

REVIEW

Cutaneous dendritic cells in allergic inflammation

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Summary

The skin represents a physical barrier, which is capable of protecting the body from damaging invaders. Moreover, the skin operates as an active immunological organ, harbouring a complex network of dendritic cells (DCs), which serve as a bridge between innate and adaptive immunity. Equipped with specific pattern recognition receptors (PRRs), DCs are able to capture, process and present antigens to naïve T cells in the skin draining lymph nodes, thereby inducing adaptive antigen-specific immunity. However, the outcome of the immune response is shaped by numerous factors including the DC subtype, maturation state of DCs, composition of PRRs expressed by DCs, type of pathogen as well as factors in the microenvironment. Thus, cutaneous DC subtypes are known to contribute to both, peripheral tolerance and the generation of allergic skin inflammation. Identifying the underlying mechanisms is a challenging task in understanding DC biology. Based on their functional diversity, cutaneous DCs might represent promising therapeutic targets, with the potential of down-modulating pro-inflammatory immune responses and inducing tolerogenic pathways, thereby ensuring the maintenance of tissue homeostasis and restoring the balance of dysregulated immune reactions in the context of allergic skin diseases. In this review, we summarize the versatile character of DC subtypes in human skin and highlight their phenotypic characteristics and role in allergic skin inflammation. In addition, we discuss current therapeutic approaches for the management of inflammatory skin diseases such as atopic dermatitis with the main focus on strategies targeting DCs. We point towards potential challenges, benefits, risks and limitations for the treatment of patients.

Keywords atopic dermatitis, cutaneous dendritic cells, skin

Abbreviations AD, atopic dermatitis; CHS, contact hypersensitivity; DCs, dendritic cells; dDCs, dermal dendritic cells; IDECs, inflammatory dendritic epidermal cells; LCs, Langerhans cells; mDCs, myeloid dendritic cells; pDCs, plasmacytoid dendritic cells.

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Introduction

Epithelial surfaces defend against potential pathogenic invaders such as allergens or microbes. Besides its function as a physical barrier, the skin operates as an active immunological organ, which is endorsed by specialized cells of the innate and the adaptive immune system. Dendritic cells (DCs) are professional antigen-presenting cells (APCs), which capture foreign antigens, either by phagocytosis or receptor-mediated endocytosis, and own the capacity to prime naïve T cells towards immunogenic or tolerogenic T cell subtypes [1]. In the skin, DCs serve as sentinels and reside in the upper part of this organ within the epithelium and dermis, where they continuously scan the environment for danger signals, repre-

senting an important link between innate and adaptive immunity [2, 3]. Once activated, they migrate to the T cell zones of the regional lymph nodes, thereby eliciting primary immune responses [4]. However, the outcome of an immune reaction is shaped by various factors such as DC subtype, DC differentiation state, cell microenvironment as well as interaction with other cells or DC subtypes. In this context, it becomes clear that cutaneous DCs are able to contribute as 'good' or 'bad guys' to both the control as well as the initiation of allergic skin inflammation [5]. In this review, we summarize the versatile character of DC subtypes in human skin and their role in inflammatory settings. We discuss current DC-based approaches for the management of atopic dermatitis (AD) and point to risks and limitations for the treatment of patients.

Ontogenesis and characteristics of cutaneous dendritic cells and their precursors

The human immune system comprises two main DC subtypes: classical myeloid dendritic cells (mDCs) and plasmacytoid dendritic cells (pDCs) [4]. MDCs circulate in the blood or reside in the peripheral tissue and secondary lymphoid organs. Although pDCs are primarily present in the peripheral blood [6], they are capable of migrating to lymphoid organs or tissues during inflammation as well. Based on the localization and expression pattern of cell surface molecules, the human skin harbours functionally distinct myeloid DC subsets as well as macrophage-like DCs and macrophages themselves (Table 1) [7]. The basal and suprabasal layers of the epidermis are populated by Langerhans cells (LCs), which express the C-type lectin receptor Langerin [8], whereas the connective tissue of the human dermis contains subpopulations of DCs, which can be further classified based on their reciprocal expression of CD1a and CD14 [9].

Langerhans cells are the only DC population present in healthy, non-inflamed epidermis and thus are the first DCs to encounter pathogens, which enter the body via the mucosa or the skin. Depending on the anatomical location of the skin, LCs comprise about 2–8% of all epidermal cells [10]. They express the C-type lectin receptors (CLRs) Langerin/CD207, which is critically

involved in the formation of cytoplasmic Birbeck granules, the hallmark organelle of LCs [8], and low levels of DEC-205/CD205, which is significantly up-regulated upon LC activation [11–13]. Langerin is involved in the recognition of pathogenic carbohydrate structures and, moreover, represents an important host factor in the protection against HIV-1 infection [14]. Recently it has been demonstrated that human LCs express another CLR, the DC immunoreceptor (DCIR) [15]. Both DEC-205 and DCIR seem to be implicated in antigen uptake in human DCs and induction of antigen-specific T cell responses [15, 16]. In contrast to DEC-205, DCIR, exerts immune-inhibitory functions as well [17]. Common to all DC subtypes LCs show expression of CD45 and major histocompatibility complex (MHC) class II molecules [18]. Furthermore, LCs express high levels of CD1a [19], enabling them to take up and present microbial lipid antigens to specific T cells [20]. In contrast to other DC subsets, LCs exhibit only low and restricted expression of Toll-like receptors (TLRs). Thus, freshly isolated LCs from human skin have been shown to express mRNA encoding TLR1, 2, 3, 5, 6 and 10 [21, 22] and TLR1, 2, 5, 6 protein on the surface as well as intracellular TLR9 protein [23]. Reduced expression of TLR2 mRNA and lack of TLR4 and TLR5 mRNA expression by LCs compared to dermal DCs as shown in one study [22], results in poor responsiveness to bacteria, but might be an important feature of LCs to tolerate

Table 1. DC subtypes and macrophages in normal skin and inflammatory skin lesions. (↓) down-regulation

Cell type	Localization	Characteristics	References
Langerhans cells (LCs)	(Supra-)basal layers of the epidermis	MHC class II, CD1a, CD45 Langerin/CD207, Birbeck granules, DEC-205/CD205, DCIR TLR 1, 2, 3, 5, 6, 10 (mRNA); TLR 1, 2, 5, 6, 9 (protein) CCR6, E-cadherin, EpCAM, TROP2 ICOS-L, IDO FcεRI, CD36 (absent in healthy skin) CXCR4, CCR7, CCR6(↓), E-cadherin(↓) (upon activation/maturation)	18, 19 8, 11–13, 15 21–23 30, 37–39 47–49 54, 55 40–42
Inflammatory dendritic epidermal cells (IDECs)	Lesional skin	MHC class II, CD1a, CD1b MMR/CD206 FcεRI, FcεRII/CD23, CD36	53 52 53–55
Dermal dendritic cells (dDCs)	Connective tissue of the superior dermis	MHC class II, CD45, CD11c, CD11b Subpopulations: CD1a, BDCA-1/CD1c, CD14, BDCA-3/CD141, DEC-205/CD205, MMR/CD206, DC-SIGN/CD209, CCR7, DC-LAMP/CD208 (upon maturation) TLR 1, 2, 4, 5, 6, 8, 10 (mRNA)	7 7, 9, 58–61 22, 62
6-Sulfo LacNAc dendritic cells (S ₆ DCs)	Lesional skin	6-Sulfo LacNAc, CD11c, FcγRIII/CD16, CD45RA, C5aR H ₁ R, H ₂ R, H ₄ R	79, 80 80
Plasmacytoid dendritic cells (pDCs)	Lesional skin	MHC class II, IL-3Rα/CD123, ILT7 BDCA-2, BDCA-4, DCIR, DEC-205/CD205, CLEC12A CMKLR1, CXCR3, CXCR4, TLR 7, TLR 9, H ₂ R, H ₄ R FcεRI (absent in healthy skin)	96, 97 96, 98–100 62, 91–94, 101 127
Macrophages	Upper dermis and level of the capillaries	MHC class II, CD14, FcγRIII/CD16, CD45, FcγRIα/CD64, CD68, CD163 MMR/CD206, DC-SIGN/CD209	7, 9, 41, 63, 64

commensal bacteria without causing inflammatory responses in the skin. Quite a similar concept was supposed in another study, which shows lack of TLR4 expression on LCs and production of interleukin (IL)-6, IL-8 and immunosuppressive IL-10 in response to TLR2/6 ligation [21]. Moreover, TLR2-activated epidermal LCs as well as monocyte-derived LCs have been shown to acquire Th17-polarizing capacities [24]. This observation further supports the hypothesis of a protective role of LCs against some pathogens. Due to lack of TLR7 and TLR8 expression, LCs seem to be unable to recognize viral components or might depend on cooperation with other cell types. LC development and differentiation relies on the presence of transforming growth factor (TGF)- β [25], and is controlled in an autocrine fashion by murine LCs. In contrast, there is no evidence for a similar control of human LC development by autocrine TGF- β . Nevertheless, it has been shown that treatment of human LCs with glucocorticosteroids *in vitro* is able to induce the production of autocrine TGF- β [26]. Moreover, TGF- β seems to be pivotal for the modulation of LC homeostasis in the steady-state, as it has been shown to inhibit LC maturation and migration *in vivo* in the murine system [27]. Anyway, it is very likely that TGF- β exerts a similar effect on human LCs, since it has been shown to prevent their functional, noncognate maturation *in vitro* [28]. In addition, TGF- β acts synergistically with the calcineurin inhibitor tacrolimus on the *in vitro* generation of human LCs and prevents their maturation by down-regulation of co-stimulatory molecules [29]. In this regard, suppressing harmful immune responses by keeping LCs in an immature state and restoring immunological homeostasis by facilitating LC differentiation from precursor cells might represent a helpful strategy to counteract allergic inflammatory skin reactions. Recently, human trophoblast cell surface antigen (TROP2) has been identified as a marker for human TGF- β 1-dependent epidermal LCs, which co-express epithelial cell adhesion molecule (EpCAM). In contrast, most murine LCs lack TROP2 expression. This might be based on structural differences of human and murine epidermal skin [30]. Mouse models provide evidence for self-renewal of epidermal LCs in the steady-state, whereas under inflammatory conditions LCs are repopulated by C-C chemokine receptor (CCR) 2^+ /granulocyte receptor (Gr)- 1^{hi} (equivalent to human CCR 2^+ CD14 $^{\text{hi}}$ CD16 $^-$) monocytes [31–34]. In patients receiving xenografts, donor-LCs proliferate *in situ* and persist in the transplants for years [35, 36]. The C-C chemokine ligand (CCL) 20 is involved in the constitutive trafficking of LCs and selective recruitment of LC precursors, which are equipped with the corresponding chemokine receptor CCR6 [37, 38]. Activation of LCs by inflammatory cytokines such as tumour necrosis factor

(TNF)- α induces down-regulation of the expression of the cell adhesion molecule E-cadherin and CCR6, which leads to their detachment from keratinocytes, migration out of the epidermis [39–41], and induces LC maturation and up-regulation of the chemokine receptors CXCR4 and CCR7 [42]. Thereby, CXCR4 is supposed to be crucial for LC migration from the epidermis to the dermis, whereas CCR7 is regarded to be important to guide them to the skin draining lymph nodes (DLNs) under both steady-state and inflammatory conditions [43, 44]. Studies in mice demonstrate that CCR7- and CXCR4-dependent migration of cutaneous DCs relies on the expression of CCL17, which is induced after DC activation and which is strongly up-regulated in sera of patients with AD [45]. In addition, elevated expression of CCL17 has been detected in atopy patch test biopsies of patients with AD [46]. Together, those data suggest that CCL17 might be implicated in human LC emigration to the skin DLNs as well. Because LCs express molecules involved in the inhibition of T cell responses such as the inducible co-stimulator ligand (ICOS-L) [47, 48] and the immunoregulatory enzyme indoleamine 2,3-dioxygenase (IDO) [49], LCs are supposed to be capable to contribute to peripheral tolerance under some circumstances [5]. Recent evidence from a mouse model suggests that the tolerogenic function of LCs can be maintained under different conditions that commonly lead to immunogenicity as long as the structural integrity of the basement membrane remains intact. Disruption of the epithelial basement membrane abolished the tolerizing response of LCs by the rapid migration and activation of dermal dendritic cells (dDCs) [50]. Therefore, knowledge about mechanisms, which promote tolerogenic functions of LCs towards commensal bacteria, is essential for the development of DC-based therapeutic strategies.

Next to LCs, the lesional skin of patients with AD, allergic contact eczema or psoriasis for instance harbours a second myeloid epidermal DC population, the so-called inflammatory dendritic epidermal cells (IDECs) [51]. Compared to LCs, IDECs lack Birbeck granules and Langerin expression, but show expression of the mannose receptor (MMR)/CD206, a member of the CLRs, providing IDECs with the ability to take up mannoseylated protein antigens [52]. IDECs are further defined as MHC class II, CD1a, CD1b and low affinity receptor for IgE (Fc ϵ RII/CD23) expressing cells [53]. In lesional skin of patients with AD, both IDECs as well as LCs show expression of the high-affinity receptor for IgE (Fc ϵ RI) and CD36; however, expression of both receptors is stronger on IDECs [54, 55], arguing for a stronger IgE-mediated response towards the allergen. IgE cross-linking on the surface of LCs *in vitro* induces the release of chemotactic factors, such as IL-16, CCL22, CCL17 and CCL2 [56], which

might contribute to the recruitment of other cells including IDECs and their precursors to the skin. In this regard, peripheral blood monocytes as well as dermal DCs are regarded as potential precursor cells of IDECs [57]. *In vitro*, binding and cross-linking of IgE on IDECs induce the release of pro-inflammatory cytokines such as IL-8 and TNF- α , as well as chemokines and soluble factors such as IL-12 and IL-18, driving naïve T cell development towards the production of interferon (IFN)- γ -producing T cells [56]. Although there are so far no *in vivo* data about this topic, it is very likely that activated IDECs migrate to the skin DLNs where they prime naïve T cells into effector T cells. With regard to current literature, we conclude that LCs fulfil tolerogenic functions in the steady-state.

The dermal tissue comprises immature dDCs and macrophages [7]. The major resident dDC population is characterized by expression of the blood dendritic cell antigen (BDCA)-1/CD1c in combination with the myeloid marker CD11c. In the steady-state, CD1c⁺ DCs are immature with modest T cell stimulatory ability, but their immunostimulatory capacity increases upon maturation [7]. Approximately half of the CD1c⁺ population is also positive for CD1a and expresses the chemokine receptor CCR7 [58]. There are reports about an additional population of dDCs which expresses CD14, but not CD1a [9, 59–61]. Both subsets have been shown to differ in their distribution within the tissue and their migratory activity [60]. In normal skin, another dDC population exists, which is characterized by the expression of CD141/BDCA-3 [7]. These CD141⁺ cells represent approximately 10% of all CD11c⁺ dDCs, but lack CD1c expression. Most of the CD11c⁺ cells express DEC-205/CD205 and dendritic cell-lysosomal associated membrane protein (DC-LAMP)/CD208 upon maturation [7]. Further, dDCs show expression of TLR 1, 2, 4, 5, 6, 8 and 10 mRNA [22, 62]. In contrast to LCs, dDCs exhibit expression of TLR4 and TLR8, enabling the recognition of Gram-negative bacteria and viral nucleic acids. Whereas LCs are able to tolerate commensal bacteria due to a restricted TLR expression profile, dDCs are activated by bacterial as well as viral components in case they infiltrate the dermis and consequently alert the immune system. Macrophages display expression of markers involved in antigen uptake, such as CD68 and CD163, as well as expression of CD64 (Fc γ RI α), CD16 (Fc γ RIII) and CD14 [9, 63]. Expression of MMR/CD206 and dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN)/CD209 as well as MHC class II and CD45 expression can be detected in both cell types [7, 9, 41, 64]. While dDCs are mainly located in the superior dermis, macrophages primarily reside at the level of the capillaries and in the upper part of the reticular dermis [63]. Both cell types origi-

nate from peripheral blood monocytes as their direct precursor cells. Under inflammatory conditions macrophages still reside in the dermal compartment, whereas dDCs release pro-inflammatory cytokines and migrate to the peripheral lymph nodes to induce cellular and humoral immunity [61, 65]. Whereas CD14⁺ dDCs are supposed to preferentially control humoral immunity by priming naïve B cells to switch isotype and become antibody secreting plasma cells, CD1a⁺ dDCs show a moderate ability to induce cytotoxic CD8⁺ effector T cells [61]. In contrast to migratory dDCs, macrophages remain within the dermis, being involved in the elimination of apoptotic cells and the maintenance of tissue homeostasis.

Mouse models with conditional ablation of Langerin⁺ cells *in vivo* have led to the discovery of a distinct Langerin⁺ DC subset in the dermal compartment of the skin that differs from its epidermal counterpart in cell origin and turnover rate [66–68]. Unlike epidermal LCs, Langerin⁺ dDCs are radiosensitive and display different repopulation kinetics [66, 67]. Their development is dependent on the cytokine FMS-like tyrosine kinase 3 ligand, but independent from TGF- β [69–71]. The recruitment of blood-derived progenitor cells to the dermis is dependent on CCR2, but does not require CCR6, whereas the migration of Langerin⁺ dDCs to the lymph nodes relies on the expression of CCR7 [66]. Previous to the discovery of Langerin⁺ dDCs, it was unclear if LCs are crucial or dispensable for the initiation of contact hypersensitivity (CHS) reactions [72, 73]. Now, the role of DCs in murine CHS models has been revisited and data from mouse models with conditional depletion of LCs and Langerin⁺ dDCs have led to the general assumption that Langerin⁺ dDCs are necessary for optimal CHS responses in transgenic mice, while LCs are supposed to play a more regulatory part by attenuating contact allergy [66, 68, 74, 75]. However, recent findings indicate that hapten dose and access to cutaneous DCs, rather than presence or function of a particular skin DC population, determine the intensity of a CHS reaction [76]. To date, no human counterpart of this Langerin⁺ dDC subset has been identified. Initially, a subpopulation of Langerin⁺, EpCAM[−] DCs was regarded as a likely candidate [77]. However, a more recent study provides evidence that human dermis lacks a population analogous to murine Langerin⁺ dDCs [30]. Based on the finding that human LCs show coexpression of EpCAM and TROP2, whereas dDCs lack EpCAM expression, but display moderate TROP2 expression, the only Langerin⁺ DC subset present in human dermis was characterized by coexpression of EpCAM and TROP2 and therefore was assigned to a population of migratory LCs [30].

About 0.5–2% of the peripheral blood mononuclear cells have been identified to be 6-sulpho LacNAc (slan)

expressing DCs (slanDCs), which are supposed to represent direct precursors of inflammatory dermal DCs and are characterized by the production of pro-inflammatory TNF- α and IL-12 in response to lipopolysaccharide (LPS) stimulation [78, 79]. slanDCs express CD11c, CD16 (Fc γ RIII), C5aR, CD45RA and histamine receptors (HR) H₁R, H₂R and H₄R, but lack CD1c and CD14 expression [79, 80]. Under inflammatory conditions, slanDCs are present in the dermis of patients suffering from psoriasis vulgaris and chronic skin lesions of AD [79, 80]. This leads to the assumption that slanDCs might play a role in Th1-mediated inflammatory skin diseases. In psoriasis they have been shown to drive strong Th17/Th1 T cell responses [81]. In AD patients, H₄R expression on slanDCs is up-regulated by IFN- γ . Stimulation with LPS in the presence of histamine leads to reduced TNF- α and IL-12 secretion resulting in a weaker pro-inflammatory capacity of slanDCs [80], thus making H₄R an attractive target on slanDCs for the treatment of allergic inflammatory skin diseases.

Plasmacytoid dendritic cells account for 0.2–0.8% of all peripheral blood mononuclear cells [82, 83]. Under steady-state conditions, pDCs are absent from skin and other peripheral non-lymphoid tissues, but they have been shown to infiltrate the dermis in view of viral infection [84] and chronic inflammation as seen in psoriasis [85–87], lupus erythematosus [88] and AD [85, 89, 90]. pDC migration is regulated by chemokine receptors, such as chemokine like receptor 1 (CMKLR1), CXCR3 and CXCR4 [91, 92]. According to recent studies, histamine acts as a chemoattractant via H₂R and H₄R on pDCs, modulating their migration to inflamed skin and to the regional LNs [93, 94]. Moreover, stimulation of H₂R and H₄R on pDCs has been shown to control inflammation by suppressing the production of TNF- α and INF- α by pDCs [93, 95]. However, in the context of AD this would implicate an increased risk for a subgroup of patients to suffer from viral skin infections. pDCs express high levels of the interleukin-3 receptor (IL-3R) α chain (CD123) and immunoglobulin-like transcript 7 (ILT7), which is exclusively expressed by human pDCs [96, 97]. The ILT7 couples with the signal adapter protein Fc ϵ RI γ transducing immunoreceptor-based tyrosine activation motif-mediated signals that regulate TLR-induced type I IFN production in human pDCs [97]. Furthermore, pDCs express CLRs including the endocytic receptors BDCA-4 and BDCA-2, the latter being exclusively expressed on pDCs [96], endocytic DCIR, which is supposed to have immune-inhibitory functions [98], and CLEC12A, which serves as an antigen delivery target in mice and humans [99]. Recently, pDCs have been shown to further express DEC-205, which is supposed to mediate antigen uptake and presentation in both resting and activated pDCs

[100]. Compared to mDCs, TLR expression of pDCs mainly comprises endosomal TLR7 and TLR9, thus providing pDCs with the ability to recognize viral- and self-nucleic acids [62, 101]. After stimulation by viral or other microbial products, pDCs produce large quantities of type I IFNs, triggering pDC maturation and migration to the LNs and further promoting the function of accessory cells of the innate immune system [82]. pDCs become activated by a regulated expression of antimicrobial peptides (AMPs) in damaged skin. However, overexpression of AMPs leads to the initiation of an autoimmune reaction, through an excessive sensing of self-nucleic acids and uncontrolled secretion of type I IFNs by pDCs as seen in psoriasis [102–104].

The multifaceted character of cutaneous DCs and their diverse expression of PRRs and other molecules involved in T cell interactions, supports the hypothesis that DC subsets play different roles in pathogen recognition and the induction of adaptive immune responses.

Cutaneous dendritic cells and allergic skin inflammation: atopic dermatitis

Atopic dermatitis is one of the most frequent chronic inflammatory skin diseases with increasing prevalence, affecting 10–20% of children and 1–3% of adults in industrialized countries [105, 106]. The pathogenesis of AD is based on a strong genetic predisposition together with influences from environmental trigger and multiple deficiencies of the innate and adaptive immune system. The breakdown of the skin barrier function promotes susceptibility of the patients to allergens or skin infections which influence the course and severity of AD (Fig. 1) [107]. Th2-associated cytokines predominate in the acute phase of AD, whereas a mixed Th1/Th0 cytokine profile characterizes the chronic phase of the disease [108, 109]. Next to Th2 and Th1 cells, increased numbers of Th17 as well as Th22 cells have been detected in AD skin lesions [110, 111]. According to recent observations both T cell subsets are supposed to play an important role in the pathogenesis of AD [112].

Mutations in the gene coding for filaggrin (*FLG*) associated with skin barrier abnormalities have been found to be implicated in the development of AD [113, 114]. In this context, IL-25-producing DCs were identified in the dermis of AD patients [115]. IL-25 inhibits *FLG* synthesis in primary keratinocytes *in vitro*. Furthermore, IL-25 functions as an inducer of Th2 responses in a murine model of asthma [116], thus providing a possible link between skin inflammation and the skin barrier dysfunction in AD [115].

High expression of the IL-7-like cytokine thymic stromal lymphopoietin (TSLP) by epidermal keratinocytes is another characteristic feature of lesional skin of

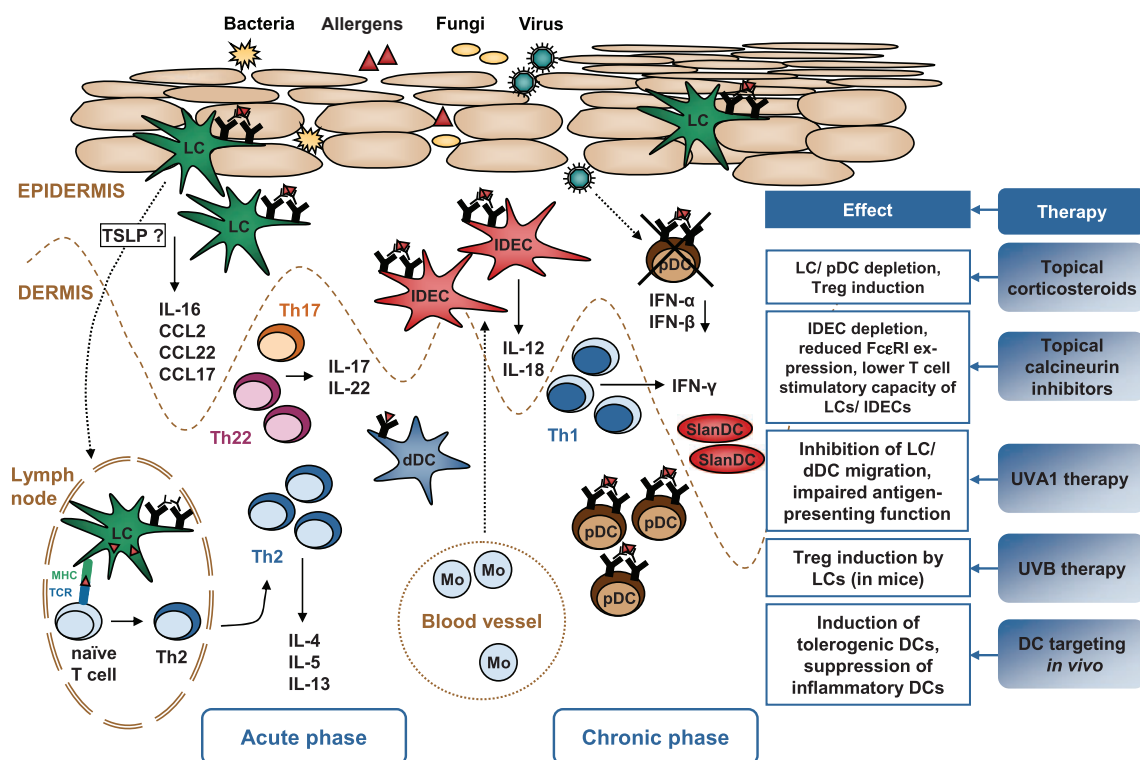


Fig. 1. Role of cutaneous DC subsets in atopic dermatitis and possible DC-based therapeutic strategies for the treatment of patients. LC, Langerhans cell; IDEC, inflammatory dendritic epidermal cell; pDC, plasmacytoid dendritic cell; dDC, dermal dendritic cell; slanDC, 6-sulpho LacNAc dendritic cell; Mo, monocyte; IL, interleukin; IFN, interferon; CCL, CC-chemokine ligand; TSLP, thymic stromal lymphopoietin.

both acute and chronic AD [117]. In this regard, pro-inflammatory (TNF- α and IL-1 α) and Th2 (IL-4 and IL-13) cytokines synergize to induce the production of TSLP in human skin explants [118]. *In vitro*, CD4⁺ naïve T cells stimulated with TSLP-treated LCs secrete a pro-allergic pattern of cytokines, which is marked by increased amounts of IL-4, IL-5, IL-13 and TNF- α and lower levels of IFN- γ and IL-10 [119]. In a mouse model of AD with epidermal TSLP overexpression, LCs seem to be the crucial DC subset for the priming of Th2 responses, thereby triggering disease development [120]. Recently, TSLP has been shown to trigger DC migration in a cell-autonomous manner, which could importantly impact on the migratory activity of DCs in inflamed human skin [121]. Moreover, data from an *in vitro* study demonstrated that murine DCs independently produce TSLP in response to TLR stimulation and that this is further increased in the presence of IL-4, which might play a crucial role in the pathogenesis of AD, but might as well have important implications for the design of novel vaccines [122].

The skin of patients with AD is characterized by the presence of LCs and IDECs, showing high surface expression of Fc ϵ RI, which enables specific allergen uptake (Fig. 1) [123]. IDECs are regarded as important

amplifiers of the allergic inflammatory reaction on the level of DCs. Compared to LCs, IDECs show higher expression of co-stimulatory molecules, thus supporting the role of IDECs as the antigen-presenting DC population in inflamed skin [51]. After activation, IDECs are supposed to migrate to the skin DLNs, where they prime naïve T cells into IFN- γ , IL-12 and IL-18 producing cells, which might explain the switch of the initial Th2 into a Th1 response *in vivo* [56]. Allergen challenge to the skin in atopy patch test reactions induces the rapid invasion of IDECs into the epidermis and the formation of eczematous skin lesions in patients with AD [124]. Eczema development is attended by a strong increase in chemokines, in particular CCL1, CCL17 and CCL18, as well as an increase of CCR5⁺ and CCR6⁺ IDECs into the previously unaffected skin [46].

Compared to other inflammatory dermatoses, AD skin lesions harbour only few numbers of pDCs within the epidermal skin layer [85, 125]. However, compared to healthy skin, AD skin lesions are marked by increased numbers of pDCs within the dermal compartment, showing an activated phenotype [89]. Investigations on psoriatic skin revealed that pDC recruitment into the dermis correlates with the expression of the inflammatory chemotactic factor chemerin, the ligand

to CMKLR1, selectively expressed on pDCs, and is an early event in the formation of psoriatic lesions [126]. In contrast, chemerin expression in AD skin lesions is weak and thus might explain the reduced infiltration of pDCs into inflamed tissue. Given that peripheral blood pDCs of patients with AD express only low levels of skin-homing molecules such as cutaneous lymphocyte antigen and L-selectin CD62L [127], this might together with the Th2 cytokines in the skin microenvironment additionally prevent efficient pDC recruitment into lesional skin. Further on, *in vitro* aggregation of FcεRI on pDCs has been shown to induce the release of tolerogenic IL-10 and to enhance the apoptosis of pDCs (Fig. 1). Stimulation of FcεRI-preactivated pDCs via TLR ligation results in reduced production of IFN-α and IFN-β, which might explain the enhanced susceptibility of patients with AD to viral infections [127].

Cutaneous dendritic cells as therapeutic targets

During the last few decades numerous advantages in the development of therapeutics have been made to improve the clinical symptoms of patients suffering from chronic inflammatory skin diseases such as AD. Thus, various medications have become available,

which have the potential to positively impact on the current state of the disease (Fig. 1 and Table 2).

Besides emollients, which aim to improve skin hydration and skin barrier, topical corticosteroids (CS), which function as anti-inflammatory suppressors of the immune system, have been widely used for the treatment of eczematous skin lesions. Topical application of CS has been shown to reduce the number of LCs by depletion and to inhibit their T cell stimulatory ability [128, 129]. *In vitro*, CS interfere with the differentiation, maturation and function of DCs by reducing their antigen-presenting and immunostimulatory properties [130, 131]. Recently, application of CS has been shown to endow human LCs to induce regulatory T cells (Tregs) *in vitro*, which is dependent on autocrine TGF-β produced by LCs themselves [26]. However, even short-term treatment with CS has been shown to interfere with the viability of LCs in AD skin lesions and DC precursors *in vitro* [132, 133], and could therefore have adverse effects on the skin immune system. Moreover, depletion of human pDCs in the peripheral blood and in skin lesions of patients with AD along with depressed IFN-α production has been reported as secondary effect of CS administration [134, 135].

More recently, topical calcineurin inhibitors such as tacrolimus and pimecrolimus have become available for

Table 2. Current and possible future DC-based therapeutic approaches for the treatment of atopic dermatitis. (?), Not investigated in AD.

Therapy	Target cells	Effect	Benefits (+) Risks (–)	Refs
Topical corticosteroids	LCs	LC depletion, reduction of antigen-presenting and T cell stimulatory properties, induction of regulatory T cells	(–) not convenient for long-term treatment of chronic AD lesions due to potential side effects (reduced LC/pDC viability)	128–135 26
Topical calcineurin inhibitors	LCs, IDECs	Reduced T cell stimulatory capacity, reduced FcεRI expression, IDEC depletion in epidermal skin lesions	(–) local side effects (low bioavailability, burning and pruritus at the application site) (+) encapsulation of the drug in lipid nanoparticles might reduce skin irritating potential (+) valuable for the long-term management of AD	29 140–142 144, 145
UV light therapy	LCs, dDCs	UVA1: inhibition of LC/dDC migration, reduction of FcεRI-positive LCs in the dermis, impaired antigen-presenting function UVB: induction of regulatory T cells (in mice)	(+) temporary improvement of skin lesions (–) lack of randomized controlled trials investigating the long-term use (–) possible long-term side effects of high-dose UVA1 (photodamage, carcinogenesis)	146–149 151, 152 158 150
Antigen loading to DCs <i>ex vivo</i>	<i>In vitro</i> -generated DC	(?)	(–) time consuming and expensive cell isolation and <i>in vitro</i> generation of DCs	162
DC targeting <i>in vivo</i>	All DC subsets	(?) Designated effect: enhancing the regulatory function of LCs, suppressing the inflammatory action of other DC subsets	(+) selective targeting of DC subsets (–) requires careful considerations of DC activation state, type and molecular nature of the target receptor, mode of antigen delivery (–) need for application and investigation in human model systems	160–162 166, 167

Note: DC, dendritic cell; AD, atopic dermatitis; LCs, Langerhans cells; dDCs, dermal dendritic cells; pDCs, plasmacytoid dendritic cells; IDECs, inflammatory dendritic epidermal cells.

the treatment of AD [136–139]. *In vivo*, topical treatment with tacrolimus results in a reduced stimulatory capacity of LCs and IDECs, combined with a lower expression of FcεRI, and a selective depletion of IDECs in the lesional epidermis of patients with AD, shifting the balance towards the LC population [29, 140–142]. Pimecrolimus treatment likewise provokes a decrease in the number of IDECs in the lesional skin of patients with AD [132, 143]. Recently, tacrolimus-loaded lipid nanoparticles have been developed to reduce local side effects that have been reported for tacrolimus ointment such as low bioavailability, burning and pruritus at the application site [144]. Skin retention and localization studies in rats revealed that in contrast to the reference drug, tacrolimus-loaded lipid nanoparticles show enhanced accumulation in the epidermal and dermal skin layer, where the target cells such as IDECs or inflammatory dermal DCs mainly reside. Since encapsulation in lipid nanoparticles avoids direct exposure of the drug to the skin, this might go along with a lower skin irritating potential, and therefore improve the tolerability of the treatment in AD [145].

An alternative anti-inflammatory approach for the treatment of more severe AD is for example treatment with ultraviolet (UV) light. High-dose (HD) UVA1 treatment has been shown to inhibit LC migration out of the epidermis and to decrease the number of IgE-bearing LCs and mast cells in the dermis of patients with AD, which was associated with the clinical improvement of skin lesions [146], as well as the decrease of the antigen-presenting function of human LCs in mixed lymphocyte reactions *in vitro* [147, 148]. Moreover, UVA irradiation of human dermal skin sheets decreased the number of emigrating dDCs due to apoptosis and impaired their phenotypic and functional maturation into potent APCs [149]. Due to concerns about possible long-term side effects of HD UVA1 therapy (photodamage, carcinogenesis), the treatment with lower doses of UVA1 is recommended and has been shown to be equally effective as higher doses in terms of improving clinical scores of patients with AD [150]. Recent data from mouse models provide evidence that LCs, but not Langerin⁺ dDCs, are essential for UV radiation (UVR)-related immunosuppression of CHS by inducing Tregs [151, 152], which not only inhibit the induction but can also suppress the elicitation of CHS, when stimulated by means of an antigen-specific boost through the skin [153]. The effect of UV phototherapy on Treg induction in humans has only rarely been investigated. In one study, treatment of patients with medium-dose UVA1 and narrow band UVB reduced clinical symptoms of AD, but the number of Tregs in healed skin lesions remained unaffected [154, 155]. However, induction of Tregs in patients has been reported in the case of extracorporeal photopheresis, a process in which peripheral

blood mononuclear cells are exposed to 8-methoxypsoralen plus UVA *ex vivo* prior to reinfusion [156]. In this regard, engagement of apoptotic cells with APCs seems likely to initiate the induction of antigen-specific Tregs [157]. Since most experiments investigating the effects of UVR on DC biology have been performed in mouse models, there is a need for performing comparable studies in human model systems to gain additional knowledge of UV therapy for the treatment of patients. Although UV light therapy can temporarily improve the severity of eczema, there is lack of randomized controlled trials comparing different phototherapeutic modalities and investigating the long-term use of this treatment [158].

Whereas current vaccination strategies simultaneously affect several DC types, the development of more recent DC-based vaccination strategies relies on the diversity and plasticity of DC subsets, and allows the selective targeting of single DC subsets, implicating the generation of distinct types of immune responses. They include two main approaches, the loading of DCs *ex vivo*, which has been successfully adopted to sustain immune responses in patients with cancer and HIV infection [159], and the novel therapeutic approach of *in vivo* targeting of DCs [6, 160–162]. The latter describes a method where antigens are delivered directly to DCs *in vivo*, using a chimeric protein composed of the respective antigen and an antibody against a DC-specific cell surface receptor [163]. In contrast to antigen loading to DCs in an *ex vivo* setting, *in vivo* targeting of DCs represents a less laborious and expensive way to target DCs for vaccination [162]. Earliest studies in mice demonstrate that antigen targeting to DCs via DEC-205 and co-administration of a DC-stimulating adjuvant results in an enhanced induction of T cell responses, whereas in the absence of proper activation and maturation stimuli, DC targeting induces tolerance [164, 165]. Thus, considering the activation and maturation state of DCs as well as the selection of the right adjuvant seems to be crucial for the development of promising vaccines. In addition, the type and molecular nature of the target receptor as well as the mode of antigen delivery (epicutaneous, subcutaneous or intradermal injection) to the target cells, which determines the accessibility to a certain DC subset, differently affect the type of the immune response [166]. In this regard, a recent study demonstrates that intradermal injection of antibodies against Langerin and DEC-205 into human or mouse skin explants *ex vivo* was able to efficiently target skin DCs, especially epidermal LCs and the murine Langerin⁺ dDC population [167], indicating that large antibody molecules deposited in the dermis can easily access the epidermis by diffusion through the basement membrane. Another study focusing on human skin DCs demonstrates enhanced expansion of antigen-

specific CD8⁺ T cells *in vitro*, when the antigen was delivered to human skin-isolated LCs via DCIR- or Langerin-specific antibodies as opposed to free antigen [15]. TLR7/8 activation further enhanced DCIR-mediated cross-presentation as well as cross-priming and increased expansion of primed CD8⁺ T cells and production of IFN- γ and TNF- α . In addition, targeting of antigen to DCIR or DEC-205 on human pDCs has been demonstrated to inhibit or to impair TLR9-induced IFN- α production, without affecting TLR-induced upregulation of costimulatory and MHC molecule expression on pDCs, thereby retaining their capacity for antigen presentation [98, 100].

Thus, besides DEC-205, Langerin and DCIR as well as the recently identified TROP2 could be attractive targets on LCs for *in vivo* antigen delivery in humans, whereas MMR/CD206, DC-SIGN, BDCA-1 and BDCA-3 might represent attractive targets on dDC subsets. In addition, pDCs could be targeted via DCIR, CLEC12A, BDCA-4 or BDCA-2. However, due to simultaneous expression on different DC subsets, certain target receptors such as DEC-205 and DCIR might not be appropriate for the targeting of a particular DC subset. Therefore, it would be important to select a target receptor that is specific for the DC subtype of interest. In this regard, BDCA-2 might be a promising target for pDCs, Langerin and TROP2 for LCs and BDCA-3 and BDCA-1 for certain dDC subsets.

Although antigen delivery to DCs *in vivo* seems to have a lot of therapeutic properties, there is no information about the clinical advantage of this approach for the treatment of allergic skin diseases such as AD, since investigations in this field are lacking. Moreover, most of the studies have been performed in mouse models, but in these cases skin DCs have only rarely been investigated. Since human studies are limited due to experimental conditions, the use of humanized mouse models might be helpful to study physiological processes *in vivo*. However, care has to be taken when translating murine experimental data into human vaccination strategies, as receptor expression patterns and functions, especially those of CLRs, differ among mice and humans as in the case of DC-SIGN for example [168]. Therefore, it still remains essential to examine the capability of human skin DC subsets as potential target cells for vaccination.

Conclusion and perspectives

The skin is equipped with a number of specialized DC subsets, with each subset fulfilling distinct tasks in controlling tissue homeostasis or promoting inflammation. In the steady-state LCs fulfil tolerogenic functions, whereas skin barrier defects as characteristic for

AD induce the formation of a proallergic microenvironment, which triggers the immunogenic potential of LCs to initiate allergic skin inflammation. Moreover, IDECs are regarded as important amplifiers of the inflammatory reaction. Based on their individuality and easy accessibility, cutaneous DCs represent attractive targets for the design of novel immunotherapeutic approaches for the management of allergic skin disorders. In this regard, targeting inflammatory DC subtypes via CLRs or other DC-specific molecules might be valuable to down-modulate the pro-inflammatory potential and induce tolerogenic properties in the target cells. On the one hand, this could be achieved by suppressing the activity of inflammatory DC subtypes such as IDECs. In this regard, receptors involved in the uptake of allergens or pathogens such as IgE receptors could be targeted to attenuate the inflammatory response in patients with AD. Enhancing the regulatory function of LCs by promoting the expression of molecules (ICOS-L or IDO) involved in the induction of Tregs is another possibility. Because LC targeting is able to directly impact on the initiation phase of allergic skin inflammation, this approach might be more promising for the treatment and prevention of AD.

Future research activities might benefit from rising knowledge about tolerogenic properties of DCs in other organ systems such as the mucosa, which might help to understand how immune tolerance can be maintained or naturally induced. Finally, it is noteworthy to re-emphasize that the manifestation of AD and most other allergic skin diseases originates from complex trigger factors. Therefore, an exclusive DC-based therapy might improve the disease, but presumably, it will be more promising to pursue an approach dealing with several aspects, such as the skin barrier defects etc. in combination with DC-based strategies. Thus, unravelling the question, which cutaneous DC subset is primarily involved in the initiation and maintenance of AD, would help to shed light on the pathogenesis of this disease and further help to improve the development of DC-based vaccination strategies or other novel therapeutic approaches.

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