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An update on the role of human dendritic cells in patients with atopic dermatitis

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Dendritic cells (DCs) are without a doubt important key skin cells that connect information from the environment with the innate and adaptive immune system. Their function is decisive for the initiation and inhibition of immune responses, and therefore they play a central role for both the healthy and diseased states of the skin. The type, maturation stage, and function of DCs, as well as the microenvironment in which they are located and their contact with cellular partners in the surrounding area, are important cofactors that direct maintenance of immune homeostasis or breakout of inflammatory reactions in patients with chronic inflammatory skin diseases, such as atopic dermatitis. Thus better knowledge about the exact proinflammatory and anti-inflammatory properties of DCs in patients with atopic dermatitis and the disease-specific roles of DC subtypes would allow us to target these important immune cells with versatile functions for therapeutic purpose. (*J Allergy Clin Immunol* 2012;■■■:■■■-■■■.)

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Atopic dermatitis (AD) is one of the most common and most intensively studied chronic inflammatory skin diseases. Several cofactors, such as an impaired skin barrier function, modifications of the immune system, and a complex genetic background, direct the course of AD.¹⁻³ Within this complex network, dendritic cells (DCs) play a pivotal role as central connecting components on the cellular level. DCs use their dendrites and surface receptors to facilitate the recognition, phagocytosis, and transmission of information between the environment and the innate and adaptive immune systems. However, DCs not only act as important messengers in patients with AD but also are directly and actively involved in the aggravation of disease-specific processes leading to the release of soluble mediators and T-cell activation. Skin

Abbreviations used

AD: Atopic dermatitis
DC: Dendritic cell
H4R: Histamine receptor 4
IDEC: Inflammatory dendritic epidermal cell
IDO: Indoleamine 2,3-dioxygenase
IRF-1: Interferon-regulatory factor 1
LC: Langerhans cell
LTA: Lipoteichoic acid
pDC: Plasmacytoid dendritic cell
TSLP: Thymic stromal lymphopoietin

barrier dysfunction is a hallmark of most patients with AD and is in part based on a strong genetic predisposition.⁴ The disrupted skin barrier allows numerous foreign antigens to enter the skin and to activate DCs as a central disease-promoting factor. In addition, specific cellular modifications and related changes of the skin microenvironment act secondarily on skin barrier function in patients with AD.⁵ In this context DCs serve a dual role because they represent integral parts of the skin barrier and are able to modulate skin barrier function. However, it is not only enhanced release of proinflammatory cytokines and chemokines by DCs that contributes to the pathophysiology of AD. It is more than likely that diminished responsiveness of DCs to IFN- γ or other factors, usually inducing pathways that counteract T_H2 immune responses, contribute to the pathophysiology of AD. Consequently, DCs represent important targets for therapeutic approaches, which might be aimed at directly or indirectly reverting individual modifications of DCs and their functions in patients with AD. In this overview we summarize the most recent developments and insights into the role of human DCs in patients with AD.

SUBTYPES OF DCs IN SKIN OF PATIENTS WITH AD

The pattern of DC subtypes and their phenotypic and functional characteristics in the different compartments change continuously with the severity of skin inflammation. The composition of skin DCs is governed by resident DCs, DCs actively recruited to the skin at onset of inflammation, emigration of DCs to the lymph nodes after antigen uptake, depletion of specific DC subtypes, and recruitment of particular DC subtypes by therapeutic agents.⁶

As a characteristic feature, DCs in the skin of patients with AD are equipped with the high-affinity receptor for IgE (Fc ϵ RI), and several subtypes of Fc ϵ RI-bearing DCs have been detected in the epidermis and dermis of nonlesional and lesional skin of patients with AD (Fig 1).

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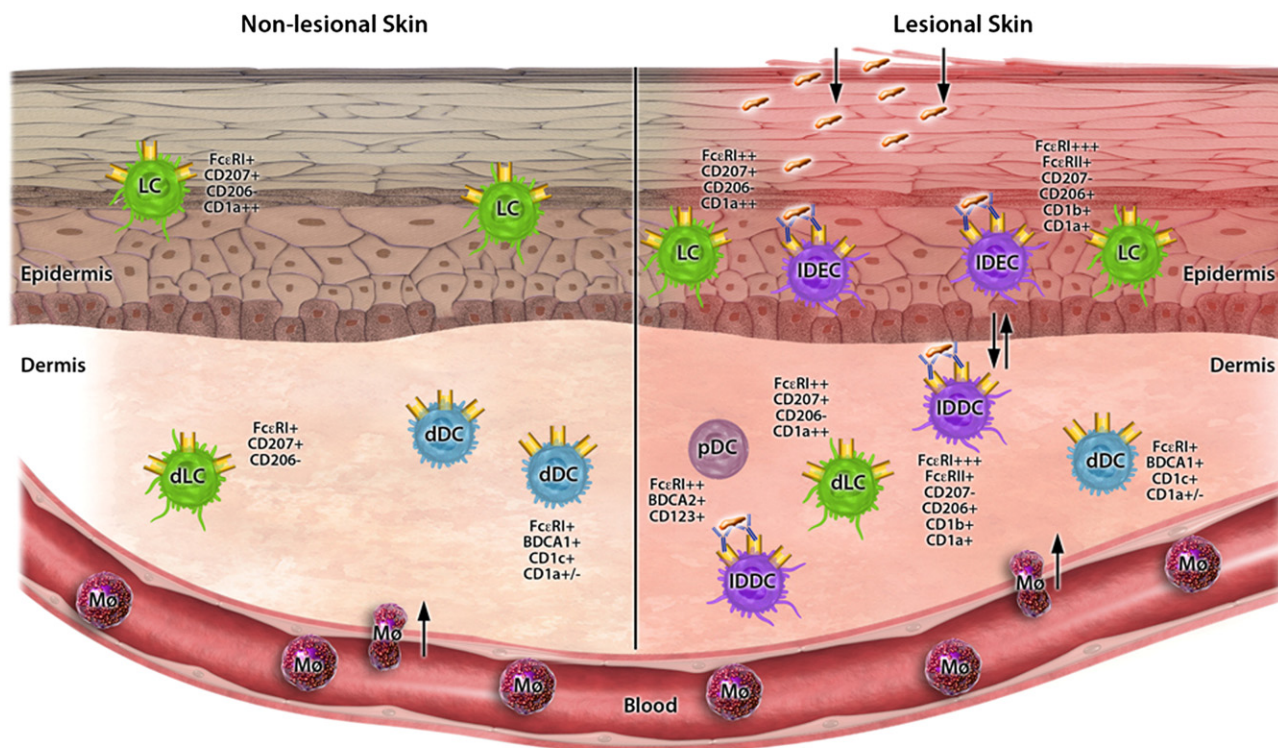


FIG 1. Schematic overview of DC subtypes in nonlesional and lesional skin of patients with AD. The pattern of DC subtypes in nonlesional versus lesional skin of patients with AD is shown. LCs predominate in the epidermis of nonlesional skin, few LCs are also present in the dermis, and the main population of the dermis are dermal DCs. These cells are supplemented by inflammatory DC subtypes in the epidermis and dermis, as well as pDCs in the dermis, in lesional skin of patients with AD. *dLC*, Dermal langerin-positive dendritic cell; *IDDC*, inflammatory dendritic dermal cell; *Mo*, monocyte.

$CD1a^{+}Fc\epsilon RI^{+}$ Langerhans cells (LCs), which express the Langerhans cell marker langerin (CD207), predominate in nonlesional epidermal skin of patients with AD.⁷ Inflammatory dendritic epidermal cells (IDECs) are recruited to the epidermis on inflammation. IDECs express, among other surface markers, mannose receptor/CD206, CD1b, and, in addition to $Fc\epsilon RI$, the low-affinity receptor for IgE ($Fc\epsilon RI/CD23$).⁸ However, inflammatory DC subtypes with quite similar surface markers have been identified in the dermal compartment of lesional skin of patients with AD as well.⁹ The dermal compartment comprises blood dendritic cell antigen 1–positive/ $CD1c^{+}/Fc\epsilon RI^{+}$ DCs and a few $CD1a^{+}/Fc\epsilon RI^{+}/CD207^{+}$ DCs.¹⁰ Approximately half of the $CD1c^{+}$ population is also positive for CD1a and expresses the chemokine receptor CCR7, which is important for their recruitment to lymph nodes.¹¹ $Fc\epsilon RI^{+}/CD123^{+}$ blood dendritic cell antigen 2–positive plasmacytoid dendritic cells (pDCs) are nearly absent from the epidermal skin of patients with AD^{10,12} but are recruited to the dermis on allergen challenge.¹³

LCs are assumed to be capable of maintaining the physiologic homeostasis of the skin. Both exogenous and endogenous danger signals increase, and epidermal LCs are supplemented by IDEC subtypes that are most likely recruited from the dermal compartment and precursor cells in the blood.¹⁴ Immigration of IDECs goes along with the development of clinically visible eczematous skin lesions of different severity.^{10,15} In addition, sequential biopsy specimens taken before and after application of allergens to the skin during atopy patch testing revealed increased $Fc\epsilon RI$

expression on epidermal DCs, rapid influx of IDECs to the epidermis, and reduction of LCs in the epidermis. After topical treatment of AD, the number of epidermal DCs decreases significantly.¹⁶

The low number of pDCs in the epidermis of patients with AD is supposed to be in part responsible for the high susceptibility of patients with AD to viral skin infections.¹² Furthermore, the near absence of epidermal pDCs and reduced release of type I interferons by pDCs after $Fc\epsilon RI$ -mediated allergen challenge¹⁷ might further contribute to the relatively low levels of type I interferons in the skin and overbalance of T_H2 cytokines. Whether pDCs of patients with AD express histamine receptor 4 (H4R), as recently shown for pDCs of patients with psoriasis,¹⁸ is currently unclear.

Changes of DC subtypes in the epidermis and dermis during eczema development is driven by a complex modification of the type and level of chemokines in the cellular microenvironment in response to allergen challenge.¹⁹ Moreover, dermal pDCs in patients with AD have been demonstrated to release high amounts of CCL22¹⁹ as a characteristic feature. CCL22 binds to the chemokine receptor CCR4 and plays a role in the recruitment of T_H2 cells to the skin in patients with AD. Both T_H2 cytokines and IL-10 present in skin of patients with AD are assumed to be in part responsible for the relatively low number of pDCs in skin of patients with AD because they are supposed to favor cell death of pDCs.^{17,20} Because pDCs play an important role in defense against viral infections, the relatively low number of pDCs in skin of patients with AD and the decreased capacity of

pDCs to release IFN- α and IFN- β in response to viral antigens after allergen challenge¹⁷ might, together with other risk factors, contribute to the high susceptibility of patients with ADs to disseminated viral skin infections.²¹⁻²³

As shown recently, components influencing the differentiation and nature of DCs in the skin include, among others, memory T_H cells.²⁴ *In vitro* experiments with monocytes and T_H cells revealed that T_{H2} cells and soluble factors released by those T cells promote the generation of DCs from human monocytes with characteristics of DCs present in lesional skin of patients with AD. Moreover, DCs generated in the presence of T_{H2} cells further support the release of T_{H2} cytokines of cocultured T_{H2} cells, indicating a feedback regulation between differentiating DC subtypes and the type of T_H cells in the microenvironment. This could lead to the amplification of disease-specific T_H cell responses *in vivo*.

It has been shown recently that both DCs enriched from the skin of patients with AD and the skin of patients with psoriasis are able to induce any kind of T-cell response *in vitro*.²⁵ This implies that the microenvironment and stimuli activating DCs in the skin specifically in the context of the respective disease influence the nature of T_H cell priming and might thereby direct disease-specific immune responses. Moreover, release of chemokines by DCs, such as CCL17, CCL18, and CCL22,²⁶ and other skin cells might further regulate the type of T_H subtypes recruited to the skin.²⁵ Consequently, the intrinsic capacity of skin DCs to drive any type of T-cell response could be targeted by using therapeutic approaches aimed at changing factors in the cellular microenvironment of DCs. In this context it has already been shown that the amount of IL-5, IL-13, and IL-10 in the skin of patients with AD decreases in response to topical treatment with calcineurin inhibitors.^{27,28} Thereby DCs could be instructed to terminate the polarization of disease-specific T cells to prime T cells with antagonistic tolerogenic properties instead to attenuate allergic skin inflammation.

ROLE OF DCs IN SKIN BARRIER FUNCTION

As one of the hallmarks of the disease, skin barrier function in patients with AD is profoundly impaired. A close and complex interrelation of skin barrier dysfunction and DCs within the skin acts as another comodulator of the course of AD. Part of the skin barrier dysfunction is based on genetic modifications, such as loss-of-function mutations in the filaggrin gene or other gene regions encoding components of the epidermal differentiation complex, proteases, and protease inhibitors.²⁹ Filaggrin mutations have been shown to be present in patients with inherited skin barrier impairment, such as ichthyosis vulgaris, and in about one third of white patients with AD. Filaggrin plays a role in the outer epidermal layer, and loss-of function mutation carriers show a reduced expression of the protein, leading to skin barrier dysfunction. Additionally, skin barrier dysfunction is secondarily impaired by disease-specific changes in the skin, such as the nature of the microenvironment (eg, T_{H2} cytokines), and soluble mediators present in the skin of patients with AD, such as thymic stromal lymphopoietin (TSLP).³⁰⁻³² The upper part of the mechanical skin barrier comprises the stratum corneum and the stratum granulosum. Among the latter, tight junctions represent transmembrane proteins, to which the claudin family belongs.³³ Claudins are capable of modulating of transepithelial electrical resistance to both maintain protection and disrupt skin barrier function.

Claudin-1 plays an important role in the enhancement of barrier function. Reduced claudin-1 levels have been observed in the skin of patients with AD, and a haplotype-tagging *CLDN1* single nucleotide polymorphism has been demonstrated to be associated with AD.³⁴ This is of particular immunologic importance because DCs in the skin closely interact with tight junctions³⁵ by elongating their dendrites in response to activation to establish cellular connections with keratinocyte tight junctions. A complex interplay of DC dendrites and keratinocyte tight junctions allows antigen uptake and penetration through DCs while the integrity of the skin barrier is maintained. Consequently, genetically predetermined deficiency of the tight junctions can lead to the disorganization of both DC function and skin barrier function and enhance the risk of penetration of particular antigens to the skin of patients with AD.

Another role of DCs in skin barrier function might derive from the capacity of epidermal LCs and dermal DCs to induce IL-22-producing CD4⁺ T cells from naive T cells, as well as T cells in the peripheral blood *in vitro*.²⁵ However, it is unclear in which way they induce T_{H22} cells, but it is very likely that IL-6 and TNF- α released by maturing DCs might contribute to this process because both cytokines have been demonstrated to be important for T_{H2} polarization.³⁶ Both CD4⁺ and CD8⁺ T_{H22} cells have been demonstrated to be present in epidermal skin lesions of patients with AD in contrast to T_{H17} T cells, which are only present in low amounts.³⁷ Because IL-22 induces hyperplasia and acanthosis of keratinocytes and downregulates expression of proteins of the epidermal differentiation complex, such as involucrin, loricin, and filaggrin,^{38,39} T_{H22} induction by DCs might directly affect skin barrier dysfunction in patients with AD.

Another way in which DCs might impair skin barrier function in patients with AD is based on their capability to produce IL-25, a cytokine that they produce in the skin of patients with AD in increased amounts.⁴⁰ This is important because IL-25 not only increases T_{H2} cell responses and cytokine production but also profoundly downregulates filaggrin synthesis of keratinocytes *in vitro*.³⁸

OVERSTIMULATION OF DCs AS A PATHOGENETIC FACTOR IN PATIENTS WITH AD

Frequent activation and stimulation of DCs results from a broad range of putative ligands available in the surrounding of skin DCs as a result of the deficient skin barrier, repetitive mechanical damage induced by scratching, and a high number of microbes that colonize the skin of patients with AD. *Staphylococcus aureus* enterotoxins,⁴¹ allergens,⁴² components of *Malassezia sympodialis*,⁴³ or others are among these trigger factors. Moreover, specific receptors, such as Fc ϵ RI or C-type lectin receptors, expressed by skin DCs in patients with AD allow the uptake of a wide range of antigens. One important stimulator of skin DCs in patients with AD is the IL-7–like cytokine TSLP, which is strongly expressed by keratinocytes in the lesional and nonlesional skin of patients with AD. Both skin barrier dysfunction and proinflammatory cytokines, such as IL-1 β , TNF- α , IL-4, or IL-13, in the skin of patients with AD are able to induce TSLP expression.^{44,45} In addition, genetic modifications that might putatively affect TSLP promoter activity have been demonstrated to be associated with AD as another reason for enhanced TSLP levels in the skin of patients with AD.⁴⁶ Furthermore, reduction of transcription factor specificity protein 1 in lesional skin of patients with AD might

indirectly enhance TSLP levels by increasing the activity of kallikrein-related peptidases.⁴⁷

Activation of human epidermal LCs with TSLP *in vitro* leads to the upregulation of MHC class II and CD86 expression and enhanced release of the T_H2 cell-attracting chemokine CCL17/thymus and activation-regulated chemokine.⁴⁸ Additionally, after coculture with TSLP-stimulated LCs, T cells produced more T_H2 cytokines, such as IL-4, IL-5, IL-13, and the inflammatory cytokine TNF- α . Most interestingly, DCs are not only target cells for TSLP, but under specific circumstances, such as stimulation with house dust mite allergens, they are also capable of producing TSLP in murine models.⁴⁹

Colonization of the skin of patients with AD with *S aureus* is high, and *S aureus* is responsible for secondary infections of the skin, which in a subgroup of patients affects the severity of the disease. *S aureus* enterotoxins, as well as other factors, such as lipoteichoic acid (LTA), as components of the bacterial cell wall are responsible for this phenomenon. With the help of wash fluids from the skin of patients with AD, it has been demonstrated that LTA in these fluids profoundly stimulates the release of the inflammatory cytokines IL-1 β , IL-6, and TNF- α by DCs *in vitro*.⁵⁰ In this way *S aureus* components, such as LTA, might contribute to DC-mediated inflammation in patients with AD. Because LTA is supposed to bind to Toll-like receptor 2 and inflammatory cytokine production was dependent on MyD88 activation in this model, this effect might be mediated through pattern-recognition receptors expressed by DCs.⁵⁰

DCs in the skin of patients with AD express the IgE receptor Fc ϵ RI in high amounts. Expression of Fc ϵ RI on the cell surface and the number of Fc ϵ RI-expressing DCs in the epidermis increase rapidly after allergen challenge.⁵¹ It is thought they are capable of taking up allergens through IgE and that this mechanism contributes to the amplification of the inflammatory reaction in the skin.⁴² Fc ϵ RI-expressing DCs in lesional skin of patients with AD coexpress CD9 and CD81.⁵² CD9 and CD81 belong to the tetraspanin family. They associate with Fc ϵ RI and enhance Fc ϵ RI-mediated signals *in vitro*. Most of the roles of tetraspanins are not related to direct ligand receptor binding but consist of their interaction with their partner proteins to enhance or silence the mediated signals. Therefore CD9 and CD81 on skin DCs in patients with AD might amplify Fc ϵ RI-mediated signals and thereby contribute to the strength and type of the initiated immune response as another cofactor that amplifies DC activation in patients with AD.

Histamine is released in high amounts by mast cells but also by other cells in the skin. Therefore an immunomodulatory role of histamine on DCs, which express histamine receptors, as well as a putative influence of therapeutic pathways targeting histamine receptors, has been discussed for a long time. Histamine promotes T_H1 polarization by DCs through H4R by reducing their capacity to release IL-12 and IL-27.¹⁸ Expression of H4R has been demonstrated for IDECs in lesional skin of patients with AD, as well as 6-sulphoLacnac (slan) expressing DCs (slan-DCs).^{53,54} Slan-DCs are present in peripheral blood and are characterized by a high capacity to produce proinflammatory cytokines, such as IL-12 or TNF- α .⁵⁴ Because stimulation of DCs through H4R agonists, as well as inhibition with H4R antagonists, profoundly changes their functional properties^{54,55} and H4R antagonist treatment attenuates DC-mediated, allergen-specific T-cell responses,⁵⁶ H4R-mediated DC stimulation might represent another important trigger factor in patients with AD.

LACK OF DC-MEDIATED COREGULATORY PATHWAYS AS ANOTHER PATHOGENETIC FACTOR IN PATIENTS WITH AD

Not only mechanisms leading to overstimulation and overactivation of DCs but also alleviated immune responses contribute to the pathophysiology of AD. Single nucleotide polymorphisms in the IFN- γ (*IFNG*) and IFN- γ receptor (*IFNGR1*) genes have been shown to be associated with AD, in particular in patients with a history of AD complicated by severe disseminated cutaneous viral infections (eczema herpeticum).⁵⁷ Lower IFN- γ protein production in PBMCs of patients with AD after stimulation with HSV antigens *in vitro* has been demonstrated as well.^{21,57} Reduced IFN- γ receptor I and IFN- γ receptor II expression of DCs in the skin of patients with AD and lower responsiveness of DCs of patients with AD to IFN- γ have been shown,⁵⁸ and is mirrored by attenuated phosphorylation of signal transducer and activator of transcription 1, induction of indoleamine 2,3-dioxygenase (IDO), interferon-regulatory factor 1 (IRF-1), and interferon-inducible protein 10 expression. The reduction in induction of these interferon-dependent parameters might result from genetic modifications, as well as factors related to the T_H2-dominated disease-specific microenvironment. Interferon-inducible protein 10/CXCL10 is released by DCs to attract T_H1 cells, and therefore reduced T_H1 cell recruitment might contribute to the T_H2 cell overbalance in patients with AD.⁵⁹ IRF-1 is important for the production of IFN- γ , and reduced IRF-1 induction might contribute further to the T_H2 overbalance in patients with AD.⁶⁰ Moreover, the tryptophan-catabolizing enzyme IDO plays a role in the induction of suppressive pathways and is directly dependent on the induction of IRF-1. Thus attenuated IDO induction is very likely to contribute to the uncontrolled inflammation seen in patients with AD.^{61,62} Together, attenuated IFN- γ induction and responsiveness of DCs in patients with AD might be the cause of alleviated T_H1 immune responses in patients with AD, which are usually strong counteractors of T_H2 immune responses. In addition to impaired or alleviated defensive immune responses, anti-inflammatory or tolerogenic pathways might be deficient in patients with AD as well. In this regard components from pollen, such as phytoprostanes or adenosine, have been demonstrated to influence DC function.⁶³ Most importantly, adenosine exerted different effects on DCs of nonatopic compared with atopic donors. Stronger induction of regulatory T cells was observed after incubation of DCs of nonatopic subjects with adenosine, whereas adenosine-preincubated DCs of atopic subjects did not induce regulatory DCs but displayed stronger induction of T_H2 cells.⁶³ On the basis of these data, missing DC-mediated tolerogenic and anti-inflammatory immune responses to immunoregulatory substances in pollen might represent an important prerequisite for the manifestation of inflammatory allergic reactions in atopic subjects, including patients with AD.

HOW TO DIRECT THE PHENOTYPE AND PATTERN OF DCs IN THE SKIN FOR THERAPEUTIC PURPOSE

On the basis of the versatile functions of DCs in AD described above, therapeutic approaches might differentially target DCs directly or indirectly. Among these, directing the differentiation, immigration, and emigration of particular DC subtypes in the skin represents a promising approach. Additionally, modulation of the cellular microenvironment and type of soluble factors around DCs to promote the positive influence of tolerogenic DC subtypes would be another interesting approach.

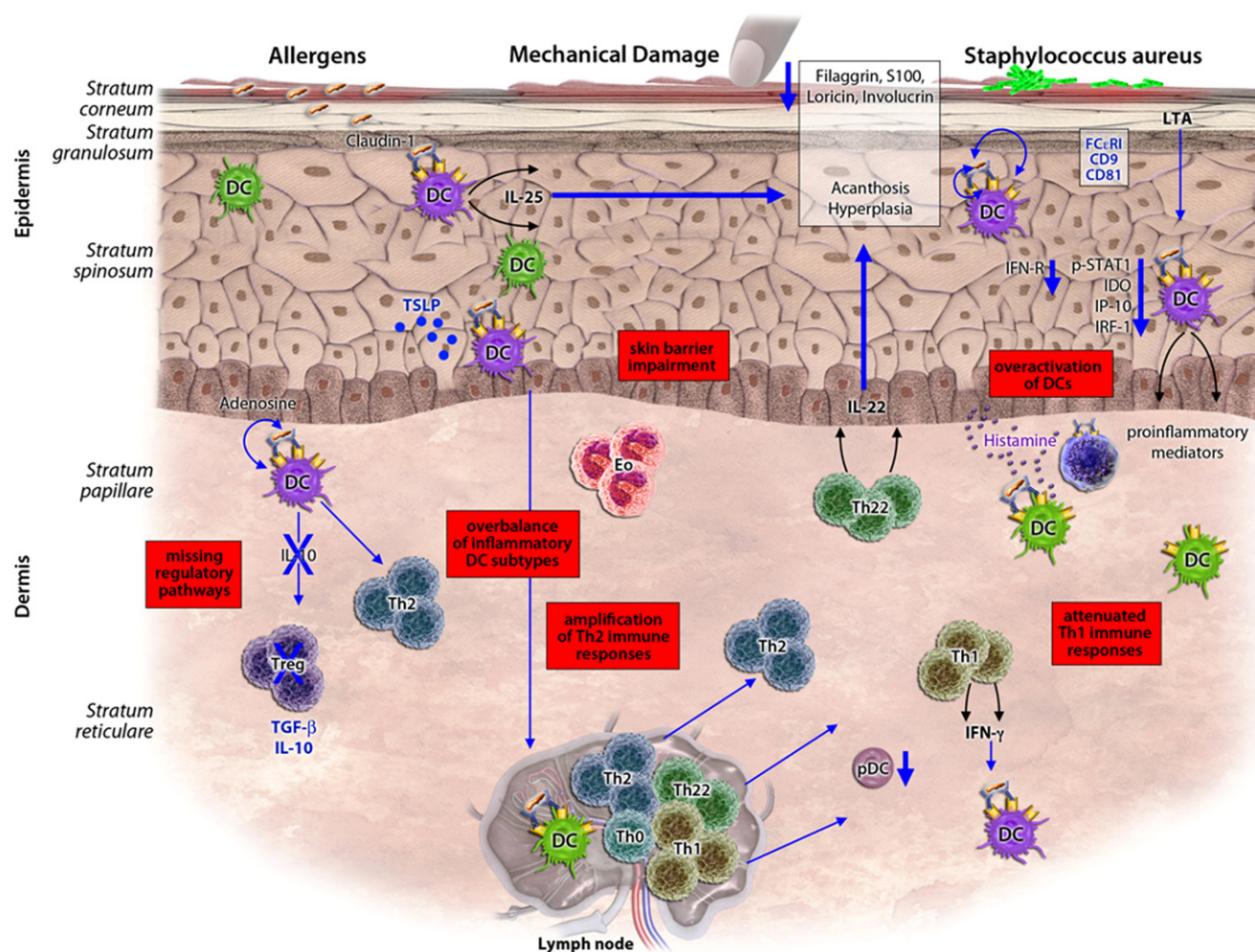


FIG 2. Summary of the versatile functions of DCs in skin of patients with AD. Pathways modified in patients with AD involving skin DCs are shown. Mechanical damage and skin barrier impairment allow penetration of the upper parts of the skin by allergens and microbial components, which come into contact with DCs. TSLP-stimulated DCs amplify T_H2 polarization, and inflammatory DC subtypes are recruited to the skin and predominate in the epidermis and dermis. In addition, regulatory pathways counteracting allergic skin inflammation are modified and attenuated in patients with AD as well. *Eo*, Eosinophil; *INF-R*, IFN- γ receptor; *IP-10*, interferon-inducible protein 10; *M*, mast cell; *p-STAT1*, phosphorylated signal transducer and activator of transcription 1; *Treg*, regulatory T cell.

Several good examples exist in support of the hypothesis that changes in the pattern of DC subtypes do not represent simply the result of changes accompanying the different disease states but are rather primarily responsible and decisive for the maintenance or restoring of a balanced immune homeostasis or the breakdown of tolerance and manifestation of allergic inflammation in the skin. With the help of murine langerin–diphtheria toxin receptor mice and selective elimination of epidermal LCs and dermal langerin-positive DCs, it has been demonstrated that allergic hypersensitivity reactions are much more intensive in the absence of epidermal LCs.⁶⁴ This implies that antigen-specific contact hypersensitivity reactions can be actively suppressed by epidermal LCs. Comparable anti-inflammatory protolerogenic properties might be exerted by epidermal LCs in patients with AD.

Because LCs represent the main epidermal DC subpopulation in nonlesional skin of patients with AD, rapid influx of other DC subtypes with inflammatory properties as a dominating feature might be responsible for the breakdown of tolerance and onset of

inflammation accompanied by eczema development in patients with AD. Therefore restoring the steady-state situation and the dominance of LCs might represent a promising therapeutic concept to attenuate the inflammatory reactions. Most likely, this could be achieved by tight control of the differentiation of DCs and their precursor cells invading from the surrounding blood vessels and dermal compartment. TGF- β is an important soluble factor supporting LC differentiation, which binds to respective TGF- β receptors. Increased expression of TGF- β receptors on LC precursor cells and enhanced LC differentiation is supposed to represent a putative way in which the topical immunomodulator tacrolimus, which has been used for the treatment of AD in clinical practice very successfully for several years now, might reduce the relative number of inflammatory DCs. This is in favor of the reconstruction of the overbalance of LCs, which accompanies improvement of the skin lesions.⁶⁵

However, not only topical immunomodulators but also glucocorticoids applied systemically are capable of modifying allergic

immune responses and target LCs. This has been demonstrated through examination of sequential skin biopsy specimens taken from patients with nickel allergy undergoing epicutaneous patch testing with nickel with and without systemic glucocorticosteroid treatment.⁶⁶ Glucocorticosteroids maintained skin LCs in an immature state and increased their TGF- β production and capacity to induce regulatory T cells. Together, these mechanisms went along with the active suppression of the development of eczematous skin lesions in nickel-sensitized subjects exposed to nickel. It is more than likely that quite similar DC-mediated tolerogenic pathways might be necessary to avoid the manifestation of allergic skin inflammation in patients with AD. As a consequence, modifications of complete absence of such counterregulatory pathways might be the basis for the propagation of allergic skin inflammation.

CONCLUSION

Much research effort over the last years has concentrated on the identification of dysregulated genetic and immunologic pathways that could lead to the manifestation of AD. Within this dense network of skin immune cells, DCs play an outstanding role and are therefore at the center of focus (Fig 2). Because of their versatile roles in the pathophysiology of AD, their multifaceted character, and their capacities to both promote and prevent the manifestation of allergic skin inflammation, DCs represent promising cellular targets for therapeutic approaches in the future.

What do we know?

- Inflammatory DC subtypes are recruited to the skin during the development of eczematous skin lesions.
- Skin barrier impairment is a critical factor in patients with AD and is part of this impairment that is genetically predetermined.
- TSLP amplifies DC-driven T_H2 cell polarization in patients with AD.
- *S aureus* (enterotoxins), *M sympodialis*, and allergens are trigger factors of AD.
- H4R is expressed by LCs, IDECs, and slan-DCs in patients with AD.
- Topical treatment with tacrolimus leads to the reduction of inflammatory DC subtypes in the skin.

What is still unknown?

- Mechanisms leading to the depletion of epidermal DCs after local glucocorticosteroid treatment
- How to target specifically skin barrier impairment and restore, for example, filaggrin reduction in patients with AD
- How to revert TSLP-driven effects on DCs in patients with AD
- In which way these factors exactly interact with DCs in patients with AD
- H4R expression and function on pDCs in patients with AD and how to target H4R in patients with AD
- Which DC subtypes are primarily targeted by different AD therapies

REFERENCES

- Novak N, Simon D. Atopic dermatitis—from new pathophysiologic insights to individualized therapy. *Allergy* 2011;66:830-9.
- Guttman-Yassky E, Nograles KE, Krueger JG. Contrasting pathogenesis of atopic dermatitis and psoriasis—part I: clinical and pathologic concepts. *J Allergy Clin Immunol* 2011;127:1110-8.
- Guttman-Yassky E, Nograles KE, Krueger JG. Contrasting pathogenesis of atopic dermatitis and psoriasis—part II: immune cell subsets and therapeutic concepts. *J Allergy Clin Immunol* 2011;127:1420-32.
- Barnes KC. An update on the genetics of atopic dermatitis: scratching the surface in 2009. *J Allergy Clin Immunol* 2010;125:16-29.
- Elias PM, Hatano Y, Williams ML. Basis for the barrier abnormality in atopic dermatitis: outside-inside-outside pathogenic mechanisms. *J Allergy Clin Immunol* 2008;121:1337-43.
- Merad M, Ginhoux F, Collin M. Origin, homeostasis and function of Langerhans cells and other langerin-expressing dendritic cells. *Nat Rev Immunol* 2008;8:935-47.
- Wollenberg A, Wen S, Bieber T. Phenotyping of epidermal dendritic cells: clinical applications of a flow cytometric micromethod. *Cytometry* 1999;37:147-55.
- Wollenberg A, Wen S, Bieber T. Langerhans cell phenotyping: a new tool for differential diagnosis of inflammatory skin diseases [letter]. *Lancet* 1995;346:1626-7.
- Guttman-Yassky E, Lowes MA, Fuentes-Duculan J, Whynt J, Novitskaya I, Cardinale I, et al. Major differences in inflammatory dendritic cells and their products distinguish atopic dermatitis from psoriasis. *J Allergy Clin Immunol* 2007;119:1210-7.
- Sary G, Bangert C, Stingl G, Kopp T. Dendritic cells in atopic dermatitis: expression of Fc ϵ RI on two distinct inflammation-associated subsets. *Int Arch Allergy Immunol* 2005;138:278-90.
- Zaba LC, Krueger JG, Lowes MA. Resident and “inflammatory” dendritic cells in human skin. *J Invest Dermatol* 2009;129:302-8.
- Wollenberg A, Wagner M, Gunther S, Towarowski A, Tuma E, Moderer M, et al. Plasmacytoid dendritic cells: a new cutaneous dendritic cell subset with distinct role in inflammatory skin diseases. *J Invest Dermatol* 2002;119:1096-102.
- Eyerich K, Huss-Marp J, Darsow U, Wollenberg A, Foerster S, Ring J, et al. Pollen grains induce a rapid and biphasic eczematous immune response in atopic eczema patients. *Int Arch Allergy Immunol* 2008;145:213-23.
- Kerschenlohr K, Decard S, Przybilla B, Wollenberg A. Atopy patch test reactions show a rapid influx of inflammatory dendritic epidermal cells in patients with extrinsic atopic dermatitis and patients with intrinsic atopic dermatitis. *J Allergy Clin Immunol* 2003;111:869-74.
- Novak N, Gros E, Bieber T, Allam JP. Human skin and oral mucosal dendritic cells as ‘good guys’ and ‘bad guys’ in allergic immune responses. *Clin Exp Immunol* 2010;161:28-33.
- Kwick B, Peng WM, Allam JP, Langner A, Bieber T, Novak N. Tacrolimus and TGF- β act synergistically on the generation of Langerhans cells. *J Allergy Clin Immunol* 2008;122:126-32, e1.
- Novak N, Allam JP, Hagemann T, Jenneck C, Laffer S, Valenta R, et al. Characterization of Fc ϵ RI-bearing CD123 blood dendritic cell antigen-2 plasmacytoid dendritic cells in atopic dermatitis. *J Allergy Clin Immunol* 2004;114:364-70.
- Gschwandtner M, Purwar R, Wittmann M, Baumer W, Kietzmann M, Werfel T, et al. Histamine upregulates keratinocyte MMP-9 production via the histamine H1 receptor. *J Invest Dermatol* 2008;128:2783-91.
- Gros E, Bussmann C, Bieber T, Forster I, Novak N. Expression of chemokines and chemokine receptors in lesional and nonlesional upper skin of patients with atopic dermatitis. *J Allergy Clin Immunol* 2009;124:753-60.
- Rissoan MC, Soumelis V, Kadowaki N, Grouard G, Briere F, de Waal Malefyt R, et al. Reciprocal control of T helper cell and dendritic cell differentiation. *Science* 1999;283:1183-6.
- Peng WM, Jenneck C, Bussmann C, Bogdanow M, Hart J, Leung DY, et al. Risk factors of atopic dermatitis patients for eczema herpeticum. *J Invest Dermatol* 2007;127:1261-3.
- Hinz T, Zaccaro D, Byron M, Brendes K, Krieg T, Novak N, et al. Atopic dermatitis syndrome is a correlate of eczema herpeticum. *Allergy* 2011;66:925-33.
- Beck LA, Boguniewicz M, Hata T, Schneider LC, Hanifin J, Gallo R, et al. Phenotype of atopic dermatitis subjects with a history of eczema herpeticum. *J Allergy Clin Immunol* 2009;124:260-9.
- Alonso MN, Wong MT, Zhang AL, Winer D, Suhoski MM, Tolentino LL, et al. TH1, TH2, and TH17 cells instruct monocytes to differentiate into specialized dendritic cell subsets. *Blood* 2011;118:3311-20.
- Fujita H, Nograles KE, Kikuchi T, Gonzalez J, Carucci JA, Krueger JG. Human Langerhans cells induce distinct IL-22-producing CD4+ T cells lacking IL-17 production. *Proc Natl Acad Sci U S A* 2009;106:21795-800.

26. Fujita H, Shemer A, Suárez-Fariñas M, Johnson-Huang LM, Tintle S, Cardinale I, et al. Lesional dendritic cells in patients with chronic atopic dermatitis and psoriasis exhibit parallel ability to activate T-cell subsets. *J Allergy Clin Immunol* 2011; 128:574-82.
27. Simon D, Vassina E, Yousefi S, Braathen LR, Simon HU. Inflammatory cell numbers and cytokine expression in atopic dermatitis after topical pimecrolimus treatment. *Allergy* 2005;60:944-51.
28. Simon D, Vassina E, Yousefi S, Kozłowski E, Braathen LR, Simon HU. Reduced dermal infiltration of cytokine-expressing inflammatory cells in atopic dermatitis after short-term topical tacrolimus treatment. *J Allergy Clin Immunol* 2004;114: 887-95.
29. Irvine AD, McLean WH, Leung DY. Filaggrin mutations associated with skin and allergic diseases. *N Engl J Med* 2011;365:1315-27.
30. Howell MD, Kim BE, Gao P, Grant AV, Boguniewicz M, De Benedetto A, et al. Cytokine modulation of atopic dermatitis filaggrin skin expression. *J Allergy Clin Immunol* 2007;120:150-5.
31. Howell MD, Fairchild HR, Kim BE, Bin L, Boguniewicz M, Redzic JS, et al. Th2 cytokines act on S100/A11 to downregulate keratinocyte differentiation. *J Invest Dermatol* 2008;128:2248-58.
32. Hatano Y, Terashi H, Arakawa S, Katagiri K. Interleukin-4 suppresses the enhancement of ceramide synthesis and cutaneous permeability barrier functions induced by tumor necrosis factor- α and interferon- γ in human epidermis. *J Invest Dermatol* 2005;124:786-92.
33. O'Neill CA, Garrod D. Tight junction proteins and the epidermis. *Exp Dermatol* 2011;20:88-91.
34. De BA, Rafaels NM, McGirt LY, Ivanov AI, Georas SN, Cheadle C, et al. Tight junction defects in patients with atopic dermatitis. *J Allergy Clin Immunol* 2011; 127:773-86.
35. Kubo A, Nagao K, Yokouchi M, Sasaki H, Amagai M. External antigen uptake by Langerhans cells with reorganization of epidermal tight junction barriers. *J Exp Med* 2009;206:2937-46.
36. Trifari S, Kaplan CD, Tran EH, Crellin NK, Spits H. Identification of a human helper T cell population that has abundant production of interleukin 22 and is distinct from T(H)-17, T(H)1 and T(H)2 cells. *Nat Immunol* 2009; 10:864-71.
37. Nogales KE, Zaba LC, Shemer A, Fuentes-Duculan J, Cardinale I, Kikuchi T, et al. IL-22-producing "T22" T cells account for upregulated IL-22 in atopic dermatitis despite reduced IL-17-producing TH17 T cells. *J Allergy Clin Immunol* 2009;123:1244-52.
38. Nogales KE, Zaba LC, Guttman-Yassky E, Fuentes-Duculan J, Suarez-Farinas M, Cardinale I, et al. Th17 cytokines interleukin (IL)-17 and IL-22 modulate distinct inflammatory and keratinocyte-response pathways. *Br J Dermatol* 2008;159: 1092-102.
39. Boniface K, Bernard FX, Garcia M, Gurney AL, Lecron JC, Morel F. IL-22 inhibits epidermal differentiation and induces proinflammatory gene expression and migration of human keratinocytes. *J Immunol* 2005;174:3695-702.
40. Hvid M, Vestergaard C, Kemp K, Christensen GB, Deleuran B, Deleuran M. IL-25 in atopic dermatitis: a possible link between inflammation and skin barrier dysfunction? *J Invest Dermatol* 2011;131:150-7.
41. Mandron M, Aries MF, Brehm RD, Tranter HS, Acharya KR, Charveron M, et al. Human dendritic cells conditioned with *Staphylococcus aureus* enterotoxin B promote TH2 cell polarization. *J Allergy Clin Immunol* 2006;117:1141-7.
42. Novak N, Valenta R, Bohle B, Laffer S, Haberkost J, Kraft S, et al. Fc ϵ RI engagement of Langerhans cell-like dendritic cells and inflammatory dendritic epidermal cell-like dendritic cells induces chemotactic signals and different T-cell phenotypes in vitro. *J Allergy Clin Immunol* 2004;113:949-57.
43. Gabrielsson S, Buentke E, Lieden A, Schmidt M, D'Amato M, Tengvall-Linder M, et al. *Malassezia sympodialis* stimulation differently affects gene expression in dendritic cells from atopic dermatitis patients and healthy individuals. *Acta Derm Venereol* 2004;84:339-45.
44. Oyoshi MK, Larson RP, Ziegler SF, Geha RS. Mechanical injury polarizes skin dendritic cells to elicit a T(H)2 response by inducing cutaneous thymic stromal lymphopoietin expression. *J Allergy Clin Immunol* 2010;126:976-84.
45. Ziegler SF. The role of thymic stromal lymphopoietin (TSLP) in allergic disorders. *Curr Opin Immunol* 2010;22:795-9.
46. Gao PS, Rafaels NM, Mu D, Hand T, Murray T, Boguniewicz M, et al. Genetic variants in thymic stromal lymphopoietin are associated with atopic dermatitis and eczema herpeticum. *J Allergy Clin Immunol* 2010;125:1403-7.
47. Bin L, Kim BE, Hall CF, Leach SM, Leung DY. Inhibition of transcription factor specificity protein 1 alters the gene expression profile of keratinocytes leading to upregulation of kallikrein-related peptidases and thymic stromal lymphopoietin. *J Invest Dermatol* 2011;131:2213-22.
48. Ebner S, Nguyen VA, Forstner M, Wang YH, Wolfram D, Liu YJ, et al. Thymic stromal lymphopoietin converts human epidermal Langerhans cells into antigen-presenting cells that induce proallergic T cells. *J Allergy Clin Immunol* 2007;119:982-90.
49. Kashyap M, Rochman Y, Spolski R, Samsel L, Leonard WJ. Thymic stromal lymphopoietin is produced by dendritic cells. *J Immunol* 2011;187:1207-11.
50. Voorhees T, Chang J, Yao Y, Kaplan MH, Chang CH, Travers JB. Dendritic cells produce inflammatory cytokines in response to bacterial products from *Staphylococcus aureus*-infected atopic dermatitis lesions. *Cell Immunol* 2011;267:17-22.
51. Steinbrink K, Mahnke K, Grabbe S, Enk AH, Jonuleit H. Myeloid dendritic cell: from sentinel of immunity to key player of peripheral tolerance? *Hum Immunol* 2009;70:289-93.
52. Peng WM, Yu CF, Kolanus W, Mazzocca A, Bieber T, Kraft S, et al. Tetraspanins CD9 and CD81 are molecular partners of trimeric Fc γ 2b on human antigen-presenting cells. *Allergy* 2011;66:605-11.
53. Dijkstra D, Stark H, Chazot PL, Shenton FC, Leurs R, Werfel T, et al. Human inflammatory dendritic epidermal cells express a functional histamine H4 receptor. *J Invest Dermatol* 2008;128:1696-703.
54. Gschwandtner M, Schakel K, Werfel T, Gutzmer R. Histamine H(4) receptor activation on human skin dendritic cells down-regulates their pro-inflammatory capacity. *Immunology* 2011;132:49-56.
55. Gschwandtner M, Rossbach K, Dijkstra D, Bäumer W, Kietzmann M, Stark H, et al. Murine and human Langerhans cells express a functional histamine H4 receptor: modulation of cell migration and function. *Allergy* 2010;65:840-9.
56. Lundberg K, Broos S, Greiff L, Borrebaeck CA, Lindstedt M. Histamine H(4) receptor antagonism inhibits allergen-specific T-cell responses mediated by human dendritic cells. *Eur J Pharmacol* 2011;651:197-204.
57. Leung DY, Gao PS, Grigoryev DN, Rafaels NM, Streib JE, Howell MD, et al. Human atopic dermatitis complicated by eczema herpeticum is associated with abnormalities in IFN- γ response. *J Allergy Clin Immunol* 2011;127:965-73.
58. Gros E, Petzold S, Maintz L, Bieber T, Novak N. Reduced IFN- γ receptor expression and attenuated IFN- γ response by dendritic cells in patients with atopic dermatitis. *J Allergy Clin Immunol* 2011;128:1015-21.
59. Bonecchi R, Bianchi G, Bordignon PP, D'Ambrosio D, Lang R, Borsatti A, et al. Differential expression of chemokine receptors and chemotactic responsiveness of type 1 T helper cells (Th1s) and Th2s. *J Exp Med* 1998;187:129-34.
60. Elser B, Lohoff M, Kock S, Giaisi M, Kirchhoff S, Krammer PH, et al. IFN- γ represses IL-4 expression via IRF-1 and IRF-2. *Immunity* 2002;17:703-12.
61. Silva NM, Rodrigues CV, Santoro MM, Reis LF, Alvarez-Leite JI, Gazzinelli RT. Expression of indoleamine 2,3-dioxygenase, tryptophan degradation, and kynurenine formation during in vivo infection with *Toxoplasma gondii*: induction by endogenous gamma interferon and requirement of interferon regulatory factor 1. *Infect Immun* 2002;70:859-68.
62. Taher YA, Piavaux BJ, Gras R, van Esch BC, Hofman GA, Bloksma N, et al. Indoleamine 2,3-dioxygenase-dependent tryptophan metabolites contribute to tolerance induction during allergen immunotherapy in a mouse model. *J Allergy Clin Immunol* 2008;121:983-91.
63. Gilles S, Fekete A, Zhang X, Beck I, Blume C, Ring J, et al. Pollen metabolome analysis reveals adenosine as a major regulator of dendritic cell-primed T(H) cell responses. *J Allergy Clin Immunol* 2011;127:454-61.
64. Bobr A, Olvera-Gomez I, Igyarto BZ, Haley KM, Hogquist KA, Kaplan DH. Acute ablation of Langerhans cells enhances skin immune responses. *J Immunol* 2010; 185:4724-8.
65. Kwiek B, Peng WM, Allam JP, Langner A, Bieber T, Novak N. Tacrolimus and TGF- β act synergistically on the generation of Langerhans cells. *J Allergy Clin Immunol* 2008;122:126-32.
66. Stary G, Klein I, Bauer W, Koszik F, Reininger B, Kohlhofer S, et al. Glucocorticosteroids modify Langerhans cells to produce TGF- β and expand regulatory T cells. *J Immunol* 2011;186:103-12.