

The skin as an immune organ: Tolerance versus effector responses and applications to food allergy and hypersensitivity reactions



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Skin is replete with immunocompetent cells that modulate signaling pathways to maintain a salubrious immunogenic/tolerogenic balance. This fertile immune environment plays a significant role in the development of allergic responses and sensitivities, but the mechanisms underlying these pathways have been underappreciated and underused with respect to developing therapeutics. Among the complex repertoire of cells that promote tolerogenic pathways in the periphery, 2 key classes include dendritic cells and regulatory T (Treg) cells. Immature dendritic cells are the first line of defense, patrolling the periphery, sampling antigens, and secreting cytokines that suppress immune cells and promote the survival of Treg cells. Skin-homing Treg cells also play a critical role in mitigating the reactivity of immune cells, secreting high levels of cytokines that promote tolerance. Therapeutic approaches that capitalize on our knowledge of the rich cellular and molecular environment are emerging and show great promise. We will discuss the advantages and challenges of 5 such strategies and how these therapies might mitigate the atopic march by facilitating tolerance. We conclude that skin is a multifaceted structure that provides a fertile ground for therapeutic discovery. Accordingly, ongoing work in this domain will no doubt continue to deliver exciting progress for improved health outcomes. (*J Allergy Clin Immunol* 2019;144:362-74.)

Key words: Allergy, inflammation, tolerance, dendritic cell, Langerhans cell, regulatory T cell, epicutaneous immunotherapy, immunotherapy

Abbreviations used

AD:	Atopic dermatitis
BDCA:	Blood dendritic cell antigen
cDC:	Classical dendritic cell
CHS:	Contact hypersensitivity
DC:	Dendritic cell
EPIT:	Epicutaneous immunotherapy
eTreg:	Effector regulatory T
Foxp3:	Forkhead box P3
LC:	Langerhans cell
LN:	Lymph node
MDSC:	Myeloid-derived suppressor cell
MHCII:	MHC class II
mo-DC:	Monocyte-derived dendritic cell
pTreg:	Peripheral regulatory T
RBC:	Red blood cell
SLIT:	Sublingual immunotherapy
T _R 1:	Type 1 regulatory T
Treg:	Regulatory T
T _{RM} :	Memory T cell
UVR:	Ultraviolet radiation

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THE SKIN AS AN IMMUNE ORGAN

The skin plays a dual role in the body's defense against pathogens. Most palpably, the skin provides a physical barrier that protects internal systems from the environment. Human skin also functions as an active immune organ, constantly providing resistance to microorganisms and other noxious environmental agents through innate and acquired immune mechanisms.^{1,2} To date, the intrinsic potential of the skin's immune cells has been underused.

In this review we will explore the immunologic capacity of the skin, both in its homeostatic resting state and during inflammation, reviewing the mechanisms underlying cutaneous immunity and how they contribute to tolerogenic or immunogenic signaling pathways. We will discuss the cells responsible for mediating cutaneous immunity and the cytokines that regulate their activity and conclude by proposing that seizing control of these pathways through immunization strategies is a viable and promising approach for treatment of food allergy and hypersensitivity.

Maintenance of tolerance in resting-state skin

Resting-state skin is replete with resident immunocompetent cells (*Fig 1*).^{3,4} Under homeostatic conditions, keratinocytes constitutively produce Toll-like receptors, cytokines, and chemokines that initiate signaling cascades to maintain the

HUMAN SKIN – TOLEROGENIC OR NON-INFLAMMATORY STATE Resident Populations of Immune Cells

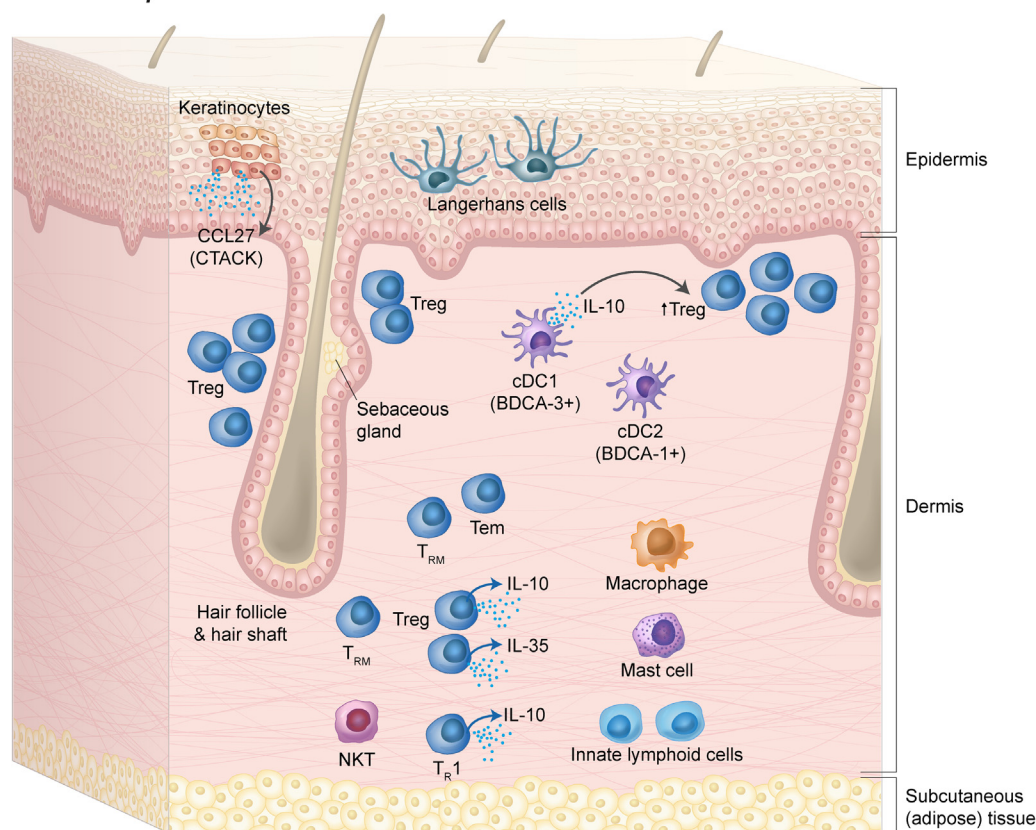


FIG 1. Resident populations of immune cells in human skin. In its baseline state tolerogenic (noninflammatory) skin contains abundant and diverse immune cells, including macrophages, mast cells, natural killer cells, lymphoid cells, T cells, and a prominent population of DCs (Table 1). Keratinocytes, LCs, and T_{RM} cells populate the epidermis, whereas cDC1s and cDC2s populate the dermis, secreting cytokines that maintain a tolerogenic environment. One major limitation to our knowledge of the tolerogenic properties of DCs is that much of it has been gleaned from forced differentiation of DCs *in vitro*. To date, few studies mapping tolerogenic pathways directed by DCs in normal human skin *in vivo* have been performed. CTACK, Cutaneous T cell-attracting chemokine; NKT, natural killer T cells; Tem, effector memory T cells.

diverse populations of leukocytes responsible for tolerance.¹ Immature antigen-presenting dendritic cells (DCs), including Langerhans cells (LCs) and classical DC subsets (cDC1 and cDC2) patrol the periphery, where they sample antigens and secrete cytokines that suppress inflammation and also promote survival of regulatory T (Treg) cells.⁵⁻⁷ Skin-homing Treg cells also play a critical role in mitigating the reactivity of immune cells, promoting tolerance in the absence of a noxious signal.^{8,9} In both the scurfy transgenic mouse and in patients with human immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome, in whom Treg cells are deficient, spontaneous (unprovoked) inflammatory responses in the skin are observed.^{10,11}

In summary, a range of resident cell populations maintain epithelial barrier protection and health. However, the immune cells of human skin are also primed to initiate innate or adaptive immune mechanisms in response to pathogenic organisms that breach or will breach the epidermal barrier.

Immune mechanisms in activated skin

Detection of an immune “danger signal” activates robust protective responses, including upregulation of immune signals in

keratinocytes, DCs, “polar” T-cell subsets mediating effector immunity, innate cell types (including granulocytes [neutrophils or eosinophils]), and other myeloid cell subsets (Fig 2).^{6,12-18} The danger signal can be detected either by Toll-like receptors synthesized by epidermal keratinocytes¹ or by LCs that project dendrites through keratinocyte junctions to sample the surface environment.¹⁹ On detection of a pathogen, keratinocytes undergo accelerated growth and differentiation, which result in a marked increase in the synthesis of antimicrobial proteins, chemokines, and cytokines that rapidly recruit and activate specific T-cell subsets responsible for orchestrating protective immunity.²⁰ This response is organism specific: extracellular bacterial or fungal infections trigger IL-17, CCL20, CXCL9, or CXCL10 synthesis to elicit T_H17 cells^{20,21} or T_H1 influx and activation²²; helminth infection activates thymic stromal lymphopoietin, IL-25, IL-33, CCL17, or CCL22 synthesis to direct T_H2 responses^{13,23-25}; intracellular bacteria, protozoa, and viruses induce type I immune responses (IL-12, IL-15, and IFN- γ)^{26,27}; and gram-negative bacteria can trigger increased production of TNF, IL-1, and other cytokines that drive increased synthesis of CXCL1, CXCL2, CXCL3, CXCL5, and CXCL8 that encourage neutrophil chemotaxis into infected sites.^{28,29}

HUMAN SKIN – INFLAMMATION, INFECTION, IMMUNE RESPONSE Added to Cells in Non-Inflammatory State

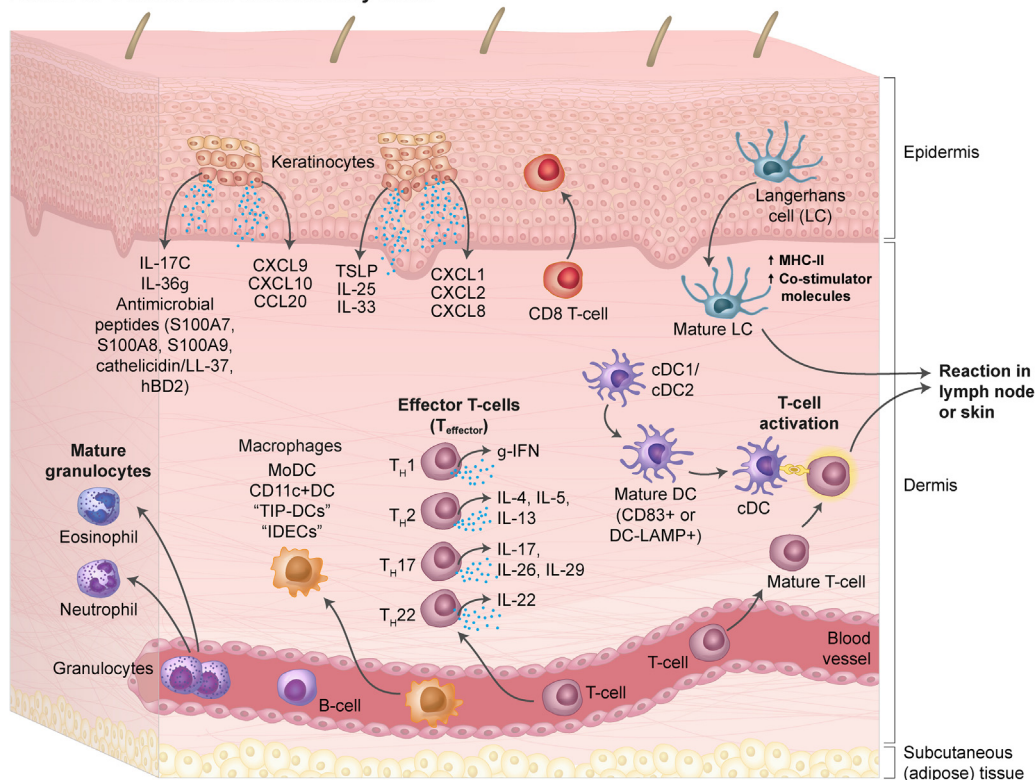


FIG 2. Effector immune response in human skin. On detection of an inflammatory signal, skin shifts from a tolerogenic to an immunogenic state. LCs become activated and migrate into the dermis and/or to the LNs to activate effector T-cell responses. There is also increased activation of DCs in the dermis, as well as production of cytokines that direct activation of specific polar T-cell subsets. Concurrently, keratinocytes proliferate and produce cytokines and chemokines that contribute to the effector immune response specific to the type of infection. The chemical milieu directs neutrophils, eosinophils, T cells, and mo-DCs to exit the vasculature, infiltrating the local tissue, where they undergo disease-specific responses. The tipping point of whether an antigen activates an immune reaction likely results from the level of “innate” local inflammation. If skin is intact, antigens might promote tolerance; however, if the skin is disrupted, that same antigen might now activate an inflammatory immune response. Unrestrained polar T-cell activation results in inflammatory diseases, such as psoriasis (T_H17 cells and TNF and inducible nitric oxide synthase-producing dendritic cells [TIP-DCs]), atopic eczema (T_H2 cells and inflammatory dendritic epidermal cells [IDECS-DCs]), and cutaneous lupus (T_H1 cells and plasmacytoid DC [pDCs]).

The keratinocyte response is supported by T cell–derived cytokines, which amplify specific immune pathways and bring cytotoxic effector pathways into play.²⁰ Cytokines secreted by T cells can direct B cells to class-switch immunoglobulins between IgG and IgE.³⁰ In parallel, as DCs are activated by the danger signal, they shift from a tolerogenic to an immunogenic phenotype, further tipping the scales toward an immune response. Mature DCs can then migrate to lymph nodes (LNs) and promote activation and differentiation of new memory T cell (T_{RM}) clones that will home back to the skin as antigen-specific effectors^{31,32} (see the “DC” and “Treg cell” sections below).

Thus immune pathways are tightly regulated by a litany of cells and chemical signals to maintain a fine balance between tolerance and immune response. When this balance is disturbed, chronic and/or overzealous activation of immune pathways through autoimmunity results in unremitting inflammation, as observed in common skin diseases, including psoriasis (T_H17 centered), cutaneous lupus (T_H1 and interferon centered),³³ and atopic dermatitis (AD; T_H2 centered).^{17,34–41} The latter illustrates the

importance and therapeutic potential of the skin as an immune organ: in AD, eosinophils are recruited into the skin by chemokines, including IL-5, and increased T_H2 activation drives production of IL-4 and IL-13, promoting IgE production. This in turn contributes to increased risk of IgE-mediated allergic reactions, food sensitivities, asthma, or autoimmunity.³⁰ Furthermore, a group of innate lymphocytes that appear in early postnatal skin,⁴² called group 2 innate lymphoid cells, have been shown to secrete cytokines comparable with T_H2 cells⁴³ and thus might also be important in shaping allergic-like responses associated with atopic eczema or other early inflammatory events. These relationships illustrate a strong link between the skin as an immune milieu and systemic allergy,⁴⁴ pointing toward an influential modality for the development of therapeutics.

In subsequent sections we further consider mechanisms by which Treg cells and DCs restrain active immunity in the skin to promote immune tolerance. We also begin a discussion of how cutaneous regulatory immune mechanisms might be manipulated to improve or restore immune tolerance in allergic diseases.

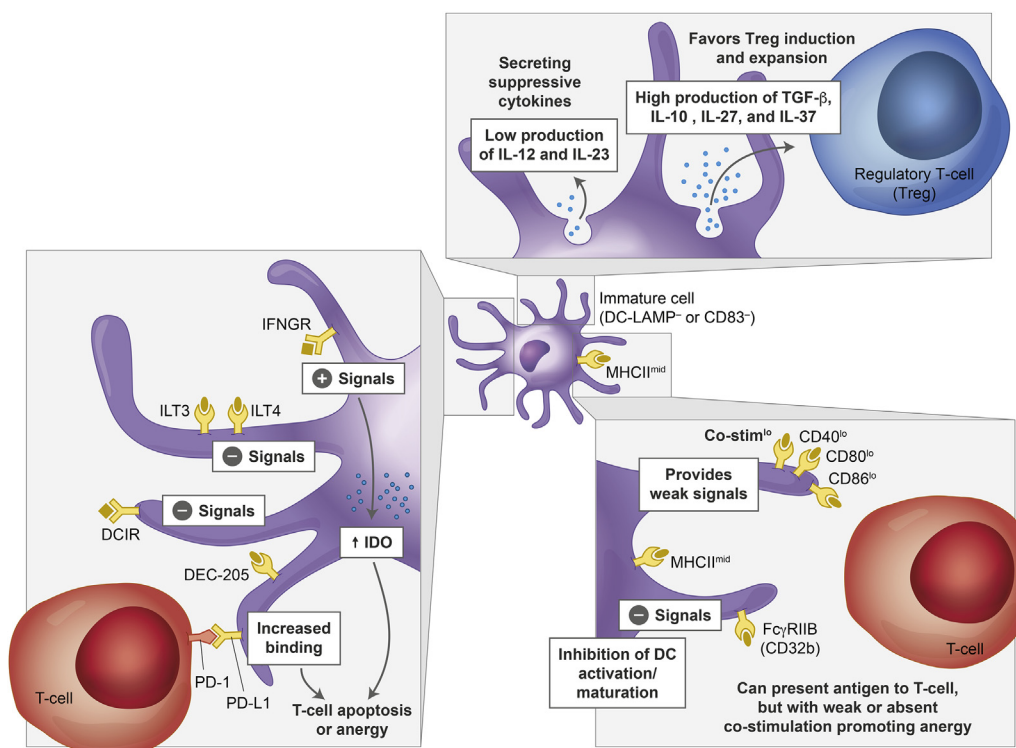


FIG 3. Characteristics of a tolerogenic DC. In their immature state DCs promote tolerance. These DCs express low levels of MHCII and costimulatory molecules, restricting their ability to present antigens to T cells and drive an immune response. High IL-10 and TGF- β production favors expansion of Treg cells (which also promote tolerance), whereas low IL-23 and IL-12 levels minimize stimulation of effector T cells. Surface expression of inhibitory receptors (CD95 ligand, immunoglobulin-like transcript 3 [ILT3], ILT4, dendritic cell immunoreceptor [DCIR], and CD32b) drives signaling pathways that ultimately result in apoptosis or anergy.

DCs

DCs are the predominant population of immunocompetent cells in the skin, where they patrol peripheral tissues, initiating immune responses or promoting tolerance.⁶ An encounter with a pathogen leads to activation, maturation, and migration of DCs to the central LNs, triggering a cascade of events ultimately designed to clear the antigenic material. This process constitutes the front line of cutaneous immunity.^{6,45}

Immature DCs are highly specialized antigen-processing cells^{6,46} that perpetually sample innocuous environmental proteins and self-antigens and traffic them to regional LNs for presentation, thereby promoting tolerance in the periphery.⁶ They also play a role in central tolerance, contributing to negative selection (clonal deletion) of developing thymocytes.⁴⁷

In their immature state DCs store MHC class II (MHCII) intracellularly in lysosomes,²⁶ drive T-cell anergy,⁴⁸ and actively contribute to immune homeostasis by secreting suppressive cytokines, such as IL-10, TGF- β , IL-27, and IL-37. On contact with a “presentable” antigen, immature DCs transition to an intermediate phenotype, which is also tolerogenic. These semimature DCs express costimulatory molecules and nonlysosomal vesicle-bound MHCII on their surfaces. Semimature DCs can migrate to skin-draining LNs or inflamed tissues to actively induce tolerance.⁴⁹

In contrast to immature and semimature DCs, mature DCs are generally considered immunogenic. Mature DCs express high levels of MHCII on the plasma membrane, conferring full antigen-presenting capacity and potent T-cell stimulatory capacity.^{6,26,50} These cells traffic antigen from the skin to the

LNs for presentation to naive T cells through distinct pathways, depending on whether this occurs during pathogen invasion or at steady state.^{51,52} Mature DCs also express high levels of costimulatory molecules, release IL-12, and downregulate expression of immunosuppressive mediators, such as IL-10, thereby promoting effector T-cell activation and decreasing Treg cell expansion.⁵³ In patients with psoriasis, activated DCs produce high levels of IL-23 and drive a T_H17 response.³⁴ In contrast, in AD, DCs express high levels of an Fc receptor for IgE and polarize T cells to T2-high cells.^{34,54-57}

It is important to note that recent evidence from a study using an *in vitro* model of DC maturation suggests that distinct transcriptional and regulatory signals can induce mature DCs to assume either a tolerogenic or immunogenic state. Mature DCs can gain tolerogenic potential in the absence of microbial stimuli through the transcription factor interferon regulatory factor 4, which elicits DC maturation and Treg cell generation. However, in the presence of microbial products, DCs mature and activate nuclear factor κ B, which facilitates the generation of effector T cells and an immunogenic profile.⁵⁸

Interestingly, the maturation state of DCs can be affected by their interaction with different types of cancer cells. Steady-state immature DCs are maintained and suppressed by cancer cells in a tumor and are also referred to as tumor-infiltrating DCs. These immature and semimature DCs have been shown to induce T-cell anergy and promote cancer cell tolerance and tumorigenesis. However, depending on the cytokine profile secreted, anticancer immunity can be facilitated by mature DCs.⁵⁹

TABLE I. DC subsets in human skin

	Human markers	Resting skin	Inflamed skin
LCs ^{6,7,51,65-67}	CD207 (Langerin), CD1a, CD1c	● Epidermis ● High abundance	● Migration to the dermis and LNs ● Acquire mature phenotype
cDCs ^{7,15,31,32,62,66,68}	cDC1: BDCA-3 (CD141), CD11c cDC2: BDCA-1 (CD1c), CD11c	● Dermis ● Low abundance ● Main subset	● Can migrate to the LNs ● Acquire mature phenotype ● Can migrate to the LNs ● Acquire mature phenotype
pDCs ^{7,15,62,68,69}	BDCA-2 (CD303)	● Dermis ● Low abundance	● Can migrate to the LNs ● Acquire mature phenotype
mo-DCs ^{*15,55,56,60-64,68,70-73}	CD11c Low expression: CD14 Other markers: variable CD1a, CD1c, CD16	● Dermis ● Low abundance	● Located in the epidermis or dermis ● Acquire mature phenotype ● Expression of disease-specific markers: ■ TIP-DC (in psoriasis) ■ IDEC-DC (in AD) ● Might be the main subset in inflammation

Subtypes of DCs have been described based on surface marker expression. These include LCs, cDC1s, cDC2s, plasmacytoid DCs (pDCs), and mo-DCs. In resting-state skin the predominant subtypes are LCs in the epidermis and cDC2s in the dermis. In this state all DC subsets are relatively immature and presumed to promote tolerance (Figs 1 and 3). On detection of an activating immune signal, DC subsets acquire a mature phenotype. Mature DCs drive T-cell stimulation in the skin and LNs (Fig 2). There is also an influx of mo-DCs, which might become the main subset of DCs in the skin under inflammatory conditions.

IDEc, Inflammatory dendritic epidermal cell; TIP, TNF and inducible nitric oxide synthase-producing.

*mo-DCs have been most convincingly demonstrated as immature DC precursors in peripheral blood and through the *in vitro* manufacture of DCs from blood monocytes.

Beyond the immature-semimature-mature distinction, DCs can be subclassified based on their surface marker expression (Table I).^{*} In skin the resident population of DCs largely comprises embryo precursor-derived LCs and bone marrow-derived cDC1 and cDC2.⁶⁰ There are also small populations of plasmacytoid DCs and monocyte-derived dendritic cells (mo-DCs). mo-DCs are less mature than resident populations in an activated state (based on MHCII and costimulatory molecules⁶¹ and the presence of positive markers of maturation, such as CD83,⁶¹ and dendritic cell lysosome-associated membrane glycoprotein)⁷⁴; however, they nonetheless possess a remarkable capacity to stimulate T-cell activation.^{61,62,74} Interestingly, mo-DCs appear to differentiate according to the underlying cause of inflammation. In patients with psoriasis, mo-DCs are also called TNF and inducible nitric oxide synthase-producing DCs, producing high levels of IL-23 and driving T_H17 activation.^{15,63} In contrast, in AD, mo-DCs, also called inflammatory dendritic epidermal cells, are marked by expression of FcE receptors and drive a T_H2 response.^{63,64} Importantly, although there is extensive conservation of immune genes between mice and human subjects, key differences have nonetheless been detected,⁷⁵ and therefore efforts to translate findings from animal models to human subjects require caution.

LCs

The primary population of skin-resident DCs are LCs, which represent 2% to 3% of epidermal cells.^{65,76} In their immature state LCs express adhesion molecules (E-cadherin), enabling formation of a 3-dimensional network that extends throughout the basal and suprabasal keratinocyte layers.⁷⁷ LCs in the epidermis elongate their dendrites, penetrating tight junctions to sample antigens that have permeated the stratum corneum skin barrier while preserving the integrity of the tight junction barrier.⁶ Thus LCs are ideally suited to their role in immune surveillance, engaging in first contact with antigens and initiating the appropriate adaptive immune response (tolerance or inflammation).⁶

In the steady state LCs maintain peripheral tolerance to self-antigens by promoting expansion and proliferation of Treg cells.^{5,78} On detection of a danger signal (ie, infection, trauma, or an active disease state), LCs induce effector T-cell responses.⁷⁹ Maturing LCs simultaneously downregulate E-cadherin and increase CCR7 levels, resulting in detachment from surrounding keratinocytes and migration, first to the lymphatic vessels and ultimately to the T-cell area of regional LNs.⁶ Throughout this migration, expression and compartmentalization of MHCII is tightly regulated, delaying antigen presentation until cells have reached the LNs.⁶ Mature LCs also secrete cytokines to drive appropriate T-cell polarization and provide an optimal milieu for processing the invading antigen.^{6,80}

Contact hypersensitivity (CHS; also termed allergic contact dermatitis) has been vital in demonstrating the critical role that LCs play in tolerance and immunogenicity both in animal models and in human skin. In animal models conflicting results have been reported. LCs have been shown to drive the immune response underlying CHS,^{6,81} whereas the CHS response is determined by the number of DCs that have access to the antigen.^{6,82} In the absence of LCs, CHS is attenuated when low concentrations of hapten are administered. However, when the hapten dose is increased, CHS returns to wild-type levels, most likely because of significant levels of hapten penetrating the epidermis to come into contact with dermal DCs.^{6,82} These findings highlight the importance of LC location and ability to sample antigens at the skin's surface. Conversely, the absence of LCs in mice deficient in epidermal LCs has been shown to result in an intensified CHS response, thus highlighting an important regulatory function of LCs.⁸³ In another study, however, CHS responses were shown to remain unaltered in mice depleted of epidermal LCs, and deficiency of both epidermal and dermal LCs was required to alleviate the CHS response.⁸⁴

LCs are also imperative for induction of Treg cells by ultraviolet radiation (UVR).^{6,85,86} Specifically, in the absence of epidermal LCs, UVR-induced Treg cells and the accompanying inhibition of CHS are significantly attenuated.⁶ In human skin tolerogenic mechanisms are perhaps best illustrated by nonreactivity to nickel, to which individuals are routinely exposed.^{87,88} This

*References 6,7,15,31,32,51,55,56, and 60-73.

tolerance is mediated by T cells, but danger signals, such as ear piercing, can activate effector T cells to direct protective immunity.⁸⁹ Exposure to UVR also alters the human epidermal microenvironment, reducing the number of LCs and increasing the number of Treg cells and levels of immunosuppressive cytokines in the epidermis,^{90,91} thus decreasing responsiveness to foreign antigens and facilitating tolerance to compounds that create sensitization under normal conditions (ie, dinitrochlorobenzene).⁹⁰ In AD, fewer antigen-presenting cells (LCs) and increased baseline expression of inflammatory cytokines lead to greater prevalence of CHS.⁹²

In summary, LCs play a key role in shaping adaptive immune responses toward effector- or tolerance-promoting T cells based on different signals indicating dangerous versus nondangerous states.

Dermal DCs

The dermis of normal human skin contains 2 major populations of myeloid (CD11c⁺) DCs, which can be divided into different functional populations by expression of blood dendritic cell antigen (BDCA)-1 and BDCA-3.⁶⁶ On average, the BDCA-3 (cDC1) population constitutes about one third of dermal DCs.⁷ This subset has been shown to produce high levels of IL-10,⁷ and it promotes differentiation of CD25^{hi} Treg cells, which were shown to suppress skin inflammation in an allotransplantation model.⁷ DCs with a similar phenotype could be generated *in vitro* from blood monocytes through incubation with vitamin D3, and these cells were also shown to suppress T cell-mediated rejection of transplanted melanomas.⁷ In contrast, the BDCA-1⁺ (cDC2) population expressed low levels of IL-10 and did not induce Treg cells, and therefore its function might be more geared to generation of effector T cells if activated by antigen exposure and/or inflammatory signals.⁷ Still, the BDCA-1⁺ DC population in normal human skin is immature⁶⁶ and has relatively weak T-cell stimulatory potential, unless it is activated by inflammatory cytokines,⁶⁶ and therefore it might also promote tolerance through other mechanisms, such as low expression of MHCII and costimulatory molecules.

TREG CELLS

T_{RM} cells are abundant in the skin, with the highest concentrations in the epidermis⁵ and in proximity to hair follicles.⁸ In contrast to DCs, which circulate between the skin and LNs to mediate immune responses, skin-homing memory T (T_{RM}) cells are relatively immobile; unable to enter LNs,²¹ T_{RM} cells protect the host from infection locally.^{5,93} A small and reproducible percentage of these cells (approximately 5%) are Ki67⁺, indicating that they are undergoing proliferation.⁵

Treg cells are a subpopulation of CD4⁺ T_{RM} cells that mediate tolerogenic immune responses to self⁹ and make up approximately 5% to 10% of the total number of skin-resident T cells.^{5,9} In normal, noninflamed skin Treg cells are characterized by expression of cutaneous lymphocyte-associated antigen (a skin-homing receptor),⁹⁴ by the costimulatory molecule CD28,⁹⁵ and by expression of chemokine receptors for CCL27/28 (CCR10),^{94,96} CCL20 (CCR6),⁹⁷ and CCL17/22 (CCR4).²⁴ They secrete high levels of cytokines that suppress inflammatory responses, including IL-10, IL-35, and TGF- β (as discussed in section 4).^{98,99} Most Treg cells express the high-affinity IL-2 receptor (CD25) and the transcription factor forkhead box P3 (Foxp3), which plays a

role in their development and function (maintenance of suppressive role and self-tolerance).⁹ Treg cells can be generated in the thymus (tTregs) or the periphery (pTregs). Thymic Treg cells and pTregs are also found in secondary lymphoid tissues^{9,98,100} and can be further classified as Foxp3⁺ or Foxp3⁻.⁹⁹⁻¹⁰¹ Treg cells can also be subclassified as central or effector regulatory T cells (cTreg or eTreg cells, respectively).⁹⁸ cTreg cells, resting Treg cells, constitute the largest proportion of Treg cells in secondary lymphoid organs, expressing high levels of CD62L and CCR7. eTreg cells are fewer in number and express high levels of surface markers, including CD44, inducible T-cell costimulator, and tissue-specific chemokine receptors. Subsets of eTreg cells have also been defined: IL-35-producing Foxp3-dependent eTreg cells express CCR7, preferentially localize to T-cell zones, and are hypothesized to be efficient at targeting autoreactive T cells.⁹⁸ IL-10-producing Blimp1-dependent eTreg cells express inducible T-cell costimulator, granzymes, and multiple chemokine receptors, which aid in their migration to peripheral nonlymphoid zones.⁹⁸ This subset might be responsible for controlling autoimmunity of T cells and suppressing peripheral inflammation. Lastly, type 1 Treg cells are CD4⁺Foxp3⁻. Type 1 Treg cells suppress antigen-specific T-cell responses, promoting tolerance, and are defined by their production of high levels of IL-10 and TGF- β .^{99,102}

MDSCs AND MAST CELLS

Recruited immune cells can be mediators of allergy. For instance, myeloid-derived suppressor cells (MDSCs) are critically involved in the modulation of immune responses in various pathologic conditions not only inside but also outside the scope of cancer.¹⁰³ MDSCs generally function in an immature state and interact with different populations of T cells in a complex manner. T_H1/T_H2 CD4⁺ T cells can modulate MDSC expansion and activity, as demonstrated by several mouse studies. Studies in cancer reported the ability of MDSCs to induce Treg cell expansion and tolerance, whereas experimental allergy studies indicated that T-cell activation reduction, Treg cell recruitment, and a decrease in airway sensitivity were monocytic MDSC mediated. MDSCs are also capable of generating, differentiating, and suppressing T_H17 cell responses in a number of *in vitro* and *in vivo* studies. Lastly, MDSCs have been shown to induce tolerance in CD8⁺ and CD4⁺ T cells, which might be antigen specific.¹⁰³

Mast cells are well-documented effector cells responsible for allergic responses mediated by IgE after exposure to an allergen for a second time and, more recently, have been shown to be initiators of innate immune responses against pathogens.¹⁰⁴ In recent studies of allergy, a possible role in allergen sensitization and exacerbation of allergic disease when accompanied by bacterial byproducts has been identified for mast cells, responses that are facilitated by the high-affinity IgE receptor (Fc ϵ RI) located on the surfaces of mast cells.¹⁰⁴ This is further exemplified by several mouse studies that report both worsening and alleviation of CHS symptoms facilitated by mast cells, which were dependent on the particular model of CHS used. Mast cells encompass a diverse range of immunomodulatory functions. They promote B-cell IgE production, immune cell recruitment, T_H2 responses, and the function of immune cells. Additionally, through production of IL-10, mast cells can inhibit production of cytokines produced by T cells and monocytes and pro-inflammatory cytokines and chemokines by keratinocytes.¹⁰⁵

FOOD ALLERGY AND TOLERANCE

The mucosal immune system of the gastrointestinal tract typically functions in a state of tolerance to food proteins,¹⁰⁶ which involves DCs and Treg cells.^{30,106} Treg cells are generated after sampling of a food antigen, resulting in antigen-specific suppression of effector T cells. Gastrointestinal DCs (CD103⁺ subset) have been shown to promote the development and differentiation of Treg cells,³⁰ including induction of Foxp3⁺ Treg cells, in murine studies.¹⁰⁶ Interestingly, a 2007 study reported an increased incidence of food allergies in patients with a dysfunction in Foxp3,¹⁰⁷ suggesting a central role for Treg cells in oral tolerance. Food allergy can develop when there is a disruption in oral tolerance and ingested food antigens are thought to stimulate an adaptive immune response, resulting in sensitization to a food allergen.¹⁰⁶ Sensitization to a food allergen can also develop through skin exposure.¹⁰⁶ This is best observed in patients with skin barrier disruptions, such as AD and loss-of-function mutations in filaggrin, an epidermal protein associated with maintaining skin barrier function, with such patients exhibiting an increased risk of sensitization to food antigens.^{30,108,109}

Given the relative abundance of data indicating the tolerogenic role of DCs, it is critical to highlight the contrary role of DCs in mediating allergy versus promoting tolerance, specifically in the context of food allergy.¹¹⁰ This is best demonstrated by studies in which naive mice received an adoptive transfer of DCs from recipient mice with milk allergy, which resulted in induction of IgG- and IgE-specific responses without antigen exposure.¹¹¹ Furthermore, development of IgE-mediated allergy might be attributed to a distinct subset of DCs that are resistant to apoptosis and promote polarization to T_H2 responses.¹¹² Several human studies have also revealed that the likelihood of food allergy might be increased with delayed allergen contact, suggesting that early exposure to antigens, as well as the quantity of antigen, are critical in developing appropriate immune responses to food.¹¹⁰

MECHANISMS OF IMMUNE TOLERANCE THROUGH Lcs AND T CELLS

Tolerance can be driven both locally in the skin and systemically. At low levels of antigen presentation, Lcs induce expansion of skin-resident memory Treg cells that suppress autologous T-cell responses locally.^{5,46} However, once a threshold of antigen is surpassed, the role of Lcs is switched to favor effector T_{RM} cells (Foxp3^{lo}, CD127⁺), with activation, proliferation, and production of the effector cytokines IFN- γ and IL-17.⁵

In addition to driving tolerance at the site of antigen detection, studies in mice have shown that skin-resident DCs migrate from their cutaneous location and induce antigen-specific generation of Foxp3⁺ Treg cells in LNs.¹¹³ This highlights an important attribute of immune tolerance: the potential to induce systemic immune responses from peripheral locales. In this way targeting skin immune cells might be sufficient for treatment of autoimmune and/or allergic conditions. Once activated (after T-cell receptor signaling), Treg cells can suppress responses of CD25⁻CD4⁺ T cells specific for another antigen¹¹⁴ by dampening the costimulatory function of DCs (CD80/CD86 and IL-2 expression), which would allow Treg cells triggered by one antigen to block effective presentation of other antigens by the same antigen-presenting cell.¹¹⁴

Work is ongoing to further elucidate the mechanisms underlying promotion of tolerance by DCs and Treg cells and

the phenotype and role of distinct subsets. Although direct cell-cell contact has been implicated in communication between DCs and T cells, there are also well-established contributions by cytokines in the determination of tolerogenic and immunogenic responses.¹¹⁵

TGF- β has been shown to drive tolerance by controlling DC development, activation, and maturation. Epidermal Lcs are lacking in both TGF- β knockout and deficient mice; TGF- β knockout mice display aberrant T-cell responses and autoimmune disease and ultimately die prematurely.^{6,116,117} It is plausible that Lcs necessitate TGF- β 1 directly from autocrine/paracrine signaling for LC development and survival.¹¹⁶ LPS-mediated DC maturation in mice through induction of IL-12 (a proinflammatory cytokine required for T-cell stimulation in the LNs) and CCR7 (which guides DCs in their migration to the T-cell area of LNs) is inhibited by TGF- β signaling, potentially through an increase in peroxisome proliferator-activated receptor γ (PPAR γ).^{6,118} In this way TGF- β plays an important role in maintenance of an immature pool of Lcs in the epidermis.^{6,119} TGF- β also contributes to Treg cell proliferation: in the periphery TGF- β produced by DCs induces Foxp3⁺CD25⁻CD4⁺ T cells to become Treg cells.¹¹⁴

TGF- β induces β -catenin in progenitor cells.⁷⁷ β -Catenin is a transcriptional regulator of the Wnt signaling pathway,⁷⁷ a conserved signal transduction pathway that regulates gene expression and various cellular processes during embryonic development¹²⁰ and modulates the link between cadherins and the cytoskeleton. Among skin DCs, only Lcs express notable levels of β -catenin,⁷⁷ likely playing a role in the formation and maintenance of the cellular scaffold adhering Lcs to keratinocytes.¹²¹ In the absence of β -catenin, Lcs are untethered and more readily activated to a migratory and immunogenic phenotype.^{77,122} Accordingly, deletion of β -catenin from CD11c⁺ DCs leads to autoimmunity.^{3,77,123} β -Catenin is a ligand-dependent coactivator of vitamin D receptors in the epithelium,⁷⁷ and 1,25 vitamin D3 (a metabolite of vitamin D) can stimulate LC precursors to produce TGF- β , β -catenin, and vitamin D receptors.⁷⁷

Immature DCs secrete high levels of IL-10, a pleiotropic cytokine that negatively regulates inflammatory responses, minimizing collateral tissue damage.^{3,6,7} Lcs also play a role in generation of IL-10-producing Foxp3⁺ Treg cells.^{5,46} IL-10 in turn inhibits macrophage function, downregulates MHCII and costimulatory molecules, decreases proinflammatory cytokines, and directs DCs toward a tolerogenic phenotype.¹²⁴ Notably, IL-10-deficient mice develop colitis.¹²⁵

IL-10-mediated tolerance is further supported by IL-27.¹²⁶ IL-27 is produced by DCs and, once released, can induce expression of CD39, suppressing T_H1 and T_H17 cell differentiation, and driving Treg cell production.¹²⁷

IL-37 has emerged as a dampener of adaptive immunity. IL-37-expressing DCs promote Treg cell generation.⁴⁹ IL-37 has a negative feedback loop with proinflammatory cytokines; it is stimulated by proinflammatory cytokines and, once expressed, shuts down expression of those same signaling molecules.⁴⁹ In mice engineered to express human IL-37 transgenically, induction of CCR7 (and thus migratory capacity) was intact. However, MHCII surface expression was diminished, and induction of T-cell proliferation was impaired. IL-37 increases levels of the anti-inflammatory cytokine IL-10 and reduces levels of proinflammatory cytokines, such as IL-1 β , IL-6, and IL-12.^{49,128-130} promoting generation of semimature DCs recognized as "tolerogenic DCs."^{49,128} These effects can

ameliorate allergic disorders, such as asthma and allergic rhinitis.^{131,132} Together, these cytokines act in concert to tightly regulate the expression and induction of tolerogenic cells and signals.

Although naturally occurring DC populations can promote cutaneous tolerance, considerable work has gone into creating tolerogenic DCs through a range of *in vitro* differentiation protocols.¹³³ Major properties that pertain to both naturally occurring and induced DCs for promotion of tolerance (which can be variably expressed within different DC populations) include high production of negative regulatory cytokines (IL-10, TGF- β , IL-27, and IL-37, as discussed above),^{49,126,133} low production of IL-12/IL-23,¹³⁴ low expression of MHCII and costimulatory molecules,^{26,53,133} secretion of indoleamine 2,3-dioxygenase,¹³³ and increased expression of immune checkpoint molecules, such as programmed death ligand 1.¹³³ Induced tolerogenic DCs have now been tested for immunosuppressive actions in clinical trials for treatment of type 1 diabetes, rheumatoid arthritis, multiple sclerosis, and Crohn disease, with early evidence of efficacy in these diseases.¹³³ Studies are also underway in allergic diseases, such as asthma.¹³³ It will be interesting to know the therapeutic potential of this approach in future studies, but ultimately, customized cellular therapy is likely to be more difficult and more expensive than other approaches that are discussed below.

APPLICATION IN FOOD ALLERGY AND HYPERSENSITIVITY

The skin has great plasticity as an immune organ, and although further work is required, we can leverage our existing knowledge of the mechanisms of immune tolerance to develop strategies for treating aberrant immune responses. The capacity of LCs and other DCs to shape the outcomes of local^{135,136} and systemic immune responses can be used toward immunomodulatory interventions. Emerging immunotherapeutic approaches capitalize on this mechanistic framework to overcome an overzealous immune system.

Sublingual immunotherapy

Sublingual immunotherapy (SLIT) is a relatively noninvasive approach to antigen-specific immune tolerance that has been gaining popularity as a strategy for priming antigen-specific tolerance. Sublingual administration of an antigen to which tolerance is desired produces a biphasic biochemical response. In a study published by Lawrence et al,¹³⁷ 4 weeks of treatment with birch pollen SLIT was associated with increases in numbers of circulating Treg cells, increases in IL-10 and Foxp3 transcription, decreases in nonspecific antigen-driven lymphocyte proliferation, and concomitant symptom improvement.¹³⁷ By 52 weeks after SLIT, pTreg cell counts and IL-10 levels returned to baseline, lymphocyte proliferation suppression was antigen specific, IL-4 levels were decreased, and IFN- γ levels were increased.¹³⁷ Thus although SLIT produces significant desensitization to allergens in numerous indications, the induction of sustained, long-term effects remains in doubt.¹³⁸ However, an earlier 15-year prospective study comparing different durations of dust mite SLIT suggested that a 4-year treatment duration is optimal because of the persistence of clinical benefit.¹³⁹ Additional limitations have also been noted. As described by Lawrence et al,¹³⁷ allergen exposure can be

reduced because of neutralizing antibodies present in saliva. Moreover, because the sublingual reaction is by definition localized, the number of DCs that can be recruited to process the allergen is limited. In studies that attempted to generate tolerance to multiple allergens, the beneficial effects for all allergens in the mixture appeared to be reduced.¹³⁷

DEC-205

Another approach to antigen-specific immunomodulation is the selective targeting of antigens to DCs in the steady state. DEC-205 is a cell-surface lectin-like receptor⁵⁰ that is highly expressed on DCs in T-cell areas. DEC-205 systematically recycles through MHCII⁺ late endosomal compartments and facilitates presentation of antigens by DCs to CD4⁺ T cells.^{140,141} When DEC-205 is coupled to an antigen, there is uptake of the complex by steady-state DCs, and antigen presentation occurs, resulting in induction of Treg cells. The process of anti-DEC-205:antigen targeting offers the possibility of inducing tolerogenic responses.^{50,140} Deletional tolerance in analogous antigen-reactive T cells is achieved with this approach. However, if anti-CD40 is coadministered, the outcome is immunity.⁵⁰ It should be noted that a possible limitation of antigen delivery to DCs in human subjects with an inflammatory milieu is a worsening of an autoimmune response to a pathogen rather than development of tolerance.¹⁴²

Engineered erythrocytes

Red blood cells (RBCs) undergo rapid turnover in the circulation. Apoptotic RBCs are phagocytosed, either by macrophages or DCs, whereupon they are recognized as self-inducing anergy. By introducing RBCs engineered to express an “antigenic payload” of interest, this mechanism can be commandeered to induce tolerance in naïve subjects. Pishesha et al¹⁴³ covalently attached autoantigens known to play a role in disease to RBCs by using the transpeptidase sortase while preserving the normal biological properties of the cells. Transfusion of these cells into mice or human subjects led to reduced autoimmune symptoms.¹⁴³ However, production of RBCs from progenitors *in vitro* is expensive and time consuming. The most parsimonious strategy is to obtain RBCs from donors and label these cells with peptides of interest *in vitro*.

Cutaneous microbiota

Emerging evidence highlights the important role of the skin microbiome in facilitating inflammatory responses to allergens. In human studies it has been observed that *Acinetobacter* species in the skin modulates the immune response in healthy versus atopic human subjects. A positive association between anti-inflammatory molecules, which included transcript levels of IL-10 and Foxp3, and the *Acinetobacter* species was exhibited in healthy but not atopic subjects. Furthermore, T_H1, T_H2, and Treg cell responses were shown to be unbalanced in atopic subjects when compared with healthy subjects.¹⁴⁴ *Staphylococcus aureus* is frequently associated with AD, possibly because of diminished expression of antimicrobial peptides in the skin of patients with AD. In children with AD, diversity in microbial communities was drastically reduced during an untreated AD flare, whereas children who had been treated for an AD flare presented with a higher bacterial diversity profile at disease sites.¹⁴⁵

Studies using mouse models of eczematous dermatitis with dysbiosis have also revealed that a microbial imbalance can drive

eczema pathophysiology. Eczematous mice displayed altered bacterial communities in the skin compared with wild-type mice, with the presence of *Corynebacterium mastitidis*, *S aureus*, and *Corynebacterium bovis* at onset of eczematous dermatitis development. Antibiotics targeted to these bacterial species alleviated skin inflammation and restored the bacterial diversity in the skin. It was determined that *S aureus* and *C bovis* specifically advanced the development of eczematous inflammation.¹⁴⁶ Determining appropriate and safe strategies to modify the skin microbiome could have a profound effect when treating patients with atopic skin disorders.

Epicutaneous immunotherapy

Epicutaneous immunotherapy (EPIT; ie, induction of immune tolerance through the skin) is the most recent immunotherapeutic approach to emerge and is currently under investigation for the treatment of food allergy. Allergen is deposited into an adhesive membrane, which can then be applied to intact skin. Antigen diffuses toward skin-resident immunocompetent cells, driving desensitization and promoting tolerance.⁴

EPIT potentially impedes the atopic march, not by reducing DC migration but by inducing Foxp3⁺ and latency-associated peptide-positive Treg cells that suppress local and systemic allergen-specific immune responses, including reduction of T_H2 inflammatory pathways and IL-4 production.^{52,147,148} As a result, EPIT can also prevent the development of new sensitizations. However, this protective effect is observed only when sensitization to additional allergens occurs subsequent to EPIT treatment for the first allergen.¹⁴⁸ Further efforts to elucidate the mechanisms by which EPIT produces this additional benefit were demonstrated by means of adoptive transfer of CD4⁺CD25⁺ T cells from sensitized animals treated with EPIT, which was comparable in preventing additional sensitizations to EPIT itself, underscoring the role of Treg cells in the response.¹⁴⁸ Additionally, prevention of CHS development was demonstrated in mice treated with epicutaneous application of repeated low doses of contact allergens resulting in low zone tolerance, which was shown to be mediated through CD4⁺CD25⁺Foxp3⁺ Treg cells.¹⁴⁹

Although EPIT has demonstrated promising potential as an immunotherapy for food allergy, it is important to discuss possible risks associated with such treatment. Systemic side effects associated with EPIT for peanut protein and grass pollen in human clinical studies have been reported; these include nonserious anaphylaxis possibly related to EPIT and a single occurrence of hives.¹⁵⁰⁻¹⁵² Additionally, clinical symptoms of anaphylaxis, including intestinal damage, have been observed with transdermal exposure to hazelnut protein in a mouse study.¹⁵³ EPIT can induce tolerance or type 1 allergy in patients with allergies depending on the level of skin barrier disruption. With allergen administration to nonvascularized epidermis through EPIT, keratinocytes can become further activated because of physical irritation of the skin by means of abrasion, adhesive tape stripping, or adjuvants, which will promote a T_H1-type immune response. Furthermore, heavily scarified skin has been shown to shift the immune response toward T_H1 responses, whereas a skin barrier with slight disruption has been shown to induce a noninflammatory type 2/Treg cell response.¹⁵⁴ Conversely, it has been observed in a mouse study that EPIT applied to noninflamed skin significantly dampened

the T_H2 immunologic response (IgE response), whereas EPIT on stripped skin strengthened this response.¹⁵⁵ Systemic allergic adverse effects are likely attributed to relative epithelial damage, such as skin abrasion or use of adhesive tape strips in skin preparation before patch application.¹⁵² Recent studies also suggest that epicutaneous exposure to food allergens is an important risk factor for sensitization to foods under suitable immune conditions.¹⁵⁶ Many children present with peanut allergy on their first known oral exposure to peanut, implying that prior environmental exposure to peanut, possibly through skin contact, might promote sensitization.¹⁵⁷⁻¹⁵⁹

In the context of the skin's primary role as a barrier between "self" and "other," EPIT bypasses risks associated with invasive techniques (ie, injection or skin scarification). Indeed, studies in animal models have shown that when applying the allergen directly onto intact skin, there is no indication of passive passage through the skin or detection of a systemic delivery.⁵² Instead, EPIT capitalizes on the immune milieu described above,^{88,135} inducing DCs at the epidermis, which then migrate to LNs to activate immune responses and allergen-specific cytokine production.⁵² Most notably, recent research indicates that the suppressive activity of Treg cells induced by EPIT is maintained for 8 weeks after treatment cessation,¹⁴⁷ underscoring the possible viability of EPIT as a long-term treatment approach for allergy.

CONCLUSIONS

The skin is a complex immune organ, demonstrating considerable influence over the body's tendency to mount tolerogenic or immunogenic responses to antigens. Determination of the response is mediated by a complex network of cells and cytokines that act in concert to regulate the balance between eliminating pathogens and avoiding resident tissue destruction. Under circumstances in which the balance between tolerance and immune response has gone awry (eg, allergy), it might be possible to therapeutically bolster tolerogenic pathways and mute the aberrant immunogenicity.

Although recent progress in the development of therapeutic approaches is very promising, it must be viewed with a measure of caution. Much of our current knowledge derives from *in vitro* systems and animal models, which benefit from the high level of control that can be exerted over experimental conditions. This also serves as a drawback, however, because the balance of available cytokines might not accurately reproduce the dynamic levels observed *in vivo*. Most *in vitro* studies also require forced differentiation of cells, which might not reliably reflect the natural state of their *in vivo* counterparts. On the other hand, *in vivo* work most often begins with animal models, and although there is reasonable overlap between mouse and human immune systems, there are also key differences.

Epidermal structure differs between mice and human subjects. Most notably, the density of hair follicles is significantly different between species, affecting Treg cell generation and the kinetics of local immune responses. Moreover, as described previously, DC subsets express distinct markers (Table I), and we have only recently begun to reliably match these subsets across species, illuminating a clearer path to translation. Despite these limitations, clinical data for emerging therapeutic strategies for the treatment of food allergy and hypersensitivity support the feasibility and promise of this field.

REFERENCES

- Silvestre MC, Sato MN, Reis V. Innate immunity and effector and regulatory mechanisms involved in allergic contact dermatitis. *An Bras Dermatol* 2018; 93:242-50.
- Salmon JK, Armstrong CA, Ansel JC. The skin as an immune organ. *West J Med* 1994;160:146-52.
- Manicassamy S, Pulendran B. Dendritic cell control of tolerogenic responses. *Immunol Rev* 2011;241:206-27.
- Mondoulet L, Dioszeghy V, Thebault C, Benhamou PH, Dupont C. Epicutaneous immunotherapy for food allergy as a novel pathway for oral tolerance induction. *Immunotherapy* 2015;7:1293-305.
- Seneschal J, Clark RA, Gehad A, Baecher-Allan CM, Kupper TS. Human epidermal Langerhans cells maintain immune homeostasis in skin by activating skin resident regulatory T cells. *Immunity* 2012;36:873-84.
- Clausen BE, Kel JM. Langerhans cells: critical regulators of skin immunity? *Immunol Cell Biol* 2010;88:351-60.
- Chu CC, Ali N, Karagiannis P, Di Meglio P, Skowera A, Napolitano L, et al. Resident CD141 (BDCA3)+ dendritic cells in human skin produce IL-10 and induce regulatory T cells that suppress skin inflammation. *J Exp Med* 2012; 209:935-45.
- Sanchez Rodriguez R, Pauli ML, Neuhaus IM, Yu SS, Arron ST, Harris HW, et al. Memory regulatory T cells reside in human skin. *J Clin Invest* 2014;124: 1027-36.
- Yamazaki S, Steinman RM. Dendritic cells as controllers of antigen-specific Foxp3+ regulatory T cells. *J Dermatol Sci* 2009;54:69-75.
- Godfrey VL, Wilkinson JE, Russell LB. X-linked lymphoreticular disease in the scurfy (sf) mutant mouse. *Am J Pathol* 1991;138:1379-87.
- Wildin RS, Smyk-Pearson S, Filipovich AH. Clinical and molecular features of the immunodysregulation, polyendocrinopathy, enteropathy, X linked (IPEX) syndrome. *J Med Genet* 2002;39:537-45.
- Guttman-Yassky E, Krueger JG. IL-17C: a unique epithelial cytokine with potential for targeting across the spectrum of atopic dermatitis and psoriasis. *J Invest Dermatol* 2018;138:1467-9.
- Divekar R, Kita H. Recent advances in epithelium-derived cytokines (IL-33, IL-25, and thymic stromal lymphopoietin) and allergic inflammation. *Curr Opin Allergy Clin Immunol* 2015;15:98-103.
- Charlesworth EN, Hood AF, Soter NA, Kagey-Sobotka A, Norman PS, Lichtenstein LM. Cutaneous late-phase response to allergen. Mediator release and inflammatory cell infiltration. *J Clin Invest* 1989;83:1519-26.
- Zaba LC, Krueger JG, Lowes MA. Resident and "inflammatory" dendritic cells in human skin. *J Invest Dermatol* 2009;129:302-8.
- Peiser M. Role of Th17 cells in skin inflammation of allergic contact dermatitis. *Clin Dev Immunol* 2013;2013:1-10.
- Guttman-Yassky E, Krueger JG. Atopic dermatitis and psoriasis: two different immune diseases or one spectrum? *Curr Opin Immunol* 2017;48:68-73.
- de Saint-Vis B, Vincent J, Vandenabeele S, Vanberghel B, Pin JJ, Ait-Yahia S, et al. A novel lysosome-associated membrane glycoprotein, DC-LAMP, induced upon DC maturation, is transiently expressed in MHC class II compartment. *Immunity* 1998;9:325-36.
- Levin C, Perrin H, Combadiere B. Tailored immunity by skin antigen-presenting cells. *Hum Vaccin Immunother* 2015;11:27-36.
- Nestle FO, Di Meglio P, Qin J-Z, Nickoloff BJ. Skin immune sentinels in health and disease. *Nat Rev Immunol* 2009;9:679-91.
- Clark RA. Skin-resident T cells: the ups and downs of on site immunity. *J Invest Dermatol* 2010;130:362-70.
- Blanco JL, Garcia ME. Immune response to fungal infections. *Vet Immunol Immunopathol* 2008;125:47-70.
- Gorelik M, Frischmeyer-Guerrero PA. Innate and adaptive dendritic cell responses to immunotherapy. *Curr Opin Allergy Clin Immunol* 2015;15:575-80.
- Sells RE, Hwang ST. Paradoxical increase in skin inflammation in the absence of CCR4. *J Invest Dermatol* 2010;130:2697-9.
- Kang Z, Swaidani S, Yin W, Wang C, Barlow JL, Gulen MF, et al. Epithelial cell-specific Act1 adaptor mediates interleukin-25-dependent helminth expulsion through expansion of Lin(-)c-Kit(+) innate cell population. *Immunity* 2012;36:821-33.
- Pierre P, Turley SJ, Gatti E, Hull M, Meltzer J, Mirza A, et al. Developmental regulation of MHC class II transport in mouse dendritic cells. *Nature* 1997; 388:787-92.
- Gurung P, Kanneganti T-D. Immune responses against protozoan parasites: a focus on the emerging role of Nod-like receptors. *Cell Mol Life Sci* 2016;73: 3035-51.
- Guilloteau K, Paris I, Pedretti N, Boniface K, Juchaux F, Huguier V, et al. Skin inflammation induced by the synergistic action of IL-17A, IL-22, oncostatin M, IL-1 α , and TNF- α recapitulates some features of psoriasis. *J Immunol* 2010; 184:5263-70.
- Tan Y, Kagan JC. A cross-disciplinary perspective on the innate immune responses to bacterial lipopolysaccharide. *Mol Cell* 2014;54:212-23.
- Chinthrajah RS, Hernandez JD, Boyd SD, Galli SJ, Nadeau KC. Molecular and cellular mechanisms of food allergy and food tolerance. *J Allergy Clin Immunol* 2016;137:984-97.
- Gittler JK, Krueger JG, Guttman-Yassky E. Atopic dermatitis results in intrinsic barrier and immune abnormalities: implications for contact dermatitis. *J Allergy Clin Immunol* 2013;131:300-13.
- Dhingra N, Gulati N, Guttman-Yassky E. Mechanisms of contact sensitization offer insights into the role of barrier defects vs. intrinsic immune abnormalities as drivers of atopic dermatitis. *J Invest Dermatol* 2013;133:2311-4.
- Achtman JC, Werth VP. Pathophysiology of cutaneous lupus erythematosus. *Arthritis Res Ther* 2015;17:182.
- Paller AS, Renert-Yuval Y, Suprun M, Esaki H, Oliva M, Huynh TN, et al. An IL-17-dominant immune profile is shared across the major orphan forms of ichthyosis. *J Allergy Clin Immunol* 2017;139:152-65.
- Czarnowicki T, Esaki H, Gonzalez J, Malajian D, Shemer A, Noda S, et al. Early pediatric atopic dermatitis shows only a cutaneous lymphocyte antigen (CLA)(+) Th2/Th1 cell imbalance, whereas adults acquire CLA(+) Th22/Tc22 cell subsets. *J Allergy Clin Immunol* 2015;136:941-951e3.
- Czarnowicki T, Esaki H, Gonzalez J, Renert-Yuval Y, Brunner P, Oliva M, et al. Alterations in B-cell subsets in pediatric patients with early atopic dermatitis. *J Allergy Clin Immunol* 2017;140:134-144e9.
- Czarnowicki T, Gonzalez J, Bonifacio KM, Shemer A, Xiangyu P, Kunjraiva N, et al. Diverse activation and differentiation of multiple B-cell subsets in patients with atopic dermatitis but not in patients with psoriasis. *J Allergy Clin Immunol* 2016;137:118-29.e5.
- Czarnowicki T, Krueger JG, Guttman-Yassky E. Novel concepts of prevention and treatment of atopic dermatitis through barrier and immune manipulations with implications for the atopic march. *J Allergy Clin Immunol* 2017;139:1723-34.
- Brunner PM, Guttman-Yassky E, Leung DY. The immunology of atopic dermatitis and its reversibility with broad-spectrum and targeted therapies. *J Allergy Clin Immunol* 2017;139(suppl):S65-76.
- Brunner PM, Israel A, Zhang N, Leonard A, Wen HC, Huynh T, et al. Early-onset pediatric atopic dermatitis is characterized by Th2/Th17/Th22-centered inflammation and lipid alterations. *J Allergy Clin Immunol* 2018;141:2094-106.
- Esaki H, Czarnowicki T, Gonzalez J, Oliva M, Talasila S, Haugh I, et al. Accelerated T-cell activation and differentiation of polar subsets characterizes early atopic dermatitis development. *J Allergy Clin Immunol* 2016;138:1473-7.e5.
- Stier MT, Zhang J, Goleniewska K, Cephus JY, Rusznak M, Wu L, et al. IL-33 promotes the egress of group 2 innate lymphoid cells from the bone marrow. *J Exp Med* 2018;215:263-81.
- Peebles RS Jr. At the bedside: the emergence of group 2 innate lymphoid cells in human disease. *J Leukoc Biol* 2015;97:469-75.
- Brunner PM, Leung DYM, Guttman-Yassky E. Immunologic, microbial, and epithelial interactions in atopic dermatitis. *Ann Allergy Asthma Immunol* 2018; 120:34-41.
- Alvarez D, Vollmann EH, von Andrian UH. Mechanisms and consequences of dendritic cell migration. *Immunity* 2008;29:325.
- King JK, Philips RL, Eriksson AU, Kim PJ, Halder RC, Lee DJ, et al. Langerhans cells maintain local tissue tolerance in a model of systemic autoimmune disease. *J Immunol* 2015;195:464-76.
- Brocker T, Riedinger M, Karjalainen K. Targeted expression of major histocompatibility complex (MHC) class II molecules demonstrates that dendritic cells can induce negative but not positive selection of thymocytes in vivo. *J Exp Med* 1997;185:541-50.
- Lutz MB, Schuler G. Immature, semi-mature and fully mature dendritic cells: which signals induce tolerance or immunity? *Trends Immunol* 2002;23:445-9.
- Luo Y, Cai X, Liu S, Wang S, Nold-Petry CA, Nold MF, et al. Suppression of antigen-specific adaptive immunity by IL-37 via induction of tolerogenic dendritic cells. *Proc Natl Acad Sci U S A* 2014;111:15178-83.
- Steinman RM, Hawiger D, Nussenzweig MC. Tolerogenic dendritic cells. *Annu Rev Immunol* 2003;21:685-711.
- Yoshino M, Yamazaki H, Nakano H, Kakiuchi T, Ryoike K, Kunisada T, et al. Distinct antigen trafficking from skin in the steady and active states. *Int Immunol* 2003;15:773-9.
- Dioszeghy V, Mondoulet L, Dhelft V, Ligouis M, Puteaux E, Benhamou PH, et al. Epicutaneous immunotherapy results in rapid allergen uptake by dendritic cells through intact skin and downregulates the allergen-specific response in sensitized mice. *J Immunol* 2011;186:5629-37.

53. Morelli AE, Thomson AW. Tolerogenic dendritic cells and the quest for transplant tolerance. *Nat Rev Immunol* 2007;7:610-21.
54. Esaki H, Brunner PM, Renert-Yuval Y, Czarnowicki T, Huynh T, Tran G, et al. Early-onset pediatric atopic dermatitis is Th2 but also Th17 polarized in skin. *J Allergy Clin Immunol* 2016;138:1639-51.
55. Fujita H, Shemer A, Suarez-Farinas 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, e1-12.
56. Guttman-Yassky E, Lowes MA, Fuentes-Duculan J, Whynot 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.
57. Shin J-S, Greer AM. The role of FcεRI expressed in dendritic cells and monocytes. *Cell Mol Life Sci* 2015;72:2349-60.
58. Vander Lugt B, Riddell J, Khan AA, Hackney JA, Lesch J, DeVoss J, et al. Transcriptional determinants of tolerogenic and immunogenic states during dendritic cell maturation. *J Cell Biol* 2017;216:779-92.
59. Dudek AM, Martin S, Garg AD, Agostinis P. Immature, semi-mature, and fully mature dendritic cells: toward a DC-cancer cells interface that augments anticancer immunity. *Front Immunol* 2013;4:438.
60. Kim TG, Kim SH, Lee MG. The origin of skin dendritic cell network and its role in psoriasis. *Int J Mol Sci* 2017;19.
61. Qu C, Brinck-Jensen N-S, Zang M, Chen K. Monocyte-derived dendritic cells: targets as potent antigen-presenting cells for the design of vaccines against infectious diseases. *Int J Infect Dis* 2014;19:1-5.
62. Collin M, McGovern N, Haniffa M. Human dendritic cell subsets. *Immunology* 2013;140:22-30.
63. Zaba LC, Fuentes-Duculan J, Eungdamrong NJ, Abello MV, Novitskaya I, Pierson KC, et al. Psoriasis is characterized by accumulation of immunostimulatory and Th1/Th17 cell polarizing myeloid dendritic cells. *J Invest Dermatol* 2009;129:79-88.
64. Segura E, Amigorena S. Inflammatory dendritic cells in mice and humans. *Trends Immunol* 2013;34:440-5.
65. Romani N, Holzmann S, Tripp CH, Koch F, Stoitzner P. Langerhans cells—dendritic cells of the epidermis. *APMIS* 2003;111:725-40.
66. Zaba LC, Fuentes-Duculan J, Steinman RM, Krueger JG, Lowes MA. Normal human dermis contains distinct populations of CD11c+BDCA-1+ dendritic cells and CD163+FXIIIa+ macrophages. *J Clin Invest* 2007;117:2517-25.
67. Deckers J, Hammad H, Hoste E. Langerhans cells: sensing the environment in health and disease. *Front Immunol* 2018;9:93.
68. Collin M, Bigley V. Human dendritic cell subsets: an update. *Immunology* 2018;154:3-20.
69. Charles J, Chaperot L, Salameire D, Di Domizio J, Aspori C, Gressin R, et al. Plasmacytoid dendritic cells and dermatological disorders: focus on their role in autoimmunity and cancer. *Eur J Dermatol* 2010;20:16-23.
70. León B, Ardavin C. Monocyte-derived dendritic cells in innate and adaptive immunity. *Immunol Cell Biol* 2008;86:320-4.
71. Segura E, Touzot M, Bohineust A, Cappuccio A, Chioecchia G, Hosmalin A, et al. Human inflammatory dendritic cells induce Th17 cell differentiation. *Immunity* 2013;38:336-48.
72. Zaba LC, Fuentes-Duculan J, Eungdamrong NJ, Johnson-Huang LM, Nograles KE, White TR, et al. Identification of TRAIL and other molecules that distinguish inflammatory DCs from resident DCs in psoriasis. *J Allergy Clin Immunol* 2010;125:1261-8.e9.
73. Haniffa M, Gunawan M, Jardine L. Human skin dendritic cells in health and disease. *J Dermatol Sci* 2015;77:85-92.
74. Rimoldi M, Chieppa M, Larghi P, Vulcano M, Allavena P, Rescigno M. Monocyte-derived dendritic cells activated by bacteria or by bacteria-stimulated epithelial cells are functionally different. *Blood* 2005;106:2818-26.
75. Shay T, Jovic V, Zuk O, Rothamel K, Puyraimond-Zemmour D, Feng T, et al. Conservation and divergence in the transcriptional programs of the human and mouse immune systems. *Proc Natl Acad Sci U S A* 2013;110:2946-51.
76. Kissenpfennig A, Malissen B. Langerhans cells—revisiting the paradigm using genetically engineered mice. *Trends Immunol* 2006;27:132-9.
77. Yasmin N, Konradi S, Eisenwort G, Schichl YM, Seyerl M, Bauer T, et al. Beta-catenin promotes the differentiation of epidermal Langerhans dendritic cells. *J Invest Dermatol* 2013;133:1250-9.
78. van der Aar AM, Picavet DI, Muller FJ, de Boer L, van Capel TM, Zaat SA, et al. Langerhans cells favor skin flora tolerance through limited presentation of bacterial antigens and induction of regulatory T cells. *J Invest Dermatol* 2013;133:1240-9.
79. Polak ME, Newell L, Taraban VY, Pickard C, Healy E, Friedmann PS, et al. CD70-CD27 interaction augments CD8+ T-cell activation by human epidermal Langerhans cells. *J Invest Dermatol* 2012;132:1636-44.
80. Romani N, Clausen BE, Stoitzner P. Langerhans cells and more: langerin-expressing dendritic cell subsets in the skin. *Immunol Rev* 2010;234:120-41.
81. Toews GB, Bergstresser PR, Streilein JW. Epidermal Langerhans cell density determines whether contact hypersensitivity or unresponsiveness follows skin painting with DNFB. *J Immunol* 1980;124:445-53.
82. Noordegraaf M, Flacher V, Stoitzner P, Clausen BE. Functional redundancy of Langerhans cells and Langerin+ dermal dendritic cells in contact hypersensitivity. *J Invest Dermatol* 2010;130:2752-9.
83. Kaplan DH, Jenison MC, Saeland S, Shlomchik WD, Shlomchik MJ. Epidermal Langerhans cell-deficient mice develop enhanced contact hypersensitivity. *Immunity* 2005;23:611-20.
84. Bursch LS, Wang L, Igyarto B, Kissenpfennig A, Malissen B, Kaplan DH, et al. Identification of a novel population of Langerin+ dendritic cells. *J Exp Med* 2007;204:3147-56.
85. Schwarz A, Noordegraaf M, Maeda A, Torii K, Clausen BE, Schwarz T. Langerhans cells are required for UVR-induced immunosuppression. *J Invest Dermatol* 2010;130:1419-27.
86. Aberer W, Schuler G, Stingl G, Honigsman H, Wolff K. Ultraviolet light depletes surface markers of Langerhans cells. *J Invest Dermatol* 1981;76:202-10.
87. Dhirga N, Shemer A, Correa da Rosa J, Rozenblit M, Fuentes-Duculan J, Gittler JK, et al. Molecular profiling of contact dermatitis skin identifies allergen-dependent differences in immune response. *J Allergy Clin Immunol* 2014;134:362-72.
88. Leonard A, Guttman-Yassky E. The unique molecular signatures of contact dermatitis and implications for treatment. *Clin Rev Allergy Immunol* 2019;56:1-8.
89. Cavani A, Mei D, Guerra E, Corinti S, Giani M, Pirrotta L, et al. Patients with allergic contact dermatitis to nickel and nonallergic individuals display different nickel-specific T cell responses. Evidence for the presence of effector CD8+ and regulatory CD4+ T cells. *J Invest Dermatol* 1998;111:621-8.
90. Cooper KD, Oberhelman L, Hamilton TA, Baadsgaard O, Terhune M, LeVee G, et al. UV exposure reduces immunization rates and promotes tolerance to epicutaneous antigens in humans: relationship to dose, CD1a-DR+ epidermal macrophage induction, and Langerhans cell depletion. *Proc Natl Acad Sci U S A* 1992;89:8497-501.
91. Kreutz M, Karrer S, Hoffmann P, Gottfried E, Szeimies RM, Hahn J, et al. Whole-body UVB irradiation during allogeneic hematopoietic cell transplantation is safe and decreases acute graft-versus-host disease. *J Invest Dermatol* 2012;132:179-87.
92. Correa da Rosa J, Malajian D, Shemer A, Rozenblit M, Dhirga N, Czarnowicki T, et al. Patients with atopic dermatitis have attenuated and distinct contact hypersensitivity responses to common allergens in skin. *J Allergy Clin Immunol* 2015;135:712-20.
93. Wakim LM, Waithman J, van Rooijen N, Heath WR, Carbone FR. Dendritic cell-induced memory T cell activation in nonlymphoid tissues. *Science* 2008;319:198-202.
94. Matsushima H, Takashima A. Bidirectional homing of Tregs between the skin and lymph nodes. *J Clin Invest* 2010;120:653-6.
95. Zhang R, Huynh A, Whitcher G, Chang J, Maltzman JS, Turka LA. An obligate cell-intrinsic function for CD28 in Tregs. *J Clin Invest* 2013;123:580-93.
96. Xia M, Hu S, Fu Y, Jin W, Yi Q, Matsui Y, et al. CCR10 regulates balanced maintenance and function of resident regulatory and effector T cells to promote immune homeostasis in the skin. *J Allergy Clin Immunol* 2014;134:634-44.e10.
97. Zhang R, Borges CM, Fan MY, Harris JE, Turka LA. Requirement for CD28 in effector regulatory T cell differentiation, CCR6 induction, and skin homing. *J Immunol* 2015;195:4154-61.
98. Wei X, Zhang J, Gu Q, Huang M, Zhang W, Guo J, et al. Reciprocal expression of IL-35 and IL-10 defines two distinct effector Treg subsets that are required for maintenance of immune tolerance. *Cell Rep* 2017;21:1853-69.
99. Zeng H, Zhang R, Jin B, Chen L. Type 1 regulatory T cells: a new mechanism of peripheral immune tolerance. *Cell Mol Immunol* 2015;12:566-71.
100. Gratz IK, Truong H-A, Yang SH-Y, Maurano MM, Lee K, Abbas AK, et al. Cutting Edge: memory regulatory T cells require IL-7 and not IL-2 for their maintenance in peripheral tissues. *J Immunol* 2013;190:4483-7.
101. Shevach EM, Thornton AM. rTregs, pTregs, and iTregs: similarities and differences. *Immunol Rev* 2014;259:88-102.
102. Levings MK, Roncarolo MG. T-regulatory 1 cells: a novel subset of CD4 T cells with immunoregulatory properties. *J Allergy Clin Immunol* 2000;106(suppl):S109-12.
103. Nagaraj S, Youn J-I, Gaborilovich DI. Reciprocal relationship between myeloid-derived suppressor cells and T cells. *J Immunol* 2013;191:17-23.

104. Hofmann AM, Abraham SN. New roles for mast cells in modulating allergic reactions and immunity against pathogens. *Curr Opin Immunol* 2009;21:679-86.
105. Galli SJ, Tsai M. Mast cells in allergy and infection: versatile effector and regulatory cells in innate and adaptive immunity. *Eur J Immunol* 2010;40:1843-51.
106. Steele L, Mayer L, Berin MC. Mucosal immunology of tolerance and allergy in the gastrointestinal tract. *Immunol Res* 2012;54:75-82.
107. Torgerson TR, Linane A, Moes N, Anover S, Mateo V, Rieux-Laucat F, et al. Severe food allergy as a variant of IPEX syndrome caused by a deletion in a noncoding region of the FOXP3 gene. *Gastroenterology* 2007;132:1705-17.
108. Tsakok T, Marrs T, Mohsin M, Baron S, du Toit G, Till S, et al. Does atopic dermatitis cause food allergy? A systematic review. *J Allergy Clin Immunol* 2016;137:1071-8.
109. Venkataraman D, Soto-Ramírez N, Kurukulaaratchy RJ, Holloway JW, Karmaus W, Ewart SL, et al. Filaggrin loss-of-function mutations are associated with food allergy in childhood and adolescence. *J Allergy Clin Immunol* 2014;134:876-82.e4.
110. Vickery BP, Scurlock AM, Jones SM, Burks AW. Mechanisms of immune tolerance relevant to food allergy. *J Allergy Clin Immunol* 2011;127:576-86.
111. Chambers SJ, Bertelli E, Winterbone MS, Regoli M, Man AL, Nicoletti C. Adoptive transfer of dendritic cells from allergic mice induces specific immunoglobulin E antibody in naïve recipients in absence of antigen challenge without altering the T helper 1/T helper 2 balance. *Immunology* 2004;112:72-9.
112. Ruiter B, Shreffler WG. The role of dendritic cells in food allergy. *J Allergy Clin Immunol* 2012;129:921-8.
113. Idozaga J, Fiorese C, Zbytniuk L, Lubkin A, Miller J, Malissen B, et al. Specialized role of migratory dendritic cells in peripheral tolerance induction. *J Clin Invest* 2013;123:844-54.
114. Yamazaki S, Inaba K, Tarbell KV, Steinman RM. Dendritic cells expand antigen-specific Foxp3+ CD25+ CD4+ regulatory T cells including suppressors of alloreactivity. *Immunol Rev* 2006;212:314-29.
115. Kornete M, Piccirillo CA. Functional crosstalk between dendritic cells and Foxp3(+) regulatory T cells in the maintenance of immune tolerance. *Front Immunol* 2012;3:165-75.
116. Kaplan DH, Li MO, Jenison MC, Shlomchik WD, Flavell RA, Shlomchik MJ. Autocrine/paracrine TGFβ1 is required for the development of epidermal Langerhans cells. *J Exp Med* 2007;204:2545-52.
117. Ohtani T, Mizuashi M, Nakagawa S, Sasaki Y, Fujimura T, Okuyama R, et al. TGF-β1 dampens the susceptibility of dendritic cells to environmental stimulation, leading to the requirement for danger signals for activation. *Immunology* 2009;126:485-99.
118. Fainaru O, Shay T, Hantisteanu S, Goldenberg D, Domany E, Groner Y. TGFβ-dependent gene expression profile during maturation of dendritic cells. *Genes Immun* 2007;8:239-44.
119. Kel JM, Girard-Madoux MJ, Reizis B, Clausen BE. TGF-β is required to maintain the pool of immature Langerhans cells in the epidermis. *J Immunol* 2010;185:3248-55.
120. Komiya Y, Habas R. Wnt signal transduction pathways. *Organogenesis* 2008;4:68-75.
121. Jakob T, Udey MC, Brown MJ. Characterization of E-cadherin-containing junctions involving skin-derived dendritic cells. *J Invest Dermatol* 1999;112:102-8.
122. Jiang A, Bloom O, Ono S, Cui W, Untchaeer J, Jiang S, et al. Disruption of E-cadherin-mediated adhesion induces a functionally distinct pathway of dendritic cell maturation. *Immunity* 2007;27:610-24.
123. Manicassamy S, Reizis B, Ravindran R, Nakaya H, Salazar-Gonzalez RM, Wang YC, et al. Activation of β-catenin in dendritic cells regulates immunity versus tolerance in the intestine. *Science* 2010;329:849-53.
124. Wu J, Xie A, Chen W. Cytokine regulation of immune tolerance. *Burns Trauma* 2014;2:11-7.
125. Kuhn R, Lohler J, Rennick D, Rajewsky K, Muller W. Interleukin-10-deficient mice develop chronic enterocolitis. *Cell* 1993;75:263-74.
126. Ilarregui JM, Croci DO, Bianco GA, Toscano MA, Salatino M, Vermeulen ME, et al. Tolerogenic signals delivered by dendritic cells to T cells through a galectin-1-driven immunoregulatory circuit involving interleukin 27 and interleukin 10. *Nat Immunol* 2009;10:981-91.
127. Mascanfroni ID, Yeste A, Vieira SM, Burns EJ, Patel B, Sloma I, et al. IL-27 acts on DCs to suppress the T cell response and autoimmunity by inducing expression of the immunoregulatory molecule CD39. *Nat Immunol* 2013;14:1054-63.
128. Dinarello CA, Nold-Petry C, Nold M, Fujita M, Li S, Kim S, et al. Suppression of innate inflammation and immunity by interleukin-37. *Eur J Immunol* 2016;46:1067-81.
129. Conti P, Carinci F, Lessiani G, Spinasi E, Kritas SK, Ronconi G, et al. Potential therapeutic use of IL-37: a key suppressor of innate immunity and allergic immune responses mediated by mast cells. *Immunol Res* 2017;65:982-6.
130. Rudloff I, Cho SX, Lao JC, Ngo D, McKenzie M, Nold-Petry CA, et al. Monocytes and dendritic cells are the primary sources of interleukin 37 in human immune cells. *J Leukoc Biol* 2017;101:901-11.
131. Schülke S. Induction of interleukin-10 producing dendritic cells as a tool to suppress allergen-specific T helper 2 responses. *Front Immunol* 2018;9:455.
132. Lv J, Xiong Y, Li W, Cui X, Cheng X, Leng Q, et al. IL-37 inhibits IL-4/IL-13-induced CCL11 production and lung eosinophilia in murine allergic asthma. *Allergy* 2018;73:1642-52.
133. Domogalla MP, Rostan PV, Raker VK, Steinbrink K. Tolerance through education: how tolerogenic dendritic cells shape immunity. *Front Immunol* 2017;8:1764.
134. Torres-Aguilar H, Aguilar-Ruiz SR, González-Pérez G, Munguía R, Bajaña S, Meraz-Ríos MA, et al. Tolerogenic dendritic cells generated with different immunosuppressive cytokines induce antigen-specific anergy and regulatory properties in memory CD4+ T cells. *J Immunol* 2010;184:1765-75.
135. Ungar B, Correa da Rosa J, Shemer A, Czarnowicki T, Estrada YD, Fuentes-Duculan J, et al. Patch testing of food allergens promotes Th17 and Th2 responses with increased IL-33: a pilot study. *Exp Dermatol* 2017;26:272-5.
136. Malik K, Ungar B, Garcet S, Dutt R, Dickstein D, Zheng X, et al. Dust mite induces multiple polar T cell axes in human skin. *Clin Exp Allergy* 2017;47:1648-60.
137. Lawrence MG, Steinke JW, Borish L. Basic science for the clinician: mechanisms of sublingual and subcutaneous immunotherapy. *Ann Allergy Asthma Immunol* 2016;117:138-42.
138. Burks AW, Sampson HA, Plaut M, Lack G, Akdis CA. Treatment for food allergy. *J Allergy Clin Immunol* 2018;141:1-9.
139. Marogna M, Spadolini I, Massolo A, Canonica GW, Passalacqua G. Long-lasting effects of sublingual immunotherapy according to its duration: a 15-year prospective study. *J Allergy Clin Immunol* 2010;126:969-75.
140. Mahnke K, Ring S, Enk AH. Antibody targeting of "steady-state" dendritic cells induces tolerance mediated by regulatory T cells. *Front Immunol* 2016;7:63.
141. Mahnke K, Guo M, Lee S, Sepulveda H, Swain SL, Nussenzweig M, et al. The dendritic cell receptor for endocytosis, DEC-205, can recycle and enhance antigen presentation via major histocompatibility complex class II-positive lysosomal compartments. *J Cell Biol* 2000;151:673-84.
142. Mukherjee G, DiLorenzo TP. The immunotherapeutic potential of dendritic cells in type 1 diabetes. *Clin Exp Immunol* 2010;161:197-207.
143. Pishesha N, Bilate AM, Wibowo MC, Huang NJ, Li Z, Deshycka R, et al. Engineered erythrocytes covalently linked to antigenic peptides can protect against autoimmune disease. *Proc Natl Acad Sci U S A* 2017;114:3157-62.
144. Fyhrquist N, Ruokolainen L, Suomalainen A, Lehtimäki S, Veckman V, Vendelin J, et al. Acinetobacter species in the skin microbiota protect against allergic sensitization and inflammation. *J Allergy Clin Immunol* 2014;134:1301-9.e11.
145. Kong HH, Oh J, Deming C, Conlan S, Grice EA, Beatson MA, et al. Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. *Genome Res* 2012;22:850-9.
146. Kobayashi T, Glatz M, Horiuchi K, Kawasaki H, Akiyama H, Kaplan DH, et al. Dysbiosis and *Staphylococcus aureus* colonization drives inflammation in atopic dermatitis. *Immunity* 2015;42:756-66.
147. Dioszeghy V, Mondoulet L, Puteaux E, Dhelft V, Ligouis M, Plaquet C, et al. Differences in phenotype, homing properties and suppressive activities of regulatory T cells induced by epicutaneous, oral or sublingual immunotherapy in mice sensitized to peanut. *Cell Mol Immunol* 2017;14:770-82.
148. Mondoulet L, Dioszeghy V, Puteaux E, Ligouis M, Dhelft V, Plaquet C, et al. Specific epicutaneous immunotherapy prevents sensitization to new allergens in a murine model. *J Allergy Clin Immunol* 2015;135:1546-57.e4.
149. Luckey U, Schmidt T, Pfender N, Romer M, Lorenz N, Martin SF, et al. Crosstalk of regulatory T cells and tolerogenic dendritic cells prevents contact allergy in subjects with low zone tolerance. *J Allergy Clin Immunol* 2012;130:781-97.e11.
150. Jones SM, Sicherer SH, Burks AW, Leung DYM, Lindblad RW, Dawson P, et al. Epicutaneous immunotherapy for the treatment of peanut allergy in children and young adults. *J Allergy Clin Immunol* 2017;139:1242-52.e9.
151. Sampson HA, Shreffler WG, Yang WH, Sussman GL, Brown-Whitehorn TF, Nadeau KC, et al. Effect of varying doses of epicutaneous immunotherapy vs placebo on reaction to peanut protein exposure among patients with peanut sensitivity: a randomized clinical trial. *JAMA* 2017;318:1798-809.

152. Senti G, von Moos S, Tay F, Graf N, Johansen P, Kündig TM. Determinants of efficacy and safety in epicutaneous allergen immunotherapy: summary of three clinical trials. *Allergy* 2015;70:707-10.
153. Birmingham NP, Parvataneni S, Hassan HMA, Harkema J, Samineni S, Navuluri L, et al. An adjuvant-free mouse model of tree nut allergy using hazelnut as a model tree nut. *Int Arch Allergy Immunol* 2007;144:203-10.
154. Senti G, Kündig TM. Novel delivery routes for allergy immunotherapy: intralymphatic, epicutaneous, and intradermal. *Immunol Allergy Clin North Am* 2016;36:25-37.
155. Mondoulet L, Dioszeghy V, Puteaux E, Ligouis M, Dhelft V, Letourneur F, et al. Intact skin and not stripped skin is crucial for the safety and efficacy of peanut epicutaneous immunotherapy (EPIT) in mice. *Clin Transl Allergy* 2012;2:22.
156. Tordesillas L, Goswami R, Benedé S, Grishina G, Dunkin D, Järvinen KM, et al. Skin exposure promotes a Th2-dependent sensitization to peanut allergens. *J Clin Invest* 2014;124:4965-75.
157. Fox AT, Sasieni P, du Toit G, Syed H, Lack G. Household peanut consumption as a risk factor for the development of peanut allergy. *J Allergy Clin Immunol* 2009; 123:417-23.
158. Hourihane JO, Dean TP, Warner JO. Peanut allergy in relation to heredity, maternal diet, and other atopic diseases: results of a questionnaire survey, skin prick testing, and food challenges. *BMJ* 1996; 313:518-21.
159. Lack G, Fox D, Northstone K, Golding J. Factors associated with the development of peanut allergy in childhood. *N Engl J Med* 2003;348:977-85.