoma tumor lesions and healthy control tissues, revealing significantly decreased LC frequencies in tumor tissue and adjacent epidermis overlying malignant tumor tissue compared to healthy skin (Maraee et al., 2020). The higher numbers of adjacent LCs were associated with a lower potential for aggressiveness of the tumor, suggesting that LCs might play a role in hindering tumor growth (Santos et al., 2010). Deckers et al. review concluded that non-melanoma skin cancers (Deckers et al., 2018), like basal cell carcinoma and squamous cell carcinoma (SCC), often show a marked decrease in LCs in both the tumor and surrounding tissue (Bluth et al., 2009). DCs, including LCs, are essential for triggering strong immune responses against tumors. However, in certain cancers, DCs can become less effective at stimulating T-cells and producing interferons, allowing the tumor to evade immune detection (Gottfried et al., 2008; Perrot et al., 2007). In SCCs, while LCs in lab settings can stimulate type 1 immune responses, yet, they migrate abnormally from the skin and have reduced T-cell activation abilities in the LNs (Fujita et al., 2012; Van De Ven et al., 2011). Several cytokines like TSLP, IL-1, and TNF, which are involved in LC migration, are linked to cancer progression in the skin (Di Piazza et al., 2012; Moore et al., 1999). Disruptions in the skin's barrier may lead to the release of these cytokines, increasing cancer susceptibility (Cipolat et al., 2014). However, it is not yet clear if enhanced LC migration is a key factor in tumor formation. Moreover, recent findings suggest that langerin-expressing cells other than LCs might be contributing to the observed tumor effects. Importantly, human LCs are more efficient than dDCs in activating naïve CD8⁺ T-cells, which could influence immune responses against tumors (Deckers et al., 2018; Klechevsky et al., 2008).

In Tumor therapy

In tumor therapy, targeting antigens to LCs in situ is an attractive possibility based on several observations in vitro indicating that human LCs are very capable of inducing CTLs. This was shown for both CD34-derived LC-like DCs (Cao et al., 2007; Ratzinger et al., 2004) as well as for 'real' LCs isolated from human epidermis (Klechevsky et al., 2008). Thus, the ability to

cross-present protein antigens was shown for murine (Stoitzner et al., 2006) and human (Klechevsky et al., 2008) LCs.

1.4. Implications & Future Directions

Targeted delivery of a vaccine protein to LCs in the human skin via the CLR langerin has proved its high efficacy in preclinical studies (Bellmann et al., 2022). Human skin is a preferred vaccination site due to its multiple DC subsets with distinct CLRs that recognize pathogens. Antigens can be delivered to these receptors by antibodies or ligands to enhance immune responses.

However, while this concept has been established in mouse models, detailed insights and clinical trials testing the effect of antigen delivery to human skin DC in situ remain limited (Bellmann et al., 2022). Bellmann et al. study showed that antibody targeting via the skin is promising for vaccines, but further optimization is needed to induce strong immune responses (Bellmann et al., 2022). The human skin explant model is useful for studying antigen delivery to skin DCs in their natural environment, aiding clinical investigations (Stoitzner et al., 2010, 2014; Tripp et al., 2021). This model enables the exploration of the function of human skin DCs in a vaccination context similar to the in vivo conditions (Bellmann et al., 2022).

Novel drug delivery platform targeting human langerin

The recent study of Wamhoff et al., 2019 described the development of a synthetic ligand highly specific for human langerin: an N-tosylated glucosamine derivative, which demonstrated high affinity and specificity to human langerin. This ligand enabled the uptake of liposomes into langerin-expressing model cell lines and primary LCs from human skin (Wamhoff et al., 2019a).

The data from the study of Schulze et al., 2019 strongly supports the efficient and specific delivery of this synthetic ligand into langerin-expressing human cell lines (Schulze et al., 2019), reinforcing the idea that the designed targeted liposome ligand is highly specific to langerin. This suggests that the liposomal delivery platform can be effectively used to deliver both small molecules and encapsulated proteins to model cell lines and primary LCs. Given that the epidermis is an easily accessible site for vaccination and langerin is specifically expressed on

LCs, this liposomal delivery platform presents a promising tool for novel therapeutic applications (Schulze et al., 2019).

Cutaneous vaccination with microneedle patches

An on mice study using an innovative approach, researchers compared the use of classical metal versus polymer microneedle patches for antigen delivery (Pulit-Penaloza et al., 2014). They found that the microneedle patches method could influence the recruitment of various skin cell subsets and enhance the interaction with skin APCs, as the different physicochemical properties of the microneedles affect the vaccine diffusion rate. Gaining a deeper understanding of the immunological mechanisms involved in cutaneous immunization, as well as identifying the specific subsets of APCs is crucial for triggering immune responses and improvements in vaccine efficacy. This could be achieved by incorporating adjuvants that target skin APCs and/or by directing antigens to specific DC subsets. This study investigates how skin langerin⁺ cells, contribute to the effectiveness of skin-delivered influenza vaccines using microneedle patches. Researchers utilized genetically modified mice that allowed for the selective depletion of langerin⁺ cells. They observed that removing these cells before vaccination led to significantly weaker immune responses, including reduced levels of certain antibodies and decreased survival rates following exposure to the influenza virus. Importantly, this impairment was specific to skin-based vaccination, whilst traditional intramuscular vaccination did not show the same dependency on langerin⁺ cells. These findings highlight the crucial role of langerin⁺ skin DCs in initiating strong protective immunity when vaccines are administered via the cutaneous route (Pulit-Penaloza et al., 2014).

Similarly, in a study done on human skin explants, a small-molecule ligand that binds specifically to langerin receptor on LCs was conjugated to a model protein antigen. Via microneedle injection, this conjugated ligand was intradermally administered into intact human skin explants, selectively loading LCs in the epidermis. This applied technique provided a highly effective delivery method to vaccines with minimally invasive administration, reduction of required treatment dosage, faster vaccine distribution & reduced off target side effects. (Rentzsch et al., 2021).

In conclusion, it is important to rationally address specific DC subsets of the skin in both mice and humans for purposes of vaccination. Depending on the subset that contributes most, the

response will be dominated by cytotoxic T cells, which may be beneficial in vaccination against infectious agents (Ueno et al., 2010).

Combining checkpoint antibodies with DC-based therapies

There are two possible scenarios to consider: A specific subset of DCs may simultaneously express various common endocytic receptors that can be targeted. The immune response could be influenced depending on which of these receptors is targeted. On the other hand, different subsets of DCs may express distinct, non-overlapping receptors that can be targeted. In this case, the immune response would depend on which DC subset is exposed to the antigen (Romani et al., 2011).

Immune checkpoint blockade antibodies have transformed cancer immunotherapy, showing impressive results in some patients. However, they can cause severe side-effects and face immune resistance. Using checkpoint antibodies together with DC-based therapies is promising as DCs effectively enhance T cell responses or even create new immune responses with minimal side-effects (Garg et al., 2017; Sharma et al., 2021). The main aim of (Bellmann et al., 2022) study was to improve our knowledge and understanding of DC-targeting approaches, so they investigated the functional consequences of targeting antigens to human skin DCs via the CLR DEC205 and langerin. Addressing solely epidermal LCs in vitro, the study demonstrated that targeting antigen to langerin or DEC-205 with antibody-antigen fusion proteins induced antigen-specific CD4⁺ T cell responses that were somewhat stronger than by untargeted antigen.

In situ in the human skin, it was found that the delivery of DEC-205-targeted antigen, addressing both LCs and dermal DCs, was more beneficial in the stimulation of antigen-specific T cell responses than langerin targeting of only LCs. This suggests that targeting antigens to defined receptors on DCs may enhance T cell immunity also in human skin, albeit not as pronounced as in mouse models. However, it is of great importance to study vaccination strategies not only with isolated cells but also with skin DCs in their natural environment by using an ex vivo skin explant model that reflects the human situation as close as possible.

To sum up, advancement in therapies targeting CLRs on human skin DCs to stimulate effective T cell responses is valuable for the future integration of cancer treatments. To enhance the effectiveness of DC-targeted immunotherapies, it is essential to combine them with checkpoint blockade antibodies. This combined strategy aims to maximize the potential of DC-based

cancer vaccines. Given that immune checkpoint inhibitor therapy currently benefits only a subset of patients and faces challenges with primary and secondary resistances. Combining these two therapy models could prove advantageous for future treatment protocols (Bellmann et al., 2022).

Different delivery methods to skin DCs in mice & humans

In a study by (Flacher et al., 2010) where a protein antigen, specifically an antibody targeting an endocytic receptor on LCs, was injected into the dermis of mice (into the ear pinna), the antigen was rapidly taken up by epidermal LCs. This finding suggests that LCs likely play a role in intradermal (ID) vaccination, even when the vaccine is not directly delivered to their primary location. A similar outcome was observed in human LCs when the antigen was applied to a skin explant culture. However, the study did not explore the mechanism by which the protein antigen crosses the basement membrane between the dermis and the epidermis. In vivo, LCs probably extend their dendrites toward the epidermal and dermal interface to sample as much antigens as possible, particularly following intradermal antigenic stimulation. This dynamic morphological behavior allows LCs to capture antigens without fully migrating from their epidermal niche (Kubo et al., 2009; Nagao et al., 2009). This mechanism ensures efficient surveillance of the skin environment and initiates the antigen uptake process prior to LC migration to the DLNs for T-cell priming (Romani, Clausen, et al., 2010). Overall, the findings indicate that during ID vaccination, all subsets of skin DCs are exposed to the antigen to guarantee maximum contribution to the immune response (Flacher et al., 2010). The direct method for accessing dDCs is through injection into the dermis, a procedure familiar to physicians from the classical tuberculin sensitivity test involving intradermal injection. Accessing epidermal LCs is more complex (Romani, Thurnher, et al., 2010) as LCs are separated from the vascularized dermis by a dense collagenous basement membrane, which is permeable to large molecules like antibodies. Aberer et al. (Aberer et al., 1986) demonstrated in mice that intraperitoneally injected antibodies (anti-MHC-II) could reach the epidermis and specifically bind to LCs which in turns efficiently capture the antibody proteins, presumably via diffusion across the basement membrane, though active sequestration by LCs reaching out through the membrane could not be ruled out (Romani, Thurnher, et al., 2010). Another method for delivering antigen to epidermal LCs is through topical application. In mice, experiments showed that upon applying unconjugated protein antigens, topically

(epicutaneously), they readily reached LCs, which processed the antigen and cross-presented it to both CD8⁺ and CD4⁺ T cells *in vivo*. This process resulted in LC-mediated protection in a mouse tumor model. Similarly, anti-DEC-205 and anti-langerin antibodies were applied epicutaneously to tape-stripped mouse skin. Tape stripping, which removes the stratum corneum and induces inflammation, has the advantage of disrupting the epidermal barrier, making the epidermis more permeable to the topically applied antibodies. These antibodies could then bind to LCs.

Notably, under these experimental conditions, anti-DEC-205 antibodies also reached epidermal LCs within hours when injected intradermally or when placed in the culture medium of human skin explant cultures, with similar results observed in human skin (Romani, Thurnher, et al., 2010). The antibodies also reached dermal langerin⁺ DCs, but not dermal langerin^{neg} DCs (Flacher et al., 2009; Stoitzner et al., 2008).

Future implications for LCs in various diseases

The finding of Kaplan et al. study is very important for the future implications of LCs regulatory properties in CHS, also their role in cutaneous HSV infection, CLE, graft-versus-host disease and tumor immunosurveillance. The use of langerin-DTA LC-deficient mice models allowed for direct and comprehensive examination of LCs' involvement in these mentioned diseases and apparently many more diseases *in vivo* in the future (Kaplan et al., 2005). Adding to that the novel discoveries of langerin presence in several non-skin cells in both humans and mice such as the gut & lungs may open novel opportunities to enhanced targeted therapy to these tissues allowing chances to treat many gut related & pulmonary diseases (S. Chang et al., 2010; S. Chang & Kweon, 2010; S.-Y. Chang et al., 2008; Xuan et al., 2022).

2. Conclusion

LCs are antigen-presenting DCs residing in the epithelia. The phenotypic hallmark is their expression of the CLR langerin (CD207). Now the use of genetically engineered mice contributes to our understanding of the role of langerin on LCs in eliciting adaptive immune responses against pathogens & tumors and/or in inducing and maintaining tolerance against self-antigens or harmless substances *in vivo*.

DC-targeted immunotherapies via langerin are promising, but their clinical translation requires deeper insight into interspecies differences. Thus, this review helps researchers to shed light on the comparative aspects between LCs and langerin receptor in mice and humans. It also offers the most recent discoveries on langerin in both mice and humans with respect to its structure, binding affinities, its cellular expression, mechanism of action and more.

Notably, to assess studies on langerin receptor in mice and relate them to humans, we must further study the immunological differences between mice and humans carefully, which requires further comparative investigations and studies. Additionally, studies regarding developing drugs (i.e. using Lipid Nanoparticles (LNPs)) with ligands targeting human langerin, should be designed also targeting and highly specific to murine langerin in order to acquire a mouse model system that allows for the preclinical in vivo studies. Implementing DC-based therapy is considered highly valuable in cancer therapy and in various skin diseases such as AD, CHS, CLE and LCH diagnosis & treatment.

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