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The Unique Molecular Signatures of Contact Dermatitis and Implications for Treatment

Alexandra Leonard[1] · Emma Guttman-Yassky[1]

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Abstract

Irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD) are common skin disorders that are characterized by inflammation, oozing, crusting, and pruritus. Atopic dermatitis (AD) is an inflammatory skin disease characterized by immune and barrier abnormalities and is additionally a risk factor for acquiring ICD and ACD. New work on allergic sensitization to common allergens (e.g., nickel and fragrance) in human skin has shown that different allergens have distinct molecular fingerprinting. For example, nickel promotes strong Th1/Th17 polarization, whereas fragrance allergy causes Th2/Th22 skewing, which is similar to the phenotype of AD. While ACD has previously been considered to be constant across all allergens, largely based on mouse models involving strong sensitizers, these new data suggest that ACD differs mechanistically according to allergen. Further, ACD in the setting of concurrent AD shows a different and attenuated phenotype as compared to healthy individuals with ACD, which influences the way AD patients respond to vaccination and other treatment modalities. As in contact sensitization, skin challenged by food patch testing shows that common food allergens (e.g., peanut and barley) also cause distinct immune polarizations in the skin. Additionally, house dust mite reactions in human skin have been profiled to show unique Th2, Th9, and Th17/22 activation as compared to controls, which are similar to the phenotype of psoriasis and contact responses to nickel. Given this information, ACD patients should be treated based on their unique allergen polarity. Refined understanding of the molecular behavior of contact dermatitis and related diseases translates to improved methods of inducing tolerance in sensitized allergic patients, such as with targeted drug therapy and epicutaneous immunotherapy.

Keywords Contact hypersensitivity · Allergic contact dermatitis · Irritant contact dermatitis · Atopic dermatitis · Immune activation · T cell polarization · Patch testing · Allergens · Human skin

Abbreviations

ACD	Allergic contact dermatitis
AD	Atopic dermatitis
CD	Contact dermatitis
dDC	Dermal dendritic cells
DEG	Differentially expressed genes
DNCB	Dinitrochlorobenzene
EPIT	Epicutaneous immunotherapy
FLG	Filaggrin
HDM	House dust mite
IDEC	Inflammatory dendritic epidermal cell
ICD	Irritant contact dermatitis
LC	Langerhans cells
LN	Lymph node
MADAD	Meta-analysis derived atopic dermatitis
SLS	Sodium lauryl sulfate
TEWL	Trans-epidermal water loss
Treg	Regulatory T cell
TSLP	Thymic stromal lymphopoietin

✉ Emma Guttman-Yassky
Emma.Guttman@mountsinai.org

[1] Department of Dermatology and the Laboratory of Inflammatory Skin Diseases, Icahn School of Medicine at Mount Sinai Medical Center, 5 E. 98th Street, New York, NY 10029, USA

Introduction

Contact dermatitis (CD) is an inflammatory skin disease characterized by erythema, edema, oozing, crusting, vesicles, and intense pruritus [1]. CD is the most common etiology of occupational skin disorder [2]. It has two forms: 80% of CD cases are irritant contact dermatitis (ICD) and 20% of CD cases are allergic contact dermatitis (ACD) [3]. Patients with atopic dermatitis (AD),

considered the most common inflammatory skin disease [4, 5], have an increased risk of developing CD, both ICD [6] and ACD [7]. Through recent advances in molecular profiling, new understanding of differential reactions to a variety of allergens in both AD and non-AD individuals has been attained, thus paving the way for innovative therapeutic methodologies that target unique immunologic pathways for patients.

Mechanisms Underlying Irritant Contact Dermatitis and Allergic Contact Dermatitis

ICD develops on skin sites exposed to irritant (either cytotoxic or chemical) agents. Direct skin damage by the irritant agent activates the body's innate immune system, which rapidly deploys a stream of pro-inflammatory cytokines to mediate the injury [7–11] (Fig. 1). At the molecular level, toxins directly compromise keratinocytes, which subsequently release the innate immune mediators IL-1α, IL-1β, TNF-α, GM-CSF, and IL-8. These cytokines activate Langerhans cells (LC), dermal dendritic cells (dDC), and endothelial cells, and the total effect is recruitment of neutrophils, lymphocytes, macrophages, and mast cells to sites of damage [7]. This sequence has been experimentally modeled using sodium lauryl sulfate (SLS), a toxin that causes similar damage to the keratinocyte as in ICD [7, 12]. Studies investigating a genetic susceptibility to ICD have pointed to a potential TNF-α polymorphism, though the relationship is still unclear [13–16]. Elimination of the irritant agent is often beneficial, and emollients and topical and systemic immune modulators (corticosteroids, tacrolimus, and pimecrolimus) can attenuate the inflammatory response [7].

Whereas ICD does not involve antigen-/allergen-specific T cells, allergic contact dermatitis is a type IV delayed-type hypersensitivity reaction caused by skin contact with haptens, or non-protein contact allergens [7, 11, 17]. ACD skin responses are characterized by oozing, bright-red lesions during the acute phase, and dull-red, scaly, lichenified lesions in the chronic phase [7]. The development of ACD is a two-phase process. In the first phase, or the sensitization phase (also called the afferent or induction phase), allergen contact with the skin induces the same innate-immunity cascade as in ICD, with the release of IL-1α, IL-1β, TNF-α, GM-CSF, and IL-8 and activation of LCs and dDCs [7, 11, 18]. At this point, however, the hapten is engulfed by LCs or dDCs, and the hapten-peptide complexes migrate to regional lymph nodes (LNs), where they prime hapten-specific T cells (Th1, Th2, Th17, and Treg cells) that proliferate and circulate in the blood, producing hapten-specific immunoglobulins [11, 19, 20]. Upon second exposure to the hapten, the elicitation phase (also called the efferent or challenge phase) occurs. The hapten diffuses into the skin and is recognized by the now-sensitized, hapten-specific T cells. These T cells trigger an inflammatory cascade of cytokines and cellular infiltrates and further stimulate keratinocytes to produce the clinical symptoms of ACD. Tables 1 and 2 summarize studies that have investigated the pathogenesis of ICD and ACD, respectively.

Allergic Contact Dermatitis Is Not a Single Process from an Immunological Standpoint; Instead, It Differs According to Distinctive Allergens

A bulk of evidence about ACD pathology stems from mice models. Mice react to strong skin sensitizers (fluorescein isothiocyanate [21], dinitrochlorobenzene [30], diphenylcyclopropenone, dinitrofluorobenzene, and trinitrochlorobenzene [17]), but not to weak sensitizers that are clinically relevant to human ACD, such as nickel and fragrance [22, 23, 30, 31]. These prior mouse-based studies assumed that molecularly, ACD is a single immunological process rather than an allergen-specific one and suggested a largely Th1/Th17-skewed profile of ACD [31, 32].

Dhingra et al. (2014) advanced the understanding of the ACD fingerprint in humans by investigating the most common contact allergens with molecular and cellular analyses in patch-tested skin from ACD patients [17]. They challenged human skin with the 15 most common allergens of the North American Contact Dermatitis Group (nickel sulfate, balsam of Peru, fragrance mix, quaternium-15, neomycin, bacitracin, formaldehyde, cobalt chloride, methyldibromo glutaronitrile/phenoxyethanol, p-phenylenediamine, potassium dichromate, carba mix, thiuram mix, diazolidinylurea, and 2-bromo-2-nitropane-1,3-diol) [33] and via analysis of skin biopsies and found that different allergens generated unique immune polarizations. Nickel induced innate immunity and Th1/Th17 polarization, while fragrance (and rubber, to a lesser extent) induced Th2/Th22 polarization with a weaker Th1/Th17 axis [17]. The fragrance molecular profile is especially compelling as it has phenotypic similarities to that of AD, whose hallmark is Th2/Th22 activation with some Th1/Th17 components in a pro-inflammatory cytokine milieu [5, 34]. Dhingra et al. (2014) thus demonstrated that from an immunological standpoint, ACD is not a single process, but rather differs mechanistically according to allergen. This concept holds therapeutic relevance for CD, as consideration of sensitivity to a specific allergen would guide treatment decisions to achieve more efficient, targeted-therapy for patients, rather than to treat all ACD patients in a uniform fashion.

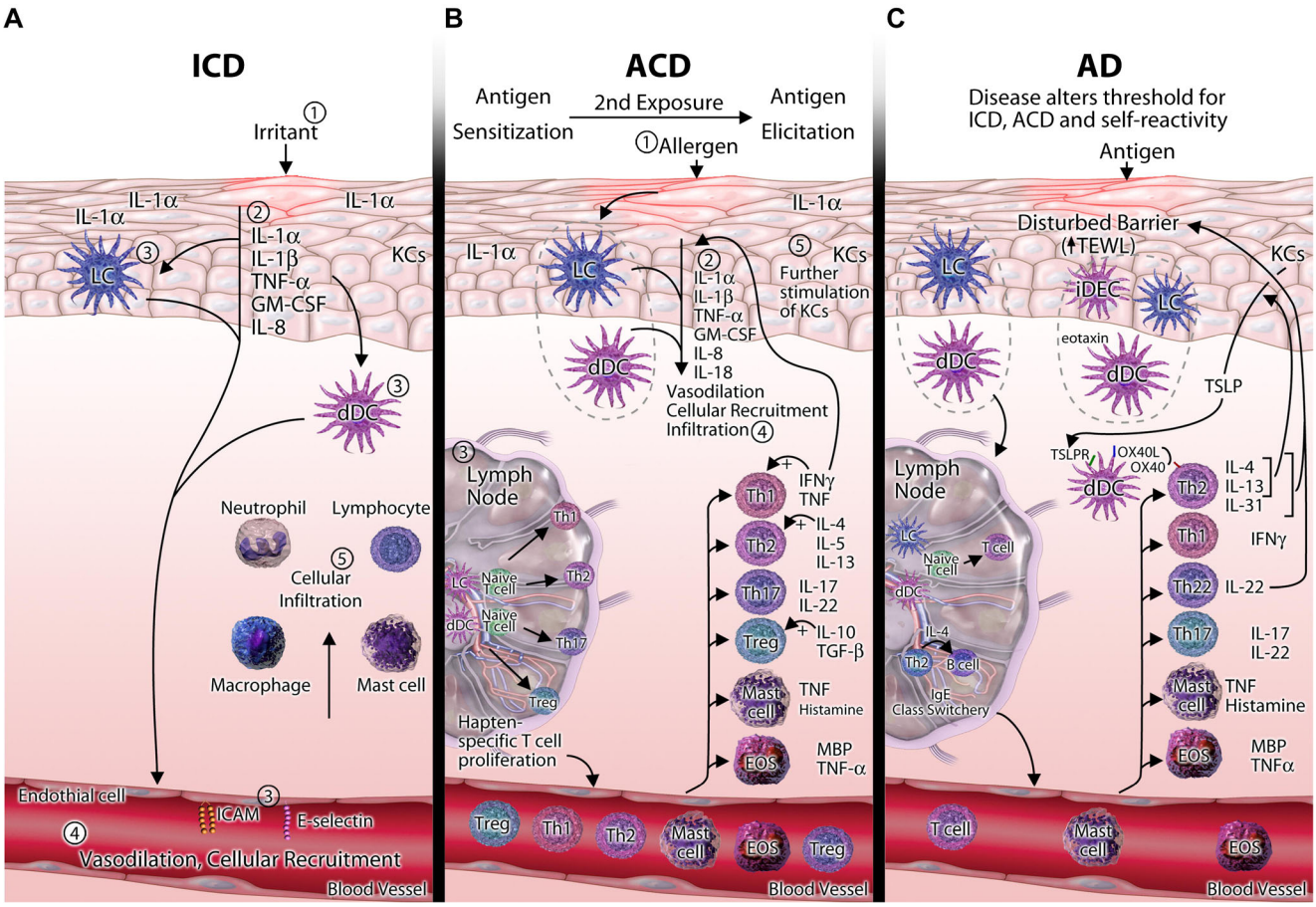

Fig. 1 Immune mechanism in the pathogenesis of ICD, ACD, and AD. **a** In patients with ICD, exposure to an irritant exerts toxic effects on keratinocytes, activating innate immunity with the release of IL-1α, IL-1β, TNF-α, GM-CSF, and IL-8 from epidermal keratinocytes. In turn, these cytokines activate LCs, dDCs, and endothelial cells, all of which contribute to cellular recruitment to the site of keratinocyte damage. Infiltrating cells include neutrophils, lymphocytes, macrophages, and mast cells, which further promote an inflammatory cascade. **b** In the sensitization phase of ACD, similar to ICD, allergens activate innate immunity through keratinocyte release of IL-1α, IL-1β, TNF-α, GM-CSF, IL-8, and IL-18, inducing vasodilation, cellular recruitment, and infiltration. LCs and dDCs encounter the allergen and migrate to the draining LNs, where they activate hapten-specific T cells, which include Th1, Th2, Th17, and regulatory T (Treg) cells. These T cells proliferate and enter the circulation and site of initial exposure, along with mast cells and eosinophils. On re-encountering the allergen, the elicitation phase occurs, in which the hapten-specific T cells, along with other inflammatory cells, enter the site of exposure and, through the release of cytokines and consequent stimulation of keratinocytes, induce an inflammatory cascade. **c** In patients with AD, a disturbed epidermal barrier leads to increased permeation of antigens, which encounter LCs, inflammatory dendritic epidermal cells (IDECs), and dDCs, activating Th2 T cells to produce IL-4 and IL-13. DCs then travel to LNs, where they activate effector T cells and induce IgE class switching. IL-4 and IL-13 stimulate keratinocytes to produce TSLP. TSLP activates OX40 ligand-expressing dDCs to induce inflammatory Th2 T cells. Cytokines and chemokines, such as IL-4, IL-5, IL-13, eotaxins, CCL17, CCL18, and CCL22, produced by Th2 T cells and DCs stimulate skin infiltration by DCs, mast cells, and eosinophils. Th2 and Th22 T cells predominate in patients with AD, but Th1 and Th17 T cells also contribute to its pathogenesis. The Th2 and Th22 cytokines (IL-4/IL-13 and IL-22, respectively) were shown to inhibit terminal differentiation and contribute to the barrier defect in patients with AD. Thus, both the barrier defects and immune activation alter the threshold for ICD, ACD, and self-reactivity in patients with AD. *EOS* eosinophil; *KCs* keratinocytes; *MBP* major basic protein. Reprinted from Gittler et al. (2013), with permission from Elsevier

Contact Hypersensitivity Reactions in the Setting of AD: How Having Contact Allergy in the Setting of AD Impacts Treatment

AD patients are more susceptible to both ICD and ACD [24, 35]. The mechanisms that predispose AD patients to contact hypersensitivity include extensive barrier abnormalities and unique immune abnormalities that are already evident in the uninvolved, or non-lesional, skin of AD patients [34, 36–38]. Together, these two mechanisms establish a lower threshold for AD patients to acquire ICD or ACD [7].

In healthy skin, there are several layers of epidermis that serve as a protective barrier to the intracellular space below. The stratum corneum is the outermost layer and is comprised of terminally differentiated corneocytes, lamellar lipids, and

Table 1 Selected studies investigating the pathogenesis of ICD

Title	Author	Year	Model	Reference
Atopic dermatitis results in intrinsic barrier and immune abnormalities: implications for contact dermatitis	Gittler et al.	2013	Human	[7]
Skin contact irritation conditions the development and severity of allergic contact dermatitis	Bonneville et al.	2007	Mouse	[10]
Impact of tumour necrosis factor-alpha polymorphisms on irritant contact dermatitis	Landeck et al.	2012	Human	[14]
Association of TNFA gene polymorphism at position -308 with susceptibility to irritant contact dermatitis	Allen et al.	2000	Human	[15]
Cytokine gene polymorphisms and susceptibility to chronic irritant contact dermatitis	de Jongh et al.	2008	Human	[16]

the cornified envelope, which is responsible for terminal differentiation of keratinocytes [39]. Genetically, the epidermal differentiation complex, located on chromosome 1q21, is responsible for generating this functional skin barrier [40, 41]. It has been shown that non-lesional AD skin is not only distinct from normal skin but is also characterized by abnormal epidermal differentiation, which results in inherent, vast barrier disruption even prior to the formation of visible lesions [34]. Additionally, Th2 and Th22 cytokines (IL-4, IL-13, IL-22, and IL-31), all of which are overexpressed in AD, inhibit terminal differentiation proteins (such as filaggrin, loricrin, and involucrin) essential to the skin barrier [42].

The meta-analysis derived atopic dermatitis (MADAD) transcriptome, as defined by differentially expressed genes (DEGs), established a comprehensive genomic disease phenotype for AD. It showed that the most dysregulated genes in AD are inflammatory markers (MMP12), T-helper activation markers, and epidermal proliferation markers [43]. Recently, Danso et al. (2017) demonstrated that the altered cytokine milieu in AD skin indeed affects the production of crucial ceramides and free fatty acids to result in increased transepidermal water loss (TEWL), which is a measure for skin barrier function [44]. The impaired barrier, characterized by TEWL, allows increased irritant and allergen penetration across the epidermis and creates an epidermal environment that is primed for immune reactivity [7, 45].

ACD in the setting of AD has been shown to involve distinct immunological mechanisms compared to patients with ACD alone. Newell et al. (2013) attempted to model the unique immune phenotype of AD patients using contact sensitization with 2,4-dinitrochlorobenzene (DNCB), an epicutaneous allergen that sensitizes most humans. They showed that the non-lesional skin of AD patients, even those without FLG mutations, reacted with Th2 skewing and

Table 2 Selected studies investigating the pathogenesis of ACD

Title	Author	Year	Model	Reference
Increased skin barrier disruption by sodium lauryl sulfate in mice expressing a constitutively active STAT6 in T cells	DaSilva et al.	2012	Mouse	[12]
Molecular profiling of contact dermatitis skin identifies allergen-dependent differences in immune response	Dhingra et al.	2014	Human	[17]
Dibutyl phthalate (DBP) induced thymic stromal lymphopoietin (TSLP) is required for Th2 contact hypersensitivity responses	Larson et al.	2010	Mouse	[21]
CD8+ T cells are effector cells of contact dermatitis to common skin allergens in mice	Vocanson et al.	2006	Mouse	[22]
Afferent and efferent phases of allergic contact dermatitis (ACD) can be induced after a singleskin contact with haptens: evidence using a mouse model of primary ACD	Saint-Mezard et al.	2003	Mouse	[23]
Cutaneous delayed-type hypersensitivity in patients with atopic dermatitis	Malajian et al.	2013	Human	[24]
Sensitization via healthy skin programs Th2 responses in individuals with atopic dermatitis	Newell et al.	2013	Mouse	[25]
Patients with atopic dermatitis have attenuated and distinct contact hypersensitivity responses to common allergens in skin	Correa da Rosa et al.	2015	Human	[26]
Patch testing of food allergens promotes Th17 and Th2 responses with increased IL-33: a pilot study	Ungar et al.	2016	Human	[27]
Skin exposure promotes a Th2-dependent sensitization to peanut allergens	Tordesillas et al.	2014	Mice	[28]
Dust mite induces multiple polar T cell axes in human skin	Malik et al.	2017	Human	[29]

generally impaired reactivity compared to the skin of healthy controls. This revealed that AD skin has a specific propensity to Th2 polarity, perhaps due to unique, altered skin immune signaling seen in this disease [25, 46]. Correa da Rosa et al. (2014) further investigated the baseline immune abnormalities in ACD in the context of AD, testing more clinically relevant contact sensitizers than DNCB (which is a chemical sensitizer not found in the human environment) [25, 26]. They showed that ACD responses are attenuated and differentially polarized in the skin of AD patients as compared to non-AD individuals [26]. Overall, there were decreases in Th1 products and some increases in Th2 and Th17 products in AD as compared to non-AD patients with ACD, and across all of the allergens, AD skin was hyporesponsive compared to controls.

This diminished immune response to contact allergens in uninvolved skin of AD patients could be caused by altered antigen presentation (caused by decreased LC and dDC function) and increased antigen permeability [46], leading to impaired T cell priming [26]. This phenomenon has several clinical implications: AD patients may have decreased response to vaccinations and may mount weaker defenses against infectious pathogens. It is suggested that treatment approaches should address strengthening the Th1 tone in AD individuals to make up for the lacking immune polarity [26].

Pathophysiology of Patch Testing with Food Allergens and Differences Between Individual Food Allergens

Just as ACD molecular profiles vary per allergen, so too do atopy food patch tests induce unique polarizations per food allergen on skin. Food allergy prevalence is rising, nearing 10% in industrialized nations [47]. Food allergy often causes immediate, IgE-mediated reaction, but can also involve a delayed T cell-mediated reaction. Ungar et al. (2017) investigated the immune mechanisms present in the delayed-type hypersensitivity food reaction via evaluation of skin biopsy, as elicited by positive atopy food patch tests in adult skin. They found that individual foods were characterized by different immune polarizations in skin. For example, beef/codfish caused Th17 and Th17/Th22 skewing, peanut showed Th17 increase and unique increases in IL-33, and barley/celery caused Th2 skewing [27]. Food patch test reactions, and especially peanut, induced high-level expression of IL-33 in the skin of food-allergic individuals compared to control skin, as well as compared to skin patch-tested with common contact allergens [27].

Knowing the unique cytokine profile of a given food allergen is important for creating food-specific targeted therapies, such as IL-33 antagonism. IL-33 has been implicated in the induction of sensitization to a variety of allergens, and Tordesillas et al. (2014) showed that IL-33 mediates an innate immune response to peanut extract application on healthy, intact skin [28]. IL-33 has also been reported to downregulate FLG expression and suppresses the epidermal barrier in normal skin and in AD [48]. A small phase I clinical trial on 12 AD patients with an anti-IL-33 antibody (ANB020) has been completed with encouraging results (ClinicalTrials.gov number, NCT02920021). This antibody could have applications in other atopic disorders such as peanut allergy and asthma [49].

Epicutaneous immunotherapy (EPIT) is another novel treatment approach that takes advantage of the cutaneous hypersensitivity responses of different foods. It is a needle-free, transdermal method of desensitizing patients that avoids the adverse effects prevalent in systemic treatments [27, 50, 51]. The biotechnology company DBV recently designed a proprietary epicutaneous delivery system for food allergy desensitization called Viaskin [52, 53], and it was tested on 74 participants with peanut allergy in a phase I multicenter, double-blind, randomized, placebo-controlled clinical trial. The study found that by week 52, treatment response was modest in approximately half of the treated patients, with the highest responses among children aged 4–11 years [54]. At present, management of severe allergy is limited to an avoidance diet and self-injectable epinephrine. EPIT shows promise as a novel immunomodulatory method to treat food allergy and related atopic conditions.

Dust Mite Hypersensitivity Reactions: Are Atopic Patch Tests Using Dust Mite a Good Model to Simulate Human AD?

Several groups have attempted to create a model for AD in humans. While several mouse models have been proposed for AD (NC/Nga, flaky tail, Flg-mutated, ovalbumin-challenged, oxazolone-challenged, and IL-23-injected mice) [55] and some models simulate certain AD characteristics, there is no single model that sufficiently reflects both the immune and barrier components of the human AD transcriptomic fingerprint [55–57].

The dust mite atopy patch test employs *D. pteronyssius/farinae* antigens to elicit a type IV delayed-type hypersensitivity reaction after application to human skin. This test sensitizes up to 40% of humans and up to 70% of patients with AD. In skin and blood studies, IL-4 and IFN-γ become elevated [58] and eosinophils, mast cells, and LCs infiltrate. Barrier disruption occurs, resulting in increased TEWL [59, 60].

Malik et al. (2017) conducted the first global skin profiling of house dust mite (HDM) reactions in humans with and without AD and addressed if the HDM reaction simulates AD or if it better simulates AD when performed in a setting of AD background skin [29]. Overall HDM responses showed Th2, Th9, and Th17/Th22 activation as compared to controls, with

similar responses seen in the setting of concurrent AD. While the HDM profile showed some similarities to AD lesions, it had greater resemblance to psoriasis and contact responses to nickel. This model may prove to be useful for AD as while AD classically shows Th2/Th22 skewing, it also has components of Th1 and Th17 inductions. Furthermore, AD is a heterogeneous disease and several AD subtypes, such as Asian, intrinsic, and early pediatric AD [61–63], show higher Th17 polarization alongside the Th2/Th22 skewing. Since the HDM molecular profile is able to induce various polar T-helper responses, this model provides potential experimental utility to simulate selected aspects of multiple inflammatory skin diseases, including ACD, AD, and psoriasis, that can be a valuable tool for early clinical trials [37].

Langerhans Cells Have Different Functions in Health Versus in Disease

Langerhans cells (LCs) are a subtype of the dendritic cell found in the epidermis [30]. LCs contribute to the induction of ACD, and AD LCs express FcεRI and the receptor for thymic stromal lymphopoietin (TSLP), an itch-inducing cytokine [64, 65]. LCs play distinct roles in healthy versus in diseased skin. In healthy skin, immature, resting epidermal LCs maintain a state of tolerance by expressing surface molecules that inhibit T cell activation and by releasing anti-inflammatory cytokines [66, 67]. Alternately, in a disease state, such as in active AD, LCs show increased FcεRI expression, release chemotactic factors, and prime naive T cells to amplify the allergic-inflammatory immune cascade [67].

EPIT, the transdermal desensitization method mentioned earlier, seeks to harness the unique physiology of LCs to induce tolerance in sensitized allergic patients. Upon epicutaneous application of the Viaskin patch, the allergen located in the patch is exposed to the patient's skin and is captured by LCs. The LCs present the allergen-protein complex to the draining LNs to activate regulatory T cells, which then downregulate Th2- and IgE-mediated allergic responses [68]. Thus, this innovative therapy takes advantage of the unique role played by LCs to mitigate the severe reactions seen in patients with contact and food allergy.

Conclusion

Since ACD shows different cytokine polarity based on the contact allergen inducing it, different therapeutic approaches may be needed. These will involve either specific cytokine blockade with anti-Th2 or Th17/IL-23 strategies or broader antagonists that will target more than one cytokine axis, such as JAK inhibitors, which seem to show promise in AD [69]. Novel mechanistic understanding in food allergy is also translating to the development of new treatments with anti-IL-33 antibodies and epicutaneous immunotherapy.

Compliance with Ethical Standards

Conflict of Interest EGY is an employee of Mount Sinai and has received research funds (grants paid to the institution) from AbbVie, Celgene, Eli Lilly, Janssen, Medimmune/AstraZeneca, Novartis, Pfizer, Regeneron, Vitae, Glenmark, Galderma, Asana, Innovaderm, Dermira, and UCB. EGY is also a consultant for Sanofi Aventis, Regeneron, Stiefel/GlaxoSmithKline, MedImmune, Celgene, Anacor, AnaptysBio, Dermira, Galderma, Glenmark, Novartis, Pfizer, Vitae, Leo Pharma, AbbVie, Eli Lilly, Kyowa, Mitsubishi Tanabe, Asana Biosciences, and Promius. AL declares no conflict of interest.

References

1. Saint-Mezard P, Rosieres A, Krasteva M, Berard F, Dubois B, Kaiserlian D, Nicolas JF (2004) Allergic contact dermatitis. Eur J Dermatol: EJD 14(5):284–295
2. Zack B, Arrandale VH, Holness DL (2017) Preventing occupational skin disease: a review of training programs. Dermat : Contact, Atopic, Occup, Drug 28(3):169–182
3. Thyssen JP, Johansen JD, Linneberg A, Menne T (2010) The epidemiology of hand eczema in the general population–prevalence and main findings. Contact Dermat 62(2):75–87
4. Eckert L, Gupta S, Amand C, Gadkari A, Mahajan P, Gelfand JM (2017) The burden of atopic dermatitis in US adults: health care resource utilization data from the 2013 National Health and Wellness Survey. J Am Acad Dermatol
5. Weidinger S, Novak N (2016) Atopic dermatitis. Lancet (London, England) 387(10023):1109–1122
6. Chew AL, Maibach HI (2003) Occupational issues of irritant contact dermatitis. Int Arch Occup Environ Health 76(5):339–346
7. Gittler JK, Krueger JG, Guttman-Yassky E (2013) Atopic dermatitis results in intrinsic barrier and immune abnormalities: implications for contact dermatitis. J Allergy Clin Immunol 131(2):300–313
8. Clark SC, Zirwas MJ (2009) Management of occupational dermatitis. Dermatol Clin 27(3):365–383 **vii-viii**
9. Nosbaum A, Vocanson M, Rozieres A, Hennino A, Nicolas JF (2009) Allergic and irritant contact dermatitis. Eur J Dermatol: EJD. 19(4):325–332
10. Bonneville M, Chavagnac C, Vocanson M, Rozieres A, Benetiere J, Pernet I, Denis A, Nicolas JF, Hennino A (2007) Skin contact irritation conditions the development and severity of allergic contact dermatitis. J Investig Dermatol 127(6):1430–1435
11. Vocanson M, Hennino A, Rozieres A, Poyet G, Nicolas JF (2009) Effector and regulatory mechanisms in allergic contact dermatitis. Allergy 64(12):1699–1714
12. DaSilva SC, Sahu RP, Konger RL, Perkins SM, Kaplan MH, Travers JB (2012) Increased skin barrier disruption by sodium lauryl sulfate in mice expressing a constitutively active STAT6 in T cells. Arch Dermatol Res 304(1):65–71
13. Koppes SA, Engebretsen KA, Agner T, Angelova-Fischer I, Berents T, Brandner J, Brans R, Clausen ML, Hummler E, Jakasa I, Jurakić-Tončic R, John SM, Khnykin D, Molin S, Holm JO, Suomela S, Thierse HJ, Kezic S, Martin SF, Thyssen JP (2017) Current knowledge on biomarkers for contact sensitization and allergic contact dermatitis. Contact Dermat 77(1):1–16

14. Landeck L, Visser M, Kezic S, John SM (2012) Impact of tumour necrosis factor-alpha polymorphisms on irritant contact dermatitis. Contact Dermat 66(4):221–227
15. Allen MH, Wakelin SH, Holloway D, Lisby S, Baadsgaard O, Barker JN et al (2000) Association of TNFA gene polymorphism at position -308 with susceptibility to irritant contact dermatitis. Immunogenetics 51(3):201–205
16. de Jongh CM, John SM, Bruynzeel DP, Calkoen F, van Dijk FJ, Khrenova L et al (2008) Cytokine gene polymorphisms and susceptibility to chronic irritant contact dermatitis. Contact Dermat 58(5):269–277
17. Dhingra N, Shemer A, Correa da Rosa J, Rozenblit M, Fuentes-Duculan J, Gittler JK, Finney R, Czarnowicki T, Zheng X, Xu H, Estrada YD, Cardinale I, Suárez-Fariñas M, Krueger JG, Guttman-Yassky E (2014) Molecular profiling of contact dermatitis skin identifies allergen-dependent differences in immune response. J Allergy Clin Immunol 134(2):362–372
18. Martin SF, Jakob T (2008) From innate to adaptive immune responses in contact hypersensitivity. Curr Opin Allergy Clin Immunol 8(4):289–293
19. Weltzien HU, Martin SF, Nicolas JF (2014) T cell responses to contact allergens. EXS 104:41–49
20. Weltzien HU, Moulon C, Martin S, Padovan E, Hartmann U, Kohler J (1996) T cell immune responses to haptens. Structural models for allergic and autoimmune reactions. Toxicology 107(2):141–151
21. Larson RP, Zimmerli SC, Comeau MR, Itano A, Omori M, Iseki M, Hauser C, Ziegler SF (2010) Dibutyl phthalate-induced thymic stromal lymphopoietin is required for Th2 contact hypersensitivity responses. J Immunol 184(6):2974–2984
22. Vocanson M, Hennino A, Cluzel-Tailhardat M, Saint-Mezard P, Benetiere J, Chavagnac C, Berard F, Kaiserlian D, Nicolas JF (2006) CD8+ T cells are effector cells of contact dermatitis to common skin allergens in mice. J Investig Dermatol. 126(4):815–820
23. Saint-Mezard P, Krasteva M, Chavagnac C, Bosset S, Akiba H, Kehren J, Nicolas JF, Berard F, Kanitakis J, Kaiserlian D (2003) Afferent and efferent phases of allergic contact dermatitis (ACD) can be induced after a single skin contact with haptens: evidence using a mouse model of primary ACD. J Investig Dermatol. 120(4): 641–647
24. Malajian D, Belsito DV (2013) Cutaneous delayed-type hypersensitivity in patients with atopic dermatitis. J Am Acad Dermatol 69(2):232–237
25. Newell L, Polak ME, Perera J, Owen C, Boyd P, Pickard C, Howarth PH, Healy E, Holloway JW, Friedmann PS, Ardern-Jones MR (2013) Sensitization via healthy skin programs Th2 responses in individuals with atopic dermatitis. J Investig Dermatol. 133(10):2372–2380
26. Correa da Rosa J, Malajian D, Shemer A, Rozenblit M, Dhingra N, Czarnowicki T, Khattri S, Ungar B, Finney R, Xu H, Zheng X, Estrada YD, Peng X, Suárez-Fariñas M, Krueger JG, Guttman-Yassky E (2015) Patients with atopic dermatitis have attenuated and distinct contact hypersensitivity responses to common allergens in skin. J Allergy Clin Immunol 135(3):712–720
27. Ungar B, Correa da Rosa J, Shemer A, Czarnowicki T, Estrada YD, Fuentes-Duculan J, Xu H, Zheng X, Peng X, Suárez-Fariñas M, Nowak-Wegrzyn A, Sampson HA, Krueger JG, Guttman-Yassky E (2017) Patch testing of food allergens promotes Th17 and Th2 responses with increased IL-33: a pilot study. Exp Dermatol 26(3):272–275
28. Tordesillas L, Goswami R, Benede S, Grishina G, Dunkin D, Jarvinen KM et al (2014) Skin exposure promotes a Th2-dependent sensitization to peanut allergens. J Clin Invest 124(11): 4965–4975
29. Malik K, Ungar B, Garcet S, Dutt R, Dickstein D, Zheng X, et al. 2017 Dust mite induces multiple polar T-cell axes in human skin. Clinical and experimental allergy: journal of the British Society for Allergy and Clin Immunol
30. Kaplan DH, Igyarto BZ, Gaspari AA (2012) Early immune events in the induction of allergic contact dermatitis. Nat Rev Immunol 12(2):114–124
31. Honda T, Egawa G, Grabbe S, Kabashima K (2013) Update of immune events in the murine contact hypersensitivity model: toward the understanding of allergic contact dermatitis. J Investig Dermatol. 133(2):303–315
32. Peiser M (2013) Role of Th17 cells in skin inflammation of allergic contact dermatitis. Clin Dev Immunol 2013:261037
33. Zug KA, Warshaw EM, Fowler JF, Jr., Maibach HI, Belsito DL, Pratt MD, et al. Patch-test results of the North American Contact Dermatitis Group 2005-2006. Dermat : Contact, Atopic, Occup, Drug. 2009;20(3):149–160
34. Suarez-Farinas M, Tintle SJ, Shemer A, Chiricozzi A, Nograles K, Cardinale I et al (2011) Nonlesional atopic dermatitis skin is characterized by broad terminal differentiation defects and variable immune abnormalities. J Allergy Clin Immunol 127(4):954–64.e1–4
35. Czarnowicki T, Krueger JG, Guttman-Yassky E (2014) Skin barrier and immune dysregulation in atopic dermatitis: an evolving story with important clinical implications. J Allergy Clin Immunol Pract 2(4):371–379 quiz 80-1
36. Brunner PM, Emerson RO, Tipton C, Garcet S, Khattri S, Coats I, Krueger JG, Guttman-Yassky E (2017) Nonlesional atopic dermatitis skin shares similar T-cell clones with lesional tissues. Allergy 72:2017–2025
37. Guttman-Yassky E, Krueger JG (2017) Atopic dermatitis and psoriasis: two different immune diseases or one spectrum? Curr Opin Immunol 48:68–73
38. Brunner PM, Silverberg JI, Guttman-Yassky E, Paller AS, Kabashima K, Amagai M, Luger TA, Deleuran M, Werfel T, Eyerich K, Stingl G, Bagot M, Hijnen DJ, Ardern-Jones M, Reynolds N, Spuls P, Taieb A (2017) Increasing comorbidities suggest that atopic dermatitis is a systemic disorder. J Investig Dermatol. 137(1):18–25
39. Candi E, Schmidt R, Melino G (2005) The cornified envelope: a model of cell death in the skin. Nat Rev Mol Cell Biol 6(4):328–340
40. Cabanillas B, Novak N (2016) Atopic dermatitis and filaggrin. Curr Opin Immunol 42:1–8
41. Bin L, Leung DY (2016) Genetic and epigenetic studies of atopic dermatitis. Allergy, Asthma, Clin Immunol : Off J Can Soc Allergy Clin Immunol 12:52
42. Howell MD, Kim BE, Gao P, Grant AV, Boguniewicz M, DeBenedetto A, Schneider L, Beck LA, Barnes KC, Leung DYM (2009) Cytokine modulation of atopic dermatitis filaggrin skin expression. J Allergy Clin Immunol 124(3 Suppl 2):R7–r12
43. Ewald DA, Malajian D, Krueger JG, Workman CT, Wang T, Tian S, Litman T, Guttman-Yassky E, Suárez-Fariñas M (2015) Meta-analysis derived atopic dermatitis (MADAD) transcriptome defines a robust AD signature highlighting the involvement of atherosclerosis and lipid metabolism pathways. BMC Med Genet 8:60
44. Danso M, Boiten W, van Drongelen V, Gmelig Meijling K, Gooris G, El Ghalbzouri A et al (2017) Altered expression of epidermal lipid bio-synthesis enzymes in atopic dermatitis skin is accompanied by changes in stratum corneum lipid composition. J Dermatol Sci 88(1):57–66
45. Dickel H, Bruckner TM, Schmidt A, Diepgen TL (2003) Impact of atopic skin diathesis on occupational skin disease incidence in a working population. J Investig Dermatol. 121(1):37–40
46. Dhingra N, Gulati N, Guttman-Yassky E (2013) Mechanisms of contact sensitization offer insights into the role of barrier defects vs. intrinsic immune abnormalities as drivers of atopic dermatitis. J Investig Dermatol. 133(10):2311–2314
47. Savage J, Johns CB (2015) Food allergy: epidemiology and natural history. Immunol Allergy Clin N Am 35(1):45–59

48. Seltmann J, Roesner LM, von Hesler FW, Wittmann M, Werfel T. IL-33 impacts on the skin barrier by downregulating the expression of filaggrin. The Journal of allergy and clinical immunology. 2015;135(6):1659–61.e4
49. AnaptysBio Initiates Multiple Ascending Dose Cohorts In ANB020 Phase 1 Clinical Trial. [press release]. July 6, 2016 2016
50. Jurakic Toncic R, Lipozencic J (2010) Role and significance of atopy patch test. Acta Dermatovenerol Croat : ADC 18(1):38–55
51. Reisacher WR, Davison W (2017) Immunotherapy for food allergy. Curr Opin Otolaryngol Head Neck Surg 25(3):235–241
52. Herve PL, Descamps D, Deloizy C, Dhelft V, Laubreton D, Bouguyon E et al (2016) Non-invasive epicutaneous vaccine against respiratory syncytial virus: preclinical proof of concept. J Control Release : Off J Control Release Soc 243:146–159
53. Mondoulet L, Dioszeghy V, Ligouis M, Dhelft V, Dupont C, Benhamou PH (2010) Epicutaneous immunotherapy on intact skin using a new delivery system in a murine model of allergy. Clin Exp Allergy : J Br Soc Allergy Clin Immunol 40(4):659–667
54. Jones SM, Sicherer SH, Burks AW, Leung DY, Lindblad RW, Dawson P et al (2017) Epicutaneous immunotherapy for the treatment of peanut allergy in children and young adults. J Allergy Clin Immunol 139(4):1242–52.e9
55. Ewald DA, Noda S, Oliva M, Litman T, Nakajima S, Li X, Xu H, Workman CT, Scheipers P, Svitacheva N, Labuda T, Krueger JG, Suárez-Fariñas M, Kabashima K, Guttman-Yassky E (2017) Major differences between human atopic dermatitis and murine models, as determined by using global transcriptomic profiling. J Allergy Clin Immunol 139(2):562–571
56. Swindell WR, Johnston A, Carbajal S, Han G, Wohn C, Lu J, Xing X, Nair RP, Voorhees JJ, Elder JT, Wang XJ, Sano S, Prens EP, DiGiovanni J, Pittelkow MR, Ward NL, Gudjonsson JE (2011) Genome-wide expression profiling of five mouse models identifies similarities and differences with human psoriasis. PLoS One 6(4): e18266
57. Bromley SK, Larson RP, Ziegler SF, Luster AD (2013) IL-23 induces atopic dermatitis-like inflammation instead of psoriasis-like inflammation in CCR2-deficient mice. PLoS One 8(3):e58196
58. Neumann C, Gutgesell C, Fliegert F, Bonifer R, Herrmann F (1996) Comparative analysis of the frequency of house dust mite specific and nonspecific Th1 and Th2 cells in skin lesions and peripheral blood of patients with atopic dermatitis. J Mol Med(Berlin, Germany) 74(7):401–406
59. Gfesser M, Rakoski J, Ring J (1996) The disturbance of epidermal barrier function in atopy patch test reactions in atopic eczema. Br J Dermatol 135(4):560–565
60. Tanaka A, Amagai Y, Oida K, Matsuda H (2012) Recent findings in mouse models for human atopic dermatitis. Exp Anim 61(2):77–84
61. Noda S, Suarez-Farinas M, Ungar B, Kim SJ, de Guzman Strong C, Xu H et al (2015) The Asian atopic dermatitis phenotype combines features of atopic dermatitis and psoriasis with increased TH17 polarization. J Allergy Clin Immunol 136(5):1254–1264
62. Suarez-Farinas M, Dhingra N, Gittler J, Shemer A, Cardinale I, de Guzman Strong C et al (2013) Intrinsic atopic dermatitis shows similar TH2 and higher TH17 immune activation compared with extrinsic atopic dermatitis. J Allergy Clin Immunol 132(2):361–370
63. Esaki H, Brunner PM, Renert-Yuval Y, Czarnowicki T, Huynh T, Tran G, Lyon S, Rodriguez G, Immaneni S, Johnson DB, Bauer B, Fuentes-Duculan J, Zheng X, Peng X, Estrada YD, Xu H, de Guzman Strong C, Suárez-Fariñas M, Krueger JG, Paller AS, Guttman-Yassky E (2016) Early-onset pediatric atopic dermatitis is TH2 but also TH17 polarized in skin. J Allergy Clin Immunol 138(6):1639–1651
64. Czarnowicki T, Krueger JG, Guttman-Yassky E (2017) Novel concepts of prevention and treatment of atopic dermatitis through barrier and immune manipulations with implications for the atopic march. J Allergy Clin Immunol 139(6):1723–1734
65. Nakajima S, Igyarto BZ, Honda T, Egawa G, Otsuka A, Hara-Chikuma M et al (2012) Langerhans cells are critical in epicutaneous sensitization with protein antigen via thymic stromal lymphopoietin receptor signaling. JAllergy Clin Immunol 129(0): 1048–55.e6
66. Steinbrink K, Mahnke K, Grabbe S, Enk AH, Jonuleit H (2009) Myeloid dendritic cell: from sentinel of immunity to key player of peripheral tolerance? Hum Immunol 70(5):289–293
67. Novak N, Gros E, Bieber T, Allam JP (2010) Human skin and oral mucosal dendritic cells as 'good guys' and 'bad guys' in allergic immune responses. Clin Exp Immunol 161(1):28–33
68. Our innovative EPIT® mechanism of action may have the potential to offer compelling clinical benefits to patients suffering from food allergies. 2014 [Available from: https://www.dbv-technologies.com/en/epit/moa]
69. Bissonnette R, Papp KA, Poulin Y, Gooderham M, Raman M, Mallbris L, Wang C, Purohit V, Mamolo C, Papacharalambous J, Ports WC (2016) Topical tofacitinib for atopic dermatitis: a phase IIa randomized trial. Br J Dermatol 175(5):902–911