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REVIEW ARTICLE

Langerhans cells: Central players in the pathophysiology of atopic dermatitis

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Abstract

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease worldwide. AD is a highly complex disease with different subtypes. Many elements of AD pathophysiology have been described, but if/how they interact with each other or which mechanisms are important in which patients is still unclear. Langerhans cells (LCs) are antigen-presenting cells (APCs) in the epidermis. Depending on the context, they can act either pro- or anti-inflammatory. Many different studies have investigated LCs in the context of AD and found them to be connected to all major mechanisms of AD pathophysiology. As APCs, LCs recruit other immune cells and shape the immune response, especially adaptive immunity via polarization of T cells. As sentinel cells, LCs are primary sensors of the skin microbiome and are important for the decision of immunity versus tolerance. LCs are also involved with the integrity of the skin barrier by influencing tight junctions. Finally, LCs are important cells in the neuro-immune crosstalk in the skin. In this review, we provide an overview about the many different roles of LCs in AD. Understanding LCs might bring us closer to a more complete understanding of this highly complex disease. Potentially, modulating LCs might offer new options for targeted therapies for AD patients.

INTRODUCTION

Langerhans cells (LCs) were discovered in 1868 and originally thought to be neurons,[1] until they were recognized to be antigen-presenting cells (APCs).[2–4] For a long time, LCs were thought to be prototypical dendritic cells (DCs) and much of the early research into DCs was done with LCs. However, over time it became clear that LCs are a special type of cell.

Langerhans cells were initially characterized ultrastructurally by their tennis racket-shaped organelles composed of superimposed and zippered membranes, the so-called Birbeck granules (BG; Figure 1a).[5] These structures were later identified as expressing Langerin (CD207). Of note, ectopic expression of Langerin in fibroblasts leads to formation of BG in these cells.[6] CD207 is helpful for identification of LCs by immunohistology or flow cytometry (Figure 1b). Human LCs are located in the basal and suprabasal layer of the epidermis and can extend their dendrites through tight junctions into the stratum corneum. This enables antigen recognition and capture both within the skin and on the skin surface.[7] Recognition of antigen can result in LC activation and migration towards the nearest lymph node (LN). Considerable numbers of LCs have been found in skin draining LN but not in mesenteric LN.[8]

In healthy epidermis, LCs are the most abundant immune cells, comprising 2%–5% of all cells in the epidermis.[9] Of note, females have more LCs than males.[10] In both sexes,

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LC numbers decline with age.[11] Langerin-expressing DCs can also be found in the nasal, oral and cervical mucosa, in the foreskin, tonsils, tongue, the upper respiratory tract and the intestine.[12,13] However, mucosal LCs are of different origin and phenotype than epidermal LCs. Similarities and differences between mucosal and epidermal LCs were recently reviewed by Brand et al.[14]

Langerhans cells are radio-resistant, therefore they are not depleted by irradiation in bone marrow chimera experiments. Otherwise, LCs are extremely sensitive. They can mature and emigrate upon contact with antigen, but LCs migrate also upon exposure to UV radiation, temperature-, mechanical- and even psychological stress.[15] In fact, the emigration of LCs upon UV exposure is so robust that in previously published studies 'UV depletion' of LCs was an accepted protocol. Of note, 'UV depletion' is not a depletion as we use the term today. Clean animal models of LC depletion use for example the Langerin-DTR system. Therefore, one must be careful when reading selected literature about LCs and comparing their findings to newer data with modern experimental models.

The sensitivity of LCs to UV is of great interest in the field of phototherapy. While UV can ameliorate AD, the underlying mechanisms remain incompletely understood. In a mouse model of contact hypersensitivity, UV acts immunosuppressive and LCs are required for the generation of regulatory T cells (T_{REG}).[16] Results from a similar model showed that indeed epidermal LCs, not CD207$^+$dDCs, are important for the anti-inflammatory effects of UV treatment.[17]

LC MARKERS

In-vivo experiments are key in researching the immunopathology of diseases. The most common animal model for LC research is the mouse. However, although similar, there are differences between human and murine skin.[18] Very basically, human epidermis and dermis are much thicker than murine, human skin is more firmly attached to underlying tissue and mice have a much higher hair density on the body than men.

In human skin, LCs comprise the vast majority of CD207-expressing cells. Mouse skin contains a second population of CD207-expressing APCs: CD207$^+$ dermal DCs (dDCs). These cells, in contrast to epidermal LCs, are derived from bone marrow and not self-renewing. They are CD103$^+$XCR1$^+$ and are excellent cross-presenters. Thus, they can be seen as Type-1 conventional dendritic cells. Markers for identifying human and mouse LCs and CD207$^+$dDCs are shown in Table 1.

Of note, in mice LCs and CD207$^+$dDCs have different functions. Epidermal LCs seem to be more anti-inflammatory/tolerogenic, while dermal CD207$^+$dDCs seem to be more pro-inflammatory. Different protocols for deleting LCs affect either one or both of these populations. The overlaps and differences between these two cell populations are the reason for much confusion in the literature.

Key points

Why was the study undertaken?

- This review aims to provide an overview about the current knowledge of the role of Langerhans cells in atopic dermatitis.

What does this study add?

- Here, we review the contribution of LCs to the different pathophysiological mechanisms underlying AD, such as immune response modulation, microbiome sensing, skin barrier integrity and neuro-immune communication, highlighting their dual pro- and anti-inflammatory functions.

What are the implications of this study for disease understanding and/or clinical care?

- Understanding the central role of LCs in AD might offer new ways to treat this very heterogeneous disease. We also point out, where our understanding is still lacking and further research is needed.

LC ontogeny

Epidermal LCs are an embryonically derived, self-renewing, bone marrow-independent cell population.[19] Originally, they were classified as DCs, but they also display similarities with macrophages (Mac).[20] Patients with GATA2 or IRF8 mutations show normal amounts of LCs. As these mutations affect DC numbers, LC development and maintenance are separate from plasmacytoid and conventional DCs (pDCs/cDCs).[21] Lineage tracing studies in mice[19,22] have shown that LCs express both Zbtb46 and Mafb, giving them a dual identity of DCs and Mac.[23]

Langerhans cells share their origin with alveolar macrophages, microglia and Kupffer cells: Precursors from the embryonic yolk sac and the fetal liver seed the epidermis during embryogenesis. LC precursors can be observed in developing mouse skin as early as embryonic day 10.5.[19] Between Days 2 and 7 after birth, these cells undergo a proliferative burst and form the LC network. LCs fully differentiate and upregulate MHC-II, CD11c and finally CD207.[24] The network settles to adult morphology around 3 weeks after birth.[25]

In the steady state, adult epidermal LCs have a half-life of about 2 months. Even in homeostasis, LCs constantly mature and migrate to the draining LN in low amounts. The network is maintained by proliferation of LCs in situ. Normally, about 5% of LCs are proliferating at any given time.[24] This self-renewal is one of the defining features of LCs and has been demonstrated in multiple models. In parabiosis experiments, LCs remain of donor origin.[26–28] In human allografts, LCs have been found to still be of donor

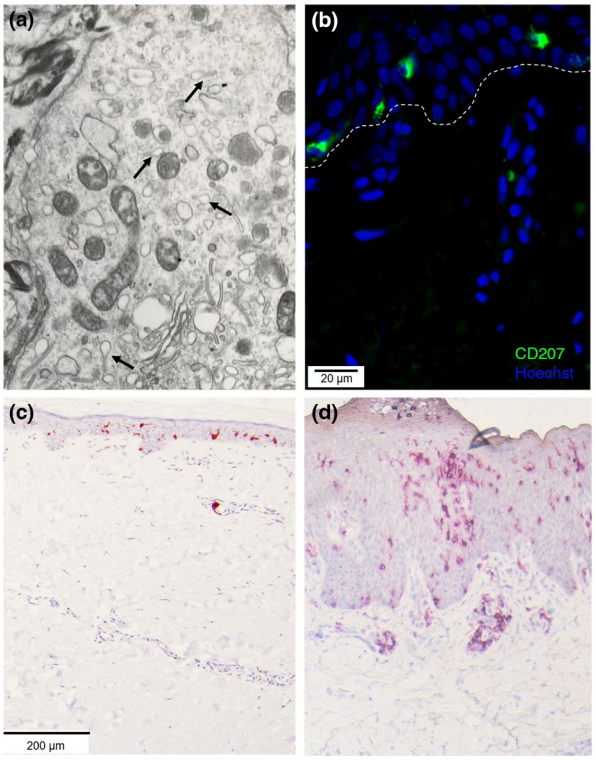

FIGURE 1 Human LCs in health and AD. (a) Electron microscopy image of cytoplasm of a Langerhans cell with arrows pointing at Birbeck granules. (b) Immunofluorescence image of healthy skin stained with anti-CD207 (Langerin) antibody and Hoechst nucleic acid stain showing CD207+ Langerhans cells within the epidermis. The dotted line highlights the epidermal–dermal junction. (c, d) Representative immunohistochemistry images of healthy skin (c) and atopic dermatitis (d) stained with anti-CD1a antibody. In healthy skin, epidermal CD1a + DCs are LCs. In AD skin, CD1a also stains infiltrating IDECs. AD, atopic dermatitis; LC, Langerhans cells; IDEC, inflammatory dendritic epidermal cells.

origin 10 years after transplantation.[29] This sets LCs apart from DCs, which have a higher turnover rate and arise from bone marrow precursors.[30] Mucosal CD207$^+$DCs (and in mouse CD207$^+$dermal DCs) are also bone marrow-derived and not self-renewing.[14]

In case of mass emigration of LCs, like in acute inflammations, the LC network is re-constituted from blood monocytes. These short-lived monocyte-derived LCs are replaced by long-lived, non-monocyte-derived LCs over the course of 3 weeks. In case of a total depletion of LCs, the LC network can also be reconstituted from an as-yet unidentified non-monocyte bone marrow precursor in an ID2-dependent manner.[31]

Langerhans cells depend in their development on the cytokine TGF-β1.[32,33] However, active TGF-β1 only appears in the epidermis after birth. Therefore, LC precursors seed the epidermis independently of TGF-β1.[34] The emergence of TGF-β1 coincides with the proliferative burst and expression of CD207. While TGF-β1 is absent, the prenatal and immediately postnatal epidermis does contain other proteins of the TGF-β-superfamily, most notably BMPs. In vitro experiments show that BMP7 can stimulate differentiation of LCs from human CD34$^+$ cord blood stem cells, just like TGF-β1. However, BMP7-generated LCs show a different phenotype than TGF-β1-LCs. Most notably, BMP7-LCs show active proliferation, altered expression of surface markers and no BG. In adult epidermis, both cytokines are present: The basal layer of the epidermis shows high levels of BMP7, while active TGF-β1 is confined to the suprabasal layers. Proliferating LCs are only found in the BMP7-dominated areas. Therefore, it is hypothesized that BMP7-LCs represent the self-renewing LCs, which then migrate upwards into the TGF-β-rich strata for terminal differentiation.[35]

LC function

The primary function of LCs is the recognition and presentation of antigen. As professional APCs, they express an extensive repertoire of pattern recognition receptors (PRRs), mostly C-type lectins (CLRs) and toll-like receptors (TLRs). CLRs detect glycans, including those expressed by commensal and pathogenic bacteria. The main CLR expressed by LCs is Langerin (CD207). Other CLRs like mannose receptor (CD206) are only expressed under special conditions.[35] CLR expression, glycan specificity and bacteria recognition have been thoroughly reviewed by Mnich et al.[36]

Toll-like receptors are a large family of PRRs. TLRs 1, 2, 4, 5 and 6 detect extracellular molecular patterns such as lipopeptides, lipopolysaccharide, mannan, phospholipids, flagellin, zymosan and viral envelope proteins. TLRs 3 and 7–10 are expressed on endosomal membranes and recognize different forms of nucleic acids, for example dsRNA or CPG DNA.[37] Human LCs have been described to express TLRs 1 through 10,[38] but different publications report very different findings.[39–41] A reason for these differences in the literature could be different types of LCs used (epidermal, mucosal or monocyte-derived LCs), different methods of analysis (RNA-Seq and flow cytometry) or different conditions (steady state and disease models). Interestingly, all studies comparing LCs to cDCs find significant differences in expressed TLRs. Flacher et al, combining qPCR with functional experiments, demonstrate that LCs functionally express TLRs 1, 2, 3, 5, 6 and 10, but not 4, 7 or 8. This specific expression pattern suggests that LCs might be specializing in defence against gram-positive bacteria, but are less active against gram-negative bacteria.[42]

As professional APCs, LCs can present antigen via MHC-I and MHC-II, as well as CD1a. Intracellular antigen is presented via MHC-I to CD8$^+$ T cells. Extracellular antigen is presented via MHC-II to CD4$^+$ T cells. LCs can also cross-present, that is, present extracellular antigen to CD8$^+$ T cells.[43,44]

Upon contact with antigen, LCs may 'mature'. In APCs, maturation means a series of phenotypical and functional alterations: they reduce their adhesion to the surrounding tissue and become highly mobile. They downregulate adhesion molecules, upregulate CCR7 and downregulate CCR6.[45] This allows for their migration out of the tissue and to the next draining LN. LC maturation with the switch from epithelial to mesenchymal characteristics is often compared to

TABLE 1 LC markers in situ.

Markers	Synonyms	Human	Mouse	Mouse	Mouse
		Epidermal LCs	Epidermal LCs	Dermal cDC1	Dermal cDC2
CD1a		+	No mouse equivalent	No mouse equivalent	No mouse equivalent
CD1c		+	No mouse equivalent	No mouse equivalent	No mouse equivalent
CD11b		+/−	+	−	+
CD11c		+	+	+	+
CD24		−	+	+	−
C103		−	−	+	−
CD172a	SIRP-alpha	+	+	−	+
CD205	DEC-205	+	+	+	+
CD207	Langerin	+	+	+	−
CD209	DC-SIGN	−	+	−	+
CD324	E-Cadherin	+	+	+	+ (low?)
CD326	EpCAM	+	+	−	−
CLEC9a	DNGR-1	−	−	+	−
F4/80		Not tested	+	−	+
MHC-II		+	+	+	+
XRC1		−	−	+	−

Abbreviation: LCs, Langerhans cells.

the epithelial-to-mesenchymal transition (EMT) observed in metastasizing cancer cells.[46]

Mature LCs downregulate phagocytosis, but upregulate MHC-II and the co-stimulatory molecules CD40, CD80, CD86 and CD83. This allows for antigen presentation and immune activation.[47] Activated, mature LCs can promote inflammation by secreting pro-inflammatory cytokines, activating naïve T cells and re-stimulating already primed T cells. LCs are able to polarize T cells towards Th1, Th2, Th17 or Th22 depending on the context.[48–50]

Langerhans cells are important for defence against pathogens. With their dendrites extending through tight junctions, LCs constantly survey the skin surface. Application of *Staphylococcus aureus* (*S. aureus*) exfoliating toxin (ET) to mouse skin did not compromise the epidermis and ET did not penetrate through tight junctions. Still, exposed mice developed neutralizing IgG against ET and were protected in subsequent intraperitoneal injections of ET. Mice depleted of LCs did not develop immunity after patch immunization. Therefore, LCs can establish adaptive immune defences against pathogens which have not even penetrated the body yet.[51]

Langerhans cells are especially important for the defence against viral infections. Their signature molecule CD207/Langerin can capture viral particles and internalize them for degradation in their BG.[52] In several mouse models of viral infection, deletion of LCs leads to decreased cytotoxic T-cell responses, higher viral loads and increased lethality.[53,54] Similarly, in Langerin-DTR mice the immune response to leishmaniasis is impaired. However, Brewig et al.[55] demonstrated that in this case the critical cells are $CD207^+$dDCs.

Langerhans cells also have important anti-inflammatory functions. In in-vivo models of contact hypersensitivity, deletion of epidermal LCs exacerbates inflammation, while deletion of $CD207^+$dDCs ameliorates inflammation.[56] Here, epidermal LCs are mostly anti-inflammatory/pro-tolerogenic, while $CD207^+$dDCs are pro-inflammatory. Further research revealed that LCs can induce immunological tolerance to haptens by pushing allergen-specific $CD8^+$ T cells into anergy or deletion and expanding T_{REGs}. Loss of LCs breaks this immunological tolerance and can result in inflammatory diseases.[57,58]

Steady-state LCs are highly phagocytic. Via the TAM-kinase Axl, LCs silently clear apoptotic cells, preventing immune activation and autoimmunity.[59] Deletion of TAM kinases results in a loss of epidermal LCs followed by spontaneous skin inflammation.[60] In a mouse model of lupus, deletion of LCs leads to increased levels of auto-antibodies and accelerated dermatitis.[61] LCs are also important for maintaining tolerance towards skin commensals. In the steady state, LCs strongly favour induction of T_{REGs} over induction of anti-bacterial effector T cells.[62]

Therefore, LCs can act both pro- and anti-inflammatory, depending on the situation.

ATOPIC DERMATITIS

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease worldwide. Approximately 80% of cases begin in infancy or childhood, the rest develop in adulthood. The point prevalence in children varies from 2.7% to 20.1% in different countries and in adults from 2.1% to 4.9%.[63]

Risk factors for AD include exposure to lower temperatures, lower humidity, tobacco and air pollutants. These effects were more pronounced in children younger than 7 years

and in women.[64] These findings are of concern, especially in regard to rising urbanization and climate change.

Clinical manifestations of AD are sensitive and dry skin and localized or disseminated eczematous lesions, usually accompanied by severe pruritus.[65] AD belongs to the spectrum of atopic diseases, which also includes food allergies, allergic asthma and allergic rhino-conjunctivitis. All these atopic diseases may occur in different combinations.[63,66,67] Patients with AD have a significantly increased risk of arthritis, Sjögren syndrome, Crohn's disease, vitiligo, alopecia areata, pernicious anaemia, ulcerative colitis, rheumatoid arthritis and hypothyroidism.[68]

Atopic dermatitis is a very heterogeneous disease and can be divided into different phenotypes and clinical manifestations defined by ethnicity, disease onset, disease severity, chronic versus acute, intrinsic versus extrinsic (IgE level), paediatric versus adult and inflammatory signature.[69] This variety of endotypes makes it difficult to uncover a common pathophysiology and to develop therapies according to the one-size-fits-all model.

Mild and moderate forms of AD are mainly treated topically, with emollients, pH-adjusted moisturizers and anti-inflammatory drugs like corticosteroids.[70] Moderate and severe forms are treated systemically with biologics or JAK inhibitors aiming at the Th2-immune response. Finally, AD can be treated successfully with phototherapy. Current and upcoming therapies have been reviewed in Bieber et al.[63]

Pathophysiology of AD

The pathophysiology of AD is very complex and although many factors and processes are known, not all of these are present in all endotypes of AD. Genetic predisposition is a major risk factor for AD. It has been estimated that up to 90% of AD cases in Europe are inherited.[71] Mutations associated with AD are related to the skin barrier and to immune regulation. Of note, although the clinical manifestations are similar, risk genes of AD differ substantially between cohorts from different ethnicities.[72]

Atopic dermatitis is a distinctly T-cell-driven disease with a strong IL-13 signature.[73] AD was originally viewed as a Th2-driven disease, but recent data show a more complex picture. In European and American patients, Th2 and Th22 dominate the acute phase with Th1 following in the chronic phase of AD. Asian patients show higher levels of Th17 and Th22 responses, while African patients show almost no Th1 and Th17 and lower levels of Th22 involvement.[74] Lesional AD skin also contains increased amounts of basophils, mast cells (MC), DCs, eosinophils and macrophages.[75–77] Most cases of AD show high levels of specific IgE to foreign and self-antigen, indicating an involvement of the humoral arm of the adaptive immune system.[78] Indeed, systemic anti-allergic therapy can ameliorate some forms of AD.[79]

Atopic dermatitis is furthermore associated with a compromised skin barrier. In AD patients, even non-lesional skin shows increased trans-epidermal water loss (TEWL).[80] Mutations in filaggrin and claudin, key components of the skin barrier, are among the alleles with the strongest association with AD.[81,82]

Whether it is a consequence or a cause of the compromised skin barrier, AD is associated with significant changes in the skin microbiome. Most prominently, AD skin displays an overgrowth of *S. aureus*.[83] Not all patients with AD do have *S. aureus* colonization of their skin, but levels of *S. aureus* correlate with disease severity and AD patients without *S. aureus* colonization have less severe skin symptoms.[84] Of note, just like the barrier disruption, the microbiome in AD patients is also changed in non-lesional skin.[85] Treatment with corticosteroids ameliorates skin lesions and leads to decreased microbial dysbiosis.[86] On the other hand, normalizing the microbiome can lead to an amelioration of the disease.[87,88] Therefore, microbial dysbiosis is both a consequence of AD and a driver of the disease.

Neuro-immune crosstalk is an important element of many diseases.[89] Especially AD is associated with increased innervation of the skin.[90] In mouse models, amelioration of AD correlates with reduced skin innervation.[91] In AD lesions, the density of nerves in the epidermis is increased with nerves displaying altered morphology.[92] Fitting to this observation, AD skin contains higher levels of nerve growth factor (NGF).[93] In a mouse model of AD, blockade of NGF reduces the innervation of the skin and improves dermatitis and scratching behaviour.[94]

How all these factors connect and if all of them are important in all forms of AD is currently still unclear. A full understanding of the pathophysiology of AD will still require much research.

LCs in AD

The prominence of LCs in the skin, as well as their dual function as potentially strong pro- and anti-inflammatory cells, makes them cells of great interest in inflammatory skin diseases. Furthermore, genome-wide association studies have found mutations in the gene encoding for CD207 to be strongly associated with risk of AD.[72] LCs in AD show greater activation and maturation[95] and increased proliferation[24] (Figure 1c,d). In several different mouse models, deletion of LCs protects from AD.[96] Xiao et al. elegantly demonstrated that specifically deletion of monocyte-derived LCs, but not CD207$^+$dDCs, ameliorates AD.[97]

It is assumed that LCs are actively involved in the pathophysiology of AD. They may however also be involved in anti-inflammatory pathways ameliorating the disease. As of yet, the definitive role of LCs in AD remains unclear. However, LCs are involved in many key processes of AD, giving them a central role in this disease.

LCs and immunology in AD

T cells are key players in the pathophysiology of AD, as exemplified by current treatments blocking T-cell-derived

cytokines. Th2-polarized helper T cells secrete the cytokines IL-4 and IL-13. Blockade of these cytokines or their receptors, for example with dupilumab, is a highly efficient treatment for AD.[98] While T cells are strong effector cells, their activation, recruitment and polarization depend on APCs. LCs are the most common APCs in the skin and have been shown to be able to polarize T cells towards Th2, making them the obvious drivers of the Th2-shift in AD.

Lesional skin of patients with AD contains high levels of the cytokine thymic stromal lymphopoietin (TSLP), produced by keratinocytes. In mice, overexpression of TSLP leads to an AD-like disease. Interestingly, depletion of LCs abolishes AD in this model. Therefore, TSLP induces AD via LCs. Specifically, TSLP-primed LCs recruit T cells to the skin via secretion of chemokines like CCL17 and CCL22 and polarize them towards a Th2-phenotype.[96,99,100]

The best studied mode of activation for T cells is via MHC-I and MHC-II, presenting peptide antigen. However, T cells can also be activated by lipid antigen presented by CD1a. In AD, CD1a-reactive T cells are strongly increased.[101] CD1a is highly expressed on LCs.[102] Therefore, LCs may drive AD pathogenesis via CD1a-dependent activation of T cells.

One important downstream effect of Th2-polarization is the induction of B-cell differentiation towards IgE-producing plasma cells. In mouse models, deletion of LCs leads to reduced levels of IgE, both in a model of OVA sensitization and in the steady state.[103] AD has long been associated with high levels of IgE.[104,105] LCs bind IgE via different structures such as the low-affinity receptor FcεRII/CD23 and the high-affinity receptor FcεRI. Both receptors are expressed on LCs in AD.[106,107] FcεRI expression on $CD1a^+$ cells correlates with serum IgE levels in patients.[108] Activation of IgE-bound FcεRI on LCs leads to secretion of chemokines such as IL-16, which recruit more helper T cells, precursors of inflammatory dendritic epidermal cells (IDECs) and eosinophils.[109] IDECs bind IgE via FcεRI, but FcεRI-activated IDECs polarize T cells in a different direction, namely towards Th1.[110]

Therefore, there exists a feedback loop in the pathogenesis of AD: LCs initiate a Th2-response, which leads to IgE-production, which is in turn bound by the LCs. Their activation upon IgE ligation leads to the recruitment of further immune cells. IgE on IDECs, as a spin off of this loop, polarizes naïve T cells towards Th1, explaining the switch form Th2 in acute to Th1 in chronic AD lesions.

Another important cell type infiltrating the skin in AD are eosinophils.[111] In-vivo, disruption of the skin barrier and immune activation with peptidoglycan cause eosinophil infiltration in the skin. This is dependent on secretion of the chemokine CCL5 by LCs.[112] In another mouse model of dermatitis, Langerin-DTR depletion of LCs leads to reduced levels of eosinophils.[113]

Therefore, LCs play an important part in recruiting and polarizing immune cells, driving the pathogenesis of AD.

LCs and skin barrier in AD

Atopic dermatitis skin is characterized by a genetically and inflammation-driven disrupted skin barrier. AD skin also contains higher numbers of more active LCs. In several different mouse models, disruption of skin barrier led to increased numbers of LCs.[114] Yoshida et al. suggested that due to their ability to penetrate tight junctions, LC may contribute to formation of skin lesions by having access to environmental allergens.[115,116]

Mice with a deletion of EGFR in the epidermis ($EGFR^{\Delta ep}$) develop a phenotype resembling severe AD. This phenotype is rescued when the mice are kept under germ-free conditions. Therefore, the skin inflammation in $EGFR^{\Delta ep}$mice is caused by invading microbes. Importantly, even germ-free, non-inflamed mice have a compromised skin barrier. In this model, skin barrier integrity loss is the initiating event of the disease, allowing for infection of bacteria into the skin and leading to the persistent inflammation.[117] In $EGFR^{\Delta ep}$mice, the disease starts when hair follicles erupt through the skin. Normal closure of the skin barrier after this disruption is impaired in these mice.

In AD patients, numbers of LCs with dendrites reaching into the stratum corneum are increased fivefold.[115] In normal skin, tight junctions close around LC dendrites to maintain the skin barrier.[7] However, AD is very prominently associated with mutations in genes coding for skin barrier components. Therefore, an increased penetration of the tight junctions by LC-dendrites, coupled with a defect in closing tight junctions, may be a contributing factor in the pathology of AD. A compromised skin barrier might attract more LCs, which might further compromise the barrier, leading to a vicious cycle driving the disease.

However, data from Lee et al. suggest an opposite hypothesis: in both Langerin-DTA and Langerin-DTR mice, two genetic models for deletion of LCs, the skin barrier is disturbed. Even in the steady state, the transepidermal water loss (TEWL) in these mice is higher than in WT controls. Also, mice without LCs show impaired skin barrier closure after tape stripping.[118] According to these results, LCs contribute to the maintenance and repair of the skin barrier. The increased amount of LC-dendrites in the tight junction area may be an attempt to 'plug the holes' in a compromised skin barrier.[119]

An intact skin barrier is essential for the tolerogenic function of LCs. Luo et al. injected OVA into the subcutis of mice, eliciting an anti-OVA immune response. If OVA was applied topically to intact skin before the injection, the anti-OVA response was attenuated significantly. This effect was lost in Langerin-DTA mice. Therefore, topical application of an antigen can lead to immunological tolerance in an LC-dependent manner. Cutaneous application of OVA on tape-stripped skin also failed to elicit immunological tolerance.[120] Therefore, the critical point of cutaneous tolerance is antigen sensing by immature LCs through an intact skin barrier. The disturbed skin barrier in AD may deprive the patient of an important

immunoregulatory mechanism. This may continue to drive the disease or contribute to the emergence of allergic comorbidities.

Uncovering the exact connections between LCs and the skin barrier in human AD will still need further research, but modifying LCs might present a way to restore the skin barrier and ameliorate the disease.

LCs and microbiome in AD

Microbial dysbiosis is very important in AD.[121] The skin and its microbiome constantly interact with each other via cell–cell interactions, structural components or secreted bioactive molecules.[122] This interaction goes both ways: Comparing germ-free to SPF mice revealed over 2800 differentially regulated genes in the skin, demonstrating the enormous effect the microbiome has on the skin even in steady state.[123] Conversely, changes in the immune system lead to alterations of the microbiome, even in the steady state.[124] In healthy mice, depletion of LCs does not affect the composition of the skin microbiome.[125] Germ-free mice, compared to SPF mice, display reduced numbers of LCs in the epidermis.[126] Therefore, LCs may be sensors of the microbiome, but not directly influence it.

In healthy skin, LCs induce T_{REGs}. When activated, however, LCs expand effector and memory T cells and decrease T_{REGs}.[127] Metabolites from skin commensals can act on LCs and induce an anti-inflammatory programme with secretion of IL-10 and IDO. Such LCs can further suppress helper T-cell proliferation and induce IL-10 secretion in T cells.[128]

In AD, the skin is often colonized by an overabundance of *S. aureus*, while other species like *Staphylococcus epidermidis* (*S. epidermidis*) are reduced. As yet unpublished data from our group show that LCs primed with *S. epidermidis* lead to IL-10-secreting T cells, while LCs primed with *S. aureus* lead to proliferating T cells secreting pro-inflammatory cytokines. Pathogens like *S. aureus* can drive T-cell-mediated inflammation via LCs. At the same time, LC-translated anti-inflammatory functions of skin commensals like *S. epidermidis* are lacking.

Iwamoto et al report that in AD LCs display significant downregulation of TLR2 and are therefore unresponsive to TLR2 ligands. Pam3Cys-stimulated LCs from AD patients produce less IL-6 and IL-10, but more IL-18.[129] Therefore, in AD LCs react to the microbiome in an atypical way.

Not only the bacterial, but also the fungal skin microbiome is dysregulated in AD. Especially species of *Malassezia* have been associated with more severe AD.[75] Of note, skin-resident fungi are strong inducers of IgE responses.[130] FcεR1-activated LCs secrete chemokines attracting T cells and IDEC precursors.[110] This may contribute to the perpetuation of AD. The pathogenicity of fungi depends on the pH of the surroundings. AD skin is less acidic than healthy skin. This leads to increased release of allergens from skin-resident fungi,[131] leading to more IgE production. Changes in the fungal microbiome could very well be the basis of the AD-specific expression of IgE receptors in LCs.

Taken together, both the presence of pro-inflammatory microbes, as well as the absence of commensals which would induce tolerogenic programmes in LCs, are important factors in AD. Transplantation of healthy microbiome can ameliorate AD in mice.[88] Clinical studies with microbiome transplantation in AD patients are already under way.[132]

LCs and neuro-immunology in AD

Skin inflammation often correlates with psychosomatic disorders. Psychological stress often leads to worsening of skin diseases.[133–137] Chronic skin conditions in turn often cause stress, via self-perceived unattractiveness of the patient or via the sensation of pain and itch. This vicious cycle contributes to persistence and worsening of chronic skin diseases.

In mice, deletion of LCs can reduce the number of specific nerve fibres.[138,139] In humans, demyelinating diseases or spinal cord injuries lead to loss of skin innervation, which in turn reduces numbers of LCs.[140,141] Thus, nerves and LCs in the skin are dependent on each other.

Zhang et al. demonstrated that long-term loss of LCs leads to reduction of specific nerve fibres. This in turn leads to increased MC degranulation, which aggravates in-vivo models of skin inflammation. However, depletion of skin nerves did not aggravate experimental AD. In other models, the opposite effect occurs: depletion of skin nerves ameliorates inflammation.[142] Neuro-immunology of the skin is very complex and will require more research to fully understand.

In AD patients, innervation of the epidermis is increased. This has been connected especially with the sensations of itch and pain.[143] Depletion of these nerves ameliorates AD.[94]

In both animal models and patients, AD is associated with a dysregulation of neuropeptides. Specifically, in AD the levels of substance P (SP) are increased and the levels of calcitonin gene-related peptide (CGRP) are decreased.[144,145] CGRP acts on LCs and impairs their ability to present antigen.[146] Injection of CGRP downregulates inflammation in-vivo.[147] SP also acts on LCs,[148] but acts pro-inflammatory by enhancing LC activation, migration and antigen presentation, leading to enhanced T-cell reactions and increased productions of immunoglobulins.[149] In AD, SP levels correlate with NGF levels and with disease severity.[150]

Thus, inflammatory LCs may increase the innervation of the skin. Inflammatory nerves in turn may polarize LCs towards a pro-inflammatory phenotype, thus creating an inflammation-driving feedback loop.

CONCLUSIONS

LCs play an important part in skin immunity. In the steady state, they maintain tissue homeostasis and immunological tolerance. At the same time, they provide immunity against invading and skin surface microbes. LCs are connected to

all major events of AD pathophysiology. However, their net effect in this disease is still unclear. LCs might be drivers of AD or they might attempt to counteract the disease. Moreover, LCs may play different roles in different subtypes and stages of AD. The literature on this topic is challenging to understand; many different models have been used and the role of LCs may vary with the exact model. Different groups use epidermal LCs, $CD207^{+}$dDCs or monocyte-derived LCs. Moreover, in vitro experiments do not replicate the microenvironment of the skin and the microbiome, which are critical for LCs. Therefore, in vitro data may not reflect the in-vivo situation very well.

More work is needed in order to deepen the understanding of LCs in the pathophysiology of AD. Studies about LC function in patients with different subtypes and stages of AD would be key to better understand their putative role in distinct subforms of AD. Hence, the behaviour of LCs in AD patients of different ethnicities and different dominant cytokine axes would be interesting to explore. Besides all challenges of investigation, LCs, as key players in the regulatory networks in AD, offer the opportunity to develop new treatment strategies and options, for example, by developing drugs modifying their function and shift them away from pro-inflammatory action.

AUTHOR CONTRIBUTIONS

YP: Conceptualization, funding acquisition, roles/writing—original draft and writing—review and editing. MH: Conceptualization, roles/writing—original draft and writing—review and editing. MAC: Conceptualization, visualization, roles/writing—original draft and writing—review and editing. TBe: Visualization. TBi: Supervision and writing—review and editing. PW: Funding acquisition, supervision and writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

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