Atopic dermatitis results in intrinsic barrier and immune abnormalities: Implications for contact dermatitis

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Atopic dermatitis (AD), as well as irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD), are common skin diseases. These diseases are characterized by skin inflammation mediated by activated innate immunity or acquired immune mechanisms. Although AD, ICD, and ACD can be encountered in pure forms by allergists and dermatologists, patients with AD often present with increased frequency of ICD and ACD. Although a disturbed barrier alone could potentiate immune reactivity in patients with AD through increased antigen penetration, additional immune mechanisms might explain the increased susceptibility of atopic patients to ICD and ACD. This review discusses cellular pathways associated with increased skin inflammation in all 3 conditions and presents mechanisms that might contribute to the increased rate of ICD and ACD in patients with AD. (J Allergy Clin Immunol 2013;131:300-13.)

Key words: *Atopic dermatitis, allergic contact dermatitis, contact hypersensitivity, irritant contact dermatitis, epidermal barrier, immune activation, T_H2, T_H17*

Abbreviations used

ACD:	Allergic contact dermatitis
AD:	Atopic dermatitis
CE:	Cornified envelope
DC:	Dendritic cell
dDC:	Dermal dendritic cell
DNCB:	2,4-dinitrochlorobenzene
FLG:	Filaggrin gene
ICAM-1:	Intercellular adhesion molecule 1
ICD:	Irritant contact dermatitis
LC:	Langerhans cell
LN:	Lymph node
SC:	Stratum corneum
SLS:	Sodium lauryl sulfate
TEWL:	Transepidermal water loss
TNCB:	Trinitrochlorobenzene
TSLP:	Thymic stromal lymphopoietin

Atopic dermatitis (AD) is a common, chronic inflammatory skin disease that causes significant impairment in quality of life. The worldwide prevalence of AD has increased 2- to 3-fold over the past 30 years and currently affects up to 18% of children and up to 5% of adults, depending on the population.[1-4] Both lesional and nonlesional AD skin are characterized by immune abnormalities and a disturbed epidermal barrier, resulting in increased transepidermal water loss (TEWL) and permeation of allergens, irritants, and microbes.[5,6] Clinically, the disease manifests as pruritic, dry, erythematous, and scaly lesions, with a proclivity toward IgE-mediated sensitization, infections, and hyperreactivity to environmental triggers.[7] Given the epidermal barrier disruption contributing to impaired protection against environmental irritants and allergens, irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD) are considered significant problems among patients with AD and can mimic its clinical presentation (Fig 1 and Table I).

ICD arises as a result of contact with highly irritating chemicals that induce activation of the innate immune system through hyperproduction of cytokines and chemokines and an infiltration of inflammatory cells.[8] It accounts for 80% of all cases of contact dermatitis. Susceptibility to irritants has been inconsistently correlated with age, although a few studies showed decreased responses to irritants in elderly patients compared with very young children (Table I).[9,10]

ACD is a delayed-type hypersensitivity response caused by skin contact with haptens that activate antigen-specific T cells in sensitized patients. It affects approximately 7% of the general population,[11] between 13.3% and 24.5% of pediatric patients,[12] and 33% to 64% of the elderly population (Table I).[13] This increased prevalence in the elderly might be due to the progressively deteriorating barrier function of the epidermis because there is a reduction in skin thickness, as well as a decrease in hydration and content of lipids and ceramides in the stratum corneum (SC).[10,14] Sensitization occurs as a result of prolonged contact with haptens in both occupational and nonoccupational environments. Nickel is one of the most common contact allergens, causing ACD in about 4% to 8% of male subjects and 18% to 30% of female subjects in the industrialized world.[15,16]

ICD, ACD, and AD potentially share common cellular mechanisms (Fig 2). This review contrasts known inflammatory mechanisms in ICD, ACD, and AD and discusses means by which the

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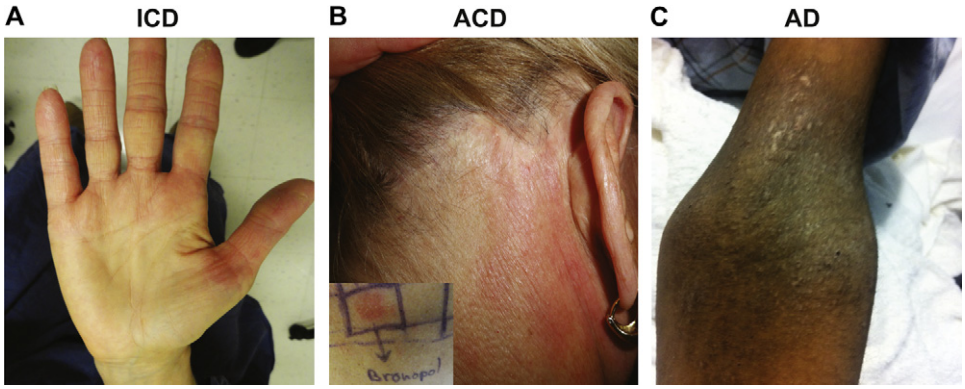

FIG 1. Characteristic lesions of ICD, ACD, and AD. **A,** ICD affecting the hands caused by frequent hand washing, demonstrating typically well-demarcated erythema. **B,** ACD in a patient with positive patch test results to Bronopol and Kathon CG, ingredients in the patient's hair dye and shampoo, respectively. ACD is characterized by erythematous patches that appear in the area of contact with allergen but can expand beyond the area of contact. **C,** AD in a patient with chronic disease, demonstrating the erythematous, scaly, and lichenified plaques in a typical location in the antecubital folds.

threshold for ICD and ACD might be lowered in patients with AD. These mechanisms include an increased frequency of ICD and ACD in the setting of disrupted background skin alone in contrast to a possible breach in tolerance triggered by ICD and ACD, which might increase skin reactivity and perpetuate chronic AD skin inflammation. This review also examines the possible mechanisms by which AD alters the threshold for ICD (irritants), ACD (allergens), and self-reactive antigens (Fig 2). We significantly expand the concept of increased antigen penetration and Langerhans cell (LC) activation in the setting of the barrier defect in patients with AD.[17] The increased irritant and allergic reactions occurring in patients with AD can be attributed to factors beyond the increased penetration of foreign agents because disruption of the epidermal barrier promotes activation of many immune mechanisms, accelerating and enhancing these responses.

THE EPIDERMAL BARRIER

The SC protects against allergens and irritants

The SC functions as the outermost layer of the epidermal barrier. The corneocytes of the SC act as bricks that form a hydrophilic wall that is surrounded by a lipophilic "mortar" made up of lipid lamellae, which fill the extracellular space.[5,18,19] These flat anucleate cells are filled with keratin fibers that arise from the differentiation of the outermost keratinocytes in the stratum granulosum. Also, as keratinocytes differentiate, their plasma membranes are replaced with the cornified envelope (CE), which is composed of structural proteins, including loricrin, involucrin, filaggrin, and small proline-rich proteins, cross-linked by transglutaminases. Meanwhile, lamellar bodies are formed in the SC and secrete lipids (ceramides and free fatty acids), providing further barrier protection to the intercellular space.[20] The CE functions to prevent passage of allergens, irritants, and microbes through the epidermis. The tight junctions that hold the corneocytes together provide additional protection against the passage of foreign agents.[20]

Barrier disruption in AD lesional skin

The epidermal differentiation process in patients with AD is disturbed, leading to deficiencies in the acid, lipid, and enzyme components of the CE.[21-23] Many of the barrier defects can be traced to primary genetic mutations in a cluster known as the epidermal differentiation complex, which is localized on chromosome 1q21.[5] The complex contains the gene filaggrin *(FLG)* that encodes profilaggrin, which is cleaved by serine proteases to the structural protein filaggrin. Filaggrin is an intercellular protein that aggregates keratin intermediate filaments within the corneocytes and draws water into the SC, promoting epidermal differentiation and hydration. Several loss-of-function mutations in *FLG* have been strongly associated with AD.[24] In addition, *FLG* deficiency has been correlated with disease severity because patients with double-allele or compound heterozygote mutations in *FLG* have been shown to have more severe, earlier onset, and longer-lasting AD.[25] Yet because *FLG* mutations have been reported in only 10% to 50% of patients with AD[5,24,26-28] and patients carrying the *FLG* mutation were reported to outgrow their disease,[29] other factors must also contribute to the barrier deficiency in patients with AD. We have shown broad cornification defects in multiple genes of the CE (eg, loricrin *[LOR]* and transglutaminase) in patients with AD that extend far beyond the *FLG* mutation.[30] Recent linkage studies have further identified mutations in several epidermal barrier genes, such as serine protease inhibitor Kazal-type 5 *(SPINK-5)*, *LOR*, involucrin *(IVL)*, and keratin 16 *(K16)*.[31] Also, we have shown that terminal differentiation proteins (ie, loricrin and periplakin) are inversely associated with the severity of AD measured by using the SCORAD index, as well as with cytokine activation.[23,32]

Some observations suggest that immune abnormalities also contribute to the barrier defects seen in patients with AD.[2,32-38] We have shown that NB-UVB treatment in patients with AD significantly suppresses the T_H2, T_H22, and T_H1 axes and reverses the epidermal hyperplasia and abnormal terminal differentiation.[32] Furthermore, the suppression of the T_H22 cytokine IL-22 with NB-UVB treatment inversely correlates with the change in expression of terminal differentiation proteins.[32] Lastly, the key cytokine players in patients with AD, specifically IL-22 and the T_H2 cytokines (IL-4, IL-13, and IL-31), inhibit terminal differentiation proteins (including filaggrin, loricrin, and involucrin), ceramides, and antimicrobial agents.[33-38]

TABLE I. Clinical, histologic, and immunologic differences in clinical features, histology, immune responses, circulating leukocytes, and treatment among AD, ICD, and ACD

AD	ICD	ACD
Clinical features		
Affects 8.7% to 18% of children and ≤5% of adults	Epidemiologic data inconclusive	Affects 13.3% to 24.5% of children and ≤7% of adults
Commonly presents in childhood (85%)	Epidemiologic data inconclusive	More commonly presents in adults
Associated with other atopic diseases (asthma and hay fever)	Increased in frequency in both children and adults with AD	Increased in frequency in both children and adults with AD
Acute: wet skin lesions	Acute: similar to a chemical burn/sunburn, with bright erythema, oozing, and possible blisters	Acute: oozing wet lesions
Chronic: dry, dull red, scaly, and lichenified lesions	Chronic: very similar to chronic AD/ACD	Chronic: dull red, scaly, and lichenified lesions
Not well demarcated from uninvolved skin	Well demarcated, usually confined to area of contact with irritant	Well demarcated but might spread past site of contact with allergen
Frequent impetiginization	Impetigo not characteristic	Impetigo not characteristic
Eczema herpeticum common	Eczema herpeticum not evident	Eczema herpeticum not evident
Prominent itch	Burning more prominent than itch	Prominent itch
High frequency of bacterial colonization	Low frequency of bacterial colonization	Low frequency of bacterial colonization
Histology		
Acute: spongiosis and vesicle formation	Acute: focal keratinocyte necrosis, dyskeratosis, spongiosis, vesicle formation, and edema	Acute: spongiosis, vesicle formation, and edema
Chronic: spongiosis less prominent, with hyperplasia and hyperkeratosis	Chronic: hyperplasia and hyperkeratosis	Chronic: less prominent spongiosis, with hy perplasia and hyperkeratosis
Orthokeratosis typical	Parakeratosis typical	Parakeratosis typical
Increased numbers of dermal eosinophils and mast cells	No eosinophils or mast cells	Increased numbers of eosinophils in the dermis and sometimes also the epidermis, controversial role of mast cells in ACD
Absent neutrophils in epidermis	Neutrophils found in epidermis	Absent neutrophils in epidermis
Hypogranulosis, sometimes absent granular layer	Normal granular layer	Normal granular layer
Vasodilation evident	Vasodilation evident	Vasodilation evident
Immune responses/infiltrates		
Innate and adaptive immunity	Innate immunity	Innate and adaptive immunity
T_H2- and T_H22-polarized disease with a component of T_H1 in chronic disease; acute disease might have a T_H17 component that is absent in chronic stage	IL-1α, IL-1β, IL-6, IL-8, TNF-α, and GM-CSF secreted by keratinocytes and amplify inflammatory response	T_H1, T_H17, and recently also T_H2 polarization evidenced
Attenuated T_H17 pathway	Unknown	T_H17 pathway prominent
Decreased antimicrobial axis	Antimicrobial axis intact	Antimicrobial axis intact
Increased numbers of LCs and several subsets of DCs, including inflammatory dendritic epidermal cells	Increased numbers of LCs	Increased numbers of LCs and dDCs
Inflammatory DCs in dermis produce T_H2 chemokines (CCL17, CCL18, CCL22)	Keratinocytes produce innate immune cytokines (IL-1α, IL-1β, IL-6, IL-8, TNF-α)	Activated T cells induce cytokines (IFN-γ, IL-17), which promote release of CXCL9 and CXCL10 from keratinocytes and dDCs
Leukocytes in circulation		
T_H2 populations increased	Unknown	Antigen-specific T cells (produce IL-17 and IFN-γ)
Increased IgE levels and eosinophil numbers in circulation in 80% of patients (extrinsic AD)	Normal IgE levels and eosinophil numbers	Normal IgE levels and eosinophil numbers
IgE autoantibodies correlated with disease activity	Lack of autoantibodies	Lack of autoantibodies
Treatment		
Reduced contact with irritants helpful but will not cure disease	Identification and elimination of irritant is curative	Identification and elimination of antigen is curative
Emollients, topical and systemic steroids, topical (tacrolimus and pimecrolimus) and systemic (eg, cyclosporine, mycophenolate mofetil) immune modulators, and UV therapy	Emollients, topical and systemic steroids, and topical immune modulators (tacrolimus and pimecrolimus)	Emollients, topical and systemic steroids, topical (tacrolimus and pimecrolimus) and systemic (eg, cyclosporine, mycophenolate mofetil) immune modulators, and UV therapy
Experimental therapies (biologic agents targeting specific T-cell pathways) currently lacking	NA	Experimental therapies (biologic agents targeting specific T-cell pathways) currently lacking

NA, Not applicable.

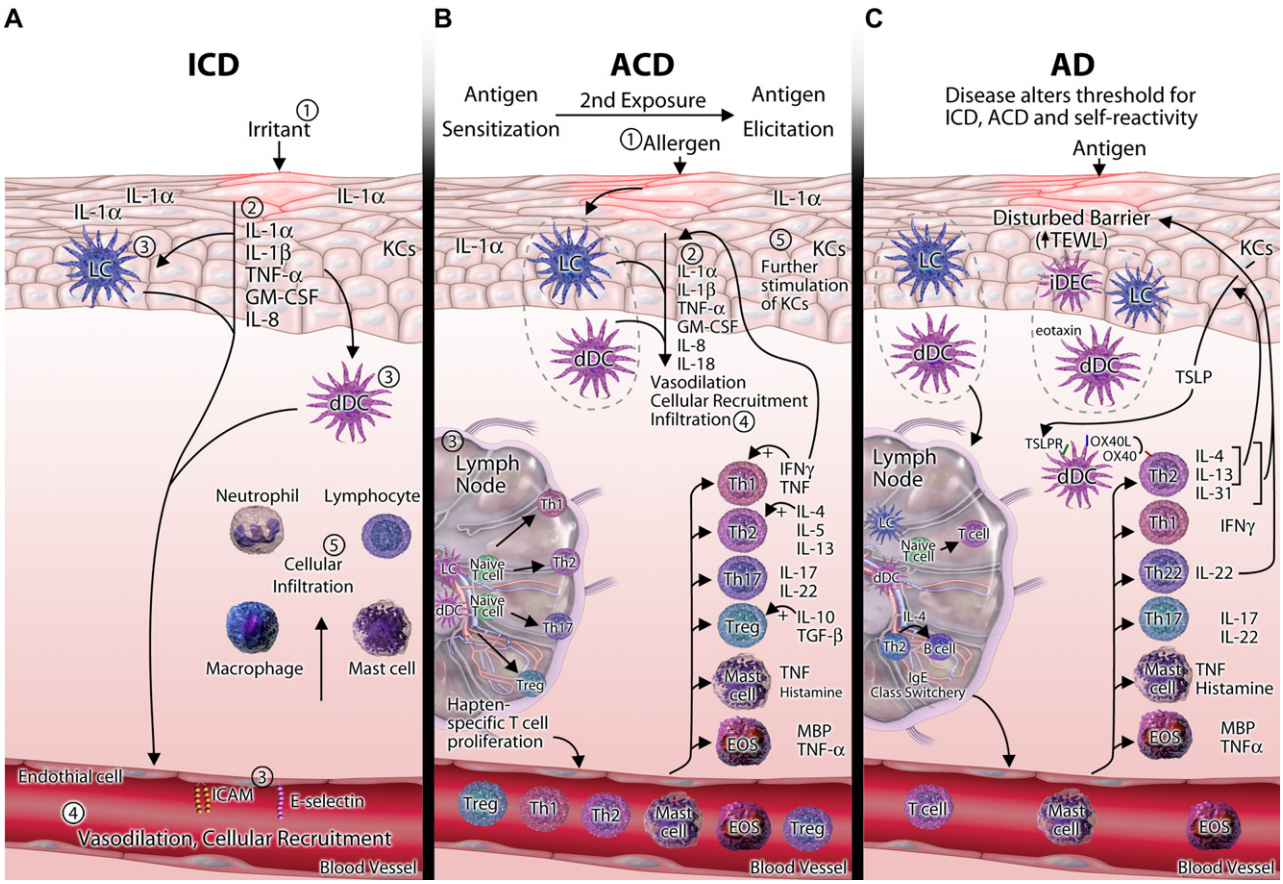

FIG 2. Immune mechanism in the pathogenesis of ICD, ACD, and AD. **A,** In patients with ICD, exposure to an irritant exerts toxic effects on keratinocytes, activating innate immunity with release of IL-1α, IL-1β, TNF-α, GM-CSF, and IL-8 from epidermal keratinocytes. In turn, these cytokines activate 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 T_H1, T_H2, T_H17 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 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 T_H2 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 T_H2 T cells. Cytokines and chemokines, such as IL-4, IL-5, IL-13, eotaxins, CCL17, CCL18, and CCL22, produced by T_H2 T cells and DCs stimulate skin infiltration by DCs, mast cells, and eosinophils. T_H2 and T_H22 T cells predominate in patients with AD, but T_H1 and T_H17 T cells also contribute to its pathogenesis. The T_H2 and T_H22 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.

Abnormal barrier also characterizes nonlesional AD skin

Clinically unaffected skin in patients with AD is also characterized by barrier defects and displays dryness and enhanced response to irritants.[2] Nonlesional AD skin also demonstrates impaired synthesis and reduced concentration of lipids. There is an inverse correlation between the reduction in ceramide levels with TEWL and the associated reduced threshold to irritants.[39,40] Through genomic and histologic profiling, we found a profound decrease in the expression of many terminal differentiation proteins (eg, involucrin, loricrin, corneodesmosin, filaggrin, late CE proteins, and small proline-rich protein 4) in nonlesional skin similar to that seen in lesional skin, suggesting a "background skin phenotype" of a defective barrier.[23] Reduced expression of other molecules, such as caspase 14, which takes part in the processing of filaggrin and the development of natural moisturizing factors, and claudin-1, a transmembrane protein that comprises tight junctions and contributes to the prevention of

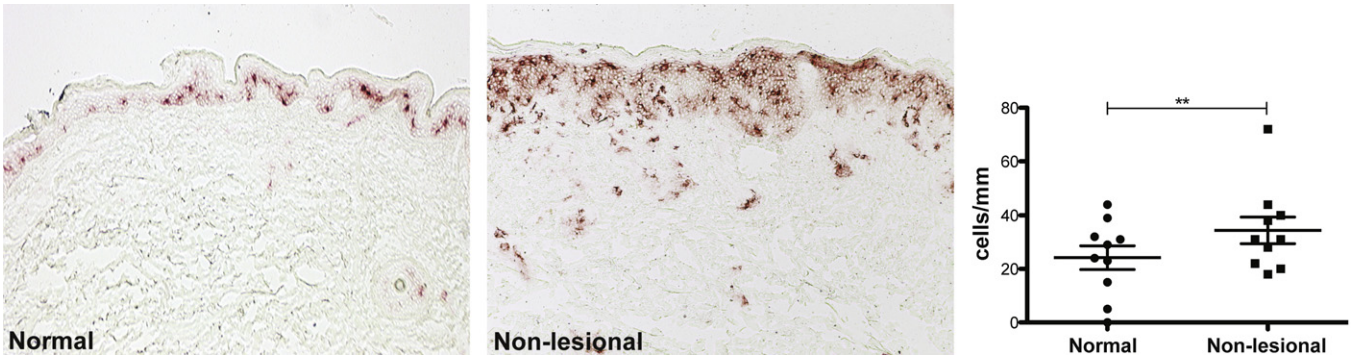

FIG 3. Representative staining of $CD1a^+$ LCs in nonlesional AD and healthy skin. There are significantly more LCs in nonlesional AD skin compared with healthy skin, as quantified by cell counts. $^{**}P < .01$.

permeation of molecules through the SC, has also been established in both lesional and nonlesional AD skin.[41,42] Similarly, a decrease in capacitance and increase in TEWL were reported in nonlesional skin,[6] which have been shown to correlate with the clinical severity of AD.[43] Thus barrier abnormalities are universal to AD skin, regardless of disease involvement. Nonlesional AD skin also demonstrates immune abnormalities,[23] which include significant increases in numbers of cellular infiltrates, including LCs, myeloid dendritic cells (DCs), and T cells, in comparison with that seen in normal skin ($P < .01$, Figs 3 and 4).[23] The predominant T_H2 infiltrate in nonlesional skin induces IL-4 and IL-13,[44] which, similarly to lesional skin, downregulate ceramides and the expression of epidermal differentiation complex genes.[34,36] Moreover, the immune abnormalities of nonlesional AD skin were also found to correlate with disease severity.[5,23]

IRRITANTS, ALLERGENS, AND THE DISTURBED BARRIER

Mechanism of ICD

Frequently, ICD is experimentally modeled by means of application of sodium lauryl sulfate (SLS) to the epidermis because SLS exerts direct toxic effects on keratinocytes, disrupting the epidermal barrier and lamellar body lipid extrusion.[45-47] Disruption of the barrier then leads to a release of innate immune mediators, such as IL-1α, IL-1β, Il-6, IL-8, and TNF-α,[48] which further induce a cytokine cascade and inflammatory reaction.[8,49] Application of SLS to the epidermis has also been demonstrated to induce LC mobilization and consequent migration to the draining lymph nodes (LNs).[50] Other irritants are recognized as "danger signals" by the innate immune system through a set of membranous and intercellular receptors called Toll-like and Nod-like receptors that activate the inflammasome and nuclear factor κB pathways, inducing release of many cytokines and chemokines.[8] Imiquimod, a well-known topical immune response modifier, can cause irritation through direct activation of the innate immune system through activation of Toll-like receptor 7.[51]

Irritant reactions might predispose to allergic reactions

Patients with ICD are more susceptible to the development of contact sensitization to allergens.[48,52,53] This finding was based on results from animal models in which the rate of skin sensitization to paraphenylenediamine allergen increased from 38% to 78% when preceded by skin irritation with 5% SLS.[54] Furthermore, pretreatment with SLS enhanced T-cell proliferative responses to 2,4-dinitrochlorobenzene (DNCB), which functions as both an irritant and an allergen.[55] In another study the intensity of the ACD response was correlated with the concentration of DNCB, which had originally induced an irritant response when it was used for sensitization.[53] Hence the DNCB-primed ICD reaction conditioned the development and severity of the ACD response.[53]

Similar results were obtained in human studies. In one report an allergen induced a contact reaction only when combined with a clinically subirritant level of SLS.[56] In addition, when patch test sites were pretreated with SLS, the threshold elicitation concentrations of contact allergens, such as cobalt and nickel, were significantly decreased.[57,58] Associations have also been observed between skin irritancy and allergic patch test reactions to nickel and colophony.[48,59,60] Thus activation of innate immunity by irritants likely reduces the threshold for the development of ACD.[57,58]

Innate immune activation stimulated by irritant reactions is necessary for allergic immune reactions.[48] ACD initially requires activation of the innate immune system, which involves recruitment of DC precursors to the skin, maturation and migration of skin DCs to draining LNs, and DC-triggered activation of specific T-cell effectors, which proliferate and migrate to the site of exposure.[8] In addition to allergenic effects, many haptens also have irritant effects because they induce cytokine release from keratinocytes and activate the innate immune system.[61] Therefore when contact with an allergen is preceded by an irritant, the allergen is introduced into an already activated innate immune system, requiring a lower threshold and resulting in a stronger ACD response.[53,57,58]

A DISTURBED BARRIER PROMOTES IMMUNE ACTIVATION: EXPERIMENTAL EVIDENCE

Increased cytokine, chemokine, and immune factor levels

In addition to lowering the threshold for development of ACD,[57,58] the immune alterations induced by barrier disruption are also likely to promote ICD and ACD reactions. For example, in aging skin, which, like AD, represents a model of a disrupted barrier,[10,14] the barrier defect produces an increased cytokine

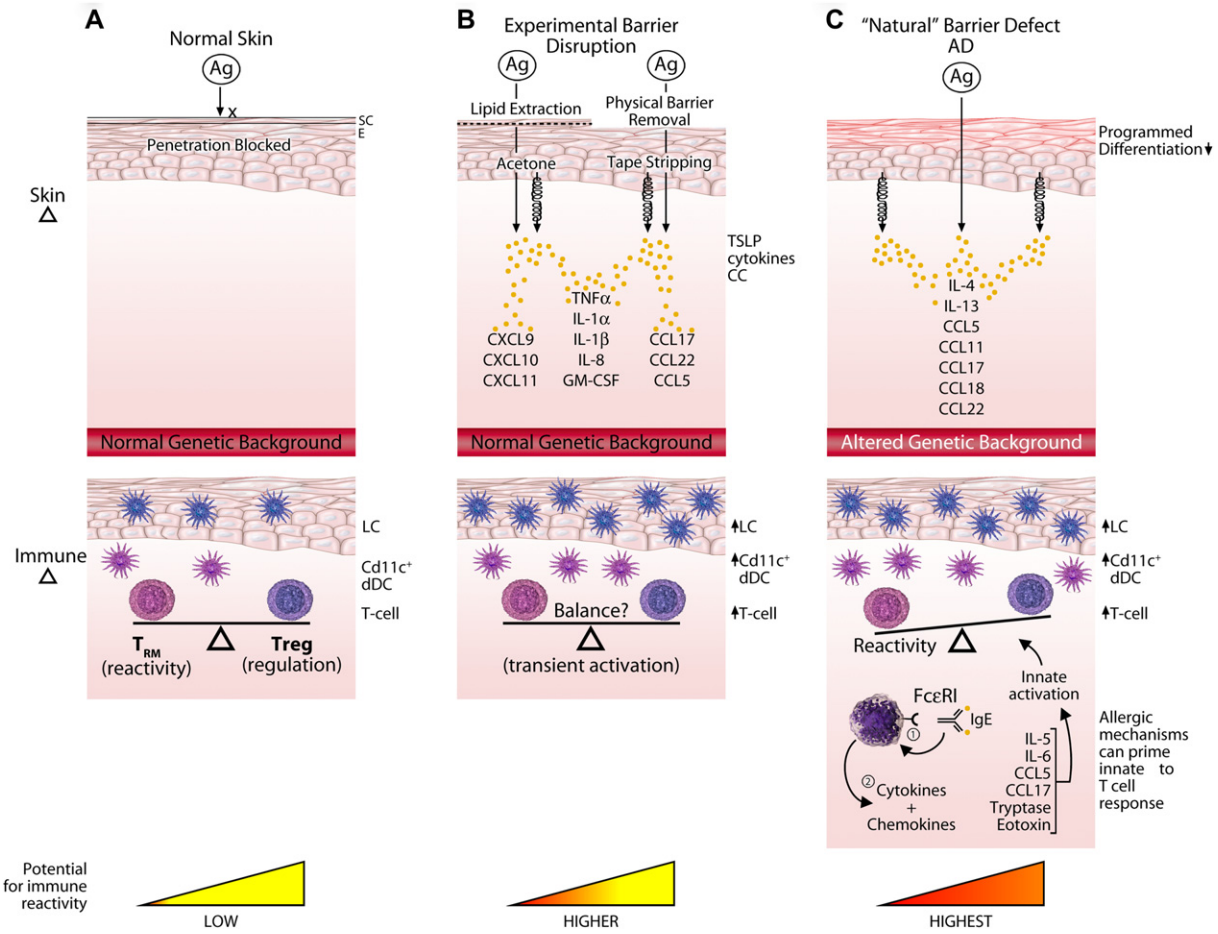

FIG 4. Factors contributing to immune reactivity in healthy skin, experimental barrier disruption, and AD skin. **A,** In healthy skin the intact SC prevents antigen penetration. Individual genetic backgrounds can alter antigen penetration, immune reactivity, or both. LCs and dDCs are not activated, and there is a steady state between effector T cells and regulatory T *(Treg)* cells. **B,** In experimental barrier disruption, by means of acetone rubbing or tape stripping, which cause lipid extraction or physical barrier removal, respectively, there is increased antigen penetration and an upregulated immune environment. Acetone rubbing induces release of T_H1 chemokines, including CXCL9 to CXCL11, and tape stripping promotes release of T_H2 chemokines, including CCL17, CCL22, and CCL5. Both methods have been shown to stimulate production of innate immune factors, such as TNF-α, IL-1α, IL-1β, IL-8, and GM-CSF. Additionally, a disrupted barrier has been associated with increased LC and dDC numbers and transient activation of T cells. **C,** AD has a "natural" barrier defect, which promotes antigen penetration. Increased LC and dDC numbers, as well as increased T-cell numbers, are found in nonlesional AD skin. Similarly, nonlesional AD skin also shows an increase in levels of cytokine and chemokines, such as IL-4, IL-13, CCL5, CCL11, CCL17, CCL18, and CCL22, and TSLP. T-cell responses in patients with AD are primed through IgE/FcεRI interactions, which cause release of inflammatory mediators (ie, IL-5, IL-6, CCL5, CCL17, tryptase, and eotaxin) from mast cells, basophils, LCs, and inflammatory dendritic epidermal cells, further activating innate and adaptive responses. In addition to increased immune activation resulting from barrier deficiency, 2 other mechanisms might increase allergic inflammation in patients with AD, including (1) a differential immune regulation in patients with AD that potentially decreases the thresholds for ICD and ACD and (2) a break in tolerance, resulting in increased reactivity.

response, as well as an increase in epidermal LC density. Thus a disturbed barrier not only alters permeation of contact allergens but might also prime immune responses.[62-64]

Many experimental studies have reported innate immune alterations attributed to epidermal barrier defects.[65-69] Two mechanisms commonly used to acutely disturb the epidermal barrier are stripping with scotch tape, which mechanically removes the SC, and rubbing with acetone, which chemically extracts lipids from the SC (Fig 4).[65-71] Through experiments using these procedures in mice, it has been shown that disruption of the barrier induces innate immune cytokines in keratinocytes, including TNF-α, IL-1α, IL-1β, and GM-CSF, and enhances expression of costimulatory molecules, such as MHC class II, CD86, and CD54, on LCs.[65,67,69] In essential fatty acid–deficient mice, a model for chronic barrier disruption, normalization of the barrier by means of latex occlusion decreased cytokine production.[68] In additional murine studies, acetone rubbing induced the production of T_H1-related chemokines, such as CXCL9, CXCL10, and CXCL11, whereas tape stripping induced the production of T_H2-mediated chemokines, such as CCL17 and CCL22, and eosinophil chemoattractants, such as CCL5, with consequent dermal infiltration of eosinophils.[66] The reduction of lipids in the

SC, in analogy to acetone rubbing, induces keratinocytes to produce T_H1 chemokines, whereas disruption of the SC with tape stripping promotes LCs to produce T_H2 chemokines (Fig 4).[66,72] Although the barrier defects in patients with AD involve reduction of lipids, the most striking abnormalities involve a major downregulation of terminal differentiation proteins.[5,23,24] Thus tape-stripping studies might be a better model for the barrier disruption in patients with AD (Fig 4). Indeed, tape stripping of healthy human skin induced IL-10 expression, which contributes to T_H1 cytokine suppression and the resultant T_H2 dominance, whereas expression of IL-10 was not observed in intact skin.[70] Other human tape-stripping studies demonstrated keratinocyte proliferation and activation leading to keratinocyte expression of intercellular adhesion molecule 1 (ICAM-1), E-selectin, and vascular cell adhesion molecule 1. The increase in adhesion molecules contributed to inflammatory infiltrates and increased epidermal mRNA gene expression of TNFA, IFNG, TGFB, TGFA, IL8, and IL10. These changes did not occur in an intact barrier in which there was undetectable epidermal expression of ICAM-1, E-selectin, and vascular cell adhesion molecule 1, as well as no epidermal and dermal TNFA, IFNG, TGFB, IL8, and IL10 mRNA expression.[65]

Increased activity of LCs and dermal DCs

LCs are specialized DCs that represent the bridge between innate and adaptive immunity. LCs form a contiguous network in the epidermis, in which they detect haptens that penetrate the epidermis, travel to local LNs, and activate hapten-specific T cells. In murine tape-stripped skin, subpopulations of LCs expressed high levels of MHC class II antigens, CD54, CD86, CD40, CD54, CD11c, and ICAM-1 markers, representing their activation and maturation, whereas in healthy skin the expression of these molecules was undetectable.[67,73] In addition, TNFA, IL1B, IL4, and GMCSF expression of which is upregulated in barrier-disrupted skin,[65,69,74,75] promote maturation of LCs into immunostimulatory DCs[67] and enhance their uptake of antigens.[69,76-78] Removal of the SC was shown to transform LC morphology to that of mature LCs.[67,79] LCs isolated from barrier-disrupted skin were shown to induce a significant increase in syngeneic and allogeneic T-cell proliferation compared with those from saline-treated skin.[73] Therefore in barrier-disrupted skin LCs become phenotypically and functionally mature and likely have more antigen-presenting capacity (Fig 4).[75,80] Results of other studies have suggested that disruption of the barrier induces migration of LCs away from the epidermis to the LNs,[81-83] although migration of LCs was shown by some to occur only with application of the antigen to a disturbed barrier.[67]

Similar results, demonstrating activation of LCs, have been reported in human studies, because tape stripping of human skin induced the epidermal expression of CCL20/macrophage inflammatory protein 3 chemokine, which is the most selective LC precursor–attracting chemokine.[84,85] Experiments with human skin treated with acetone, SDS, or tape stripping showed an increase in LC density in the epidermis compared with that seen in healthy skin (Fig 4), which correlated linearly with the degree of barrier disruption.[64] When barrier function was artificially restored by means of latex occlusion, the increase in LC density was significantly reduced, strengthening the association between LC density and integrity of the epidermal barrier.[64] Barrier disruption also altered the localization of LCs from the suprabasal to the basal layer, whereas LCs remain mainly in the suprabasal layers in untreated skin.[64] With latex occlusion, LCs were again absent from the basal layer.[64]

Although LCs have been historically considered the prominent cell population responsible for initiation of responses to cutaneous allergens, recent studies have highlighted the important role of dermal dendritic cells (dDCs) in initiating hapten-induced T-cell responses (Fig 4).[86-92] Both Langerin-positive and Langerin-negative dDCs were shown to play a role in inducing ACD reactions.[86-90,93] Murine studies that involved ablation of Langerin-positive populations showed that on hapten application, Langerin-positive dDCs, which, unlike LCs, repopulated the dermis rapidly after ablation, mediated sensitization in the absence of epidermal LCs.[87,89,90,92] Because the ACD response was not completely diminished when the Langerin-positive dDCs were fully ablated, a role for other DCs, including Langerin-negative dDCs, was suggested.[87,88,92] In addition, when LCs and dDCs were isolated from the LNs of these mice, only dDCs were able to present antigen to T cells and induce proliferation.[88] Thus haptens are potentially acquired by both LCs and dDCs, which then migrate to LNs, where they present the antigen to T cells and induce T-cell proliferation.[94]

Antigen application on a disturbed barrier induces further immune activation

Because barrier disruption alone permits increased permeation of foreign agents and induces activation of innate immunity and LC responses, the response to application of haptens onto a disturbed epidermal barrier has been characterized.[63,67-69,71,75,95-100] In mice fluorescein isothiocyanate–labeled protein applied to a disrupted epidermal barrier was rapidly picked up by LCs. Within 2 hours, the majority of LCs migrated to the draining LNs, whereas few LCs migrated when the protein was applied to intact skin or when saline was applied to disrupted skin.[67] In human subjects allergen application onto a disrupted barrier was shown to further increase TEWL and LC density within the epidermis itself beyond that induced by disruption of the barrier alone.[63] The increase in LC density was accompanied by strong allergic test reactions.[63] This increase in epidermal LC numbers might be due to inflammatory mediators released from keratinocytes in the setting of a disturbed barrier.

In the setting of a disrupted barrier, increased LC responsiveness in conjunction with an enhanced cytokine milieu likely contributes to amplified T-cell responses (Fig 4). In fatty acid–deficient mice there was enhanced T-cell activation by epidermal cells, which was attributed to increased class II MHC antigen expression on keratinocytes in the skin. This possibly provides keratinocytes, in addition to LCs, with antigen-presenting capabilities. In healthy skin class II MHC antigen is expressed exclusively on LCs.[100] In *ft/ft* mice, which harbor a spontaneous *FLG* mutation, cutaneous allergen application induced an infiltrate of lymphocytes, eosinophils, and mononuclear cells; an antigen-specific antibody response; and a cytokine response representing T_H2 (IL-4, IL-5, IL-13, and IL-10), T_H1 (IFN-γ), and T_H17 (IL-17) immune axes.[95,98,99] These immune cell infiltrates were not observed in mice with an intact epidermal barrier. Likewise, along with increased activity of IL-1α and upregulation of costimulatory molecules necessary for T-cell activation on LCs (MHC class II, CD54, and CD86), hapten application and pretreatment with acetone rubbing induced enhanced proliferation

of hapten-specific T cells in sensitized mice. Indeed, tape stripping and acetone rubbing augmented contact sensitization reactions in murine epidermis.[75]

Although LCs and dDCs mediate contact hypersensitivity reactions, they have also been implicated as counterregulators in contact hypersensitivity responses.[86,89,90,94,101] However, their precise roles in promoting tolerogenicity of the skin are not yet elucidated, and the vast majority of these studies originated in mice.[102] Both the immunogenic and tolerogenic functions of these cells require antigen transport to the LN, but the differential outcome potentially depends on the doses and time intervals of hapten application, the maturation grade of LCs, the status of the epidermal barrier (intact vs disrupted), and the cytokine microenvironment.[102,103] Intact skin was shown to promote tolerance in sensitized mice.[104,105] Repeated applications of an allergen on intact skin of sensitized mice induced a downmodulation of allergen-specific local and systemic responses, possibly through the induction of regulatory T cells ($CD25^+$, forkhead box protein 3–positive, $CD4^+$ T cells).[106]

Activation of T_H2 responses on antigen application

Several studies showed that hapten or antigen application on tape-stripped murine skin induced predominant T_H2 responses characterized by increased expression of IL-4 and IL-13, increased levels of serum IgE and IgG_1, and reduced expression of T_H1-related cytokines (IFN-γ) and serum antibodies (IgG_{2a}).[66,96,97] Increased levels of thymic stromal lymphopoietin (TSLP) receptor, which plays an integral role in T_H2 polarization, were also detected in barrier-disrupted skin.[97] Recently, because the TSLP receptor is found on LCs, the role of LCs through TSLP signaling was studied in LC-depleted mice subjected to epicutaneous sensitization of tape-stripped skin.[107] LC ablation caused a weakened allergic response and a decreased production of specific IgEs, T-cell proliferation, and IL-4 mRNA expression in the draining LNs. Even in steady state, LC depletion caused decreased serum IgE levels. Thus LCs are critical in T_H2 induction on epicutaneous sensitization.[107] Additionally, the TSLP receptor on LCs was found to be dispensable for antigen-specific T-cell proliferation but vital for T_H2 induction.[107]

Other murine studies have shown that application of antigen to tape-stripped skin amplified subsequent T_H2 responses to the antigen through induction by LCs and prevented the development of T_H1 responses induced through subcutaneous injection of antigen with an adjuvant. Furthermore, antigen application and the associated T_H2 response converted an established T_H1 response to a T_H2 response.[67,71] This disparity between T_H2 and T_H1 responses might be explained by access of LCs to antigens applied epicutaneously and access of dDCs to antigens injected subcutaneously into the dermis.[67] This is because LCs promote T_H2 induction on epicutaneous sensitization, whereas dDCs have been suggested to promote T_H1 responses.[107] Correspondingly, T cells cultured with LCs produce IL-4 and induce IgE production by B cells, which is consistent with a T_H2-biased response.[108] Furthermore, predominant activation of T_H2-related molecules in tape-stripped skin correlated with enhanced delayed-type hypersensitivities[66] and contrasted with the combined T_H1 and T_H2 responses induced by antigen application to intact skin.[96] In addition, demonstrating the direct association between barrier disruption and T_H2 responses, expression of IL-4, but not IFN-γ, varied according to the severity of the barrier disruption.[96] This antigen-specific T_H2 response to epicutaneous exposure has also been detected systemically in mice after subsequent oral and inhalational antigen exposure.[109,110]

Of note, experimental studies in mice have also implicated T_H17 activation after application of antigen to tape-stripped murine epidermis.[98,111] However, the resultant immune responses lacked specificity because there was a concomitant activation of the T_H2 and T_H1 axes. T_H2- and T_H17-associated cytokines in a disrupted epidermis were recently postulated to have autocrine effects that create a feedback loop, further exacerbating the barrier disturbance.[17] These effects, which are mainly attributed to T_H2 cytokines,[34,36] are mediated by proteinase-activated receptor 2 activation or keratinocyte immune receptors activated by "epithelial-derived danger signals."[17]

Collectively, these studies demonstrate T_H2-dominant responses in barrier-disrupted skin. Upon antigen application to a disturbed barrier with intrinsic innate and T_H2 immune activation, further amplification of T_H2 responses is induced through antigen uptake and subsequent migration of LCs to local LNs. It is important to note that in mice immune responses to antigen application on a disturbed barrier varied according to the particular strain of mouse.[66] For example, BALB/c mice were more susceptible to tape stripping, producing more T_H2-specific chemokines and eosinophil chemoattractants than C57BL/6 mice.[66] This suggests that the genetic background might predispose individual strains to differential immune reactions, which could manifest in diverse reactivity to topical irritants and allergens.

Increased penetration and amplified irritant reactions in patients with AD

The barrier abnormalities that characterize AD allow for increased penetration of irritants and allergens (Fig 4).[99] It has been shown that a disturbed barrier permits increased permeation of water, salts, and compounds, such as theophylline, polyethylene glycol, and SLS, through the SC.[46,112,113] In the *ft/ft* murine model of AD, an enhanced paracellular permeability to epicutaneously applied water-soluble antigens, such as nickel, was reported,[28,99] as well as a reduced threshold for the development of both ACD and ICD.[99,114] Similarly, downregulation of other barrier genes, such as claudin-1, and the late CE family of genes in patients with AD has also been associated with increased epidermal permeability and the development of ACD, respectively.[41,115] Recent studies also associated a history of AD and a loss-of–function *FLG* mutation with both contact sensitization to nickel and development of ICD.[46,116]

The association between AD and ICD is supported by epidemiologic studies that document the increased rate of irritant reactions in patients with AD.[117,118] Because of the increased susceptibility to irritants in patients with AD,[118] these patients have double the risk of ICD, particularly in occupations involving a wet environment.[117] Exposure of skin lesions from patients with AD to SLS increased TEWL and produced greater perivascular infiltrates of $CD1a^+$, $CD4^+$, and $HLA\text{-}DR^+$ inflammatory cells compared with those seen in patients without AD.[119] Thus the disrupted barrier of AD amplifies the epidermal damage and inflammation in response to irritants.

In addition, the frequency of irritant reactions has been found to correlate with both an increased number of allergic responses and the occurrence of atopy,[120] suggesting that a barrier defect might

exist in patients with AD that would allow increased irritant and allergic substance penetration (Fig 2).

Increased ACD in patients with AD

ACD was previously thought to occur less frequently in patients with AD because of early reports of diminished immune reactions.[121] This concept was emphasized by studies that demonstrated that patients with AD were not readily sensitized by repeated applications of DNCB but were only sensitized once the AD improved.[122] However, more recent studies show that rates of ACD or contact sensitization to common allergens, such as nickel, cobalt, thimerosal, and fragrance mix, are at least as frequent in patients with AD as in the general population, with frequency rates of up to 40%.[11,123-125] A more recent study has reported significantly higher sensitization rates (65.0%) in atopic subjects compared with those seen in nonatopic subjects (57.4%).[126]

Similarly, recent pediatric studies have demonstrated that ACD and contact sensitizations to allergens are at least as prevalent in atopic children as in healthy children.[127-132] Additionally, among a group of subjects with relevant positive patch test reactions, there was a higher rate of AD among children (34.0%) compared with adults (11.2%), suggesting that AD might be a more significant risk factor for ACD in children than adults.[132] Both the extent and severity of AD in children, as measured by the Eczema Area and Severity Index score, as well as the duration of the disease in both children and adults, have been found to correlate with the prevalence of contact sensitization, further underscoring this association between AD and ACD.[123,129]

The severity of AD is known to affect patch test results and produce false-positive patch test reactions.[133] Because many contact allergens also have irritant qualities and can cause skin irritation, one must be aware of irritant reactions complicating patch test readings. In one study there were more ambiguous and irritant patch test reactions in patients with AD compared with patients without AD.[133] This might be due to an increased skin irritability of patients with AD,[125] which could be both a consequence of their disturbed epidermal barrier and a cause for the increased incidence of both ICD and ACD in these patients. The increased irritant reactions in patients with AD potentially result in higher susceptibility to allergic contact sensitization.[117]

An important factor for the increased ACD reactions in patients with AD is the high expression levels of FcεRI on LCs, inflammatory dendritic epidermal cells, and mast cells in AD lesional skin and nonlesional skin.[134-137] Once the antigen-antibody complexes bind to FcεRI,[138,139] these cells release cytokines and chemokines (eg, IL-5, IL-6, CCL5, CCL17, CCL22, tryptase, and eotaxin) that prime T-cell reactions, promoting antigen-driven allergic inflammation in patients with AD (Fig 4).[134]

The fact that AD often improves and even resolves with age, despite the genetically encoded and constant barrier defects, suggests that other immune mechanisms beyond those triggered by the barrier disruption might contribute to the decreased skin sensitization threshold. Two other mechanisms (in addition to the increased immune activation resulting from barrier deficiency) might increase allergic inflammation in patients with AD. These include (1) a differential immune regulation in patients with AD that potentially decreased the thresholds for ICD and ACD and (2) a break in tolerance, resulting in increased reactivity to self-antigens.[140-143] IgE sensitization to self-antigens was shown to occur in 8.7% to 29% of patients with AD. IgE from sera of patients with AD was demonstrated to bind recombinant human self-antigens, whereas IgE from healthy control subjects did not.[144] These autoreactive IgEs have also been associated with AD disease severity.[140-143]

Thus AD can lead to increased skin reactivity to both self-antigen and non–self-antigens, further perpetuating endogenous chronic skin inflammation (Fig 2). Furthermore, increased reactivity to self-antigens,[5,140-143] irritants,[117,118,145] and allergens[123,126,129] was correlated with AD disease activity, supporting their role in perpetuating chronic inflammation. Thus endogenous AD inflammation might involve a breach of tolerance through mechanisms similar to those involved in ACD.

Potential contribution of LCs to increased ACD in atopic patients

In addition to the critical role that LCs have in mediating contact hypersensitivity reactions, LCs were also shown to be critical to the pathogenesis of AD[146] and potentially contribute to the increased incidence of allergic reactions in patients with AD. Although in healthy skin LCs were shown to primarily induce T_H2 and T_H22 T-cell subsets,[147,148] in the setting of a disrupted barrier, such as in patients with AD, LCs were shown to broadly expand T_H1, T_H2, T_H17, and T_H22 T-cell subsets.[149] Through engagement of FcεRI, these cells augment allergen presentation and induce a proallergic T_H2 state in patients with AD.[146] The T_H2 cytokine production results in an amplification loop, which induces further IgE production and increased innate immune cytokine levels that augment T_H2 and possibly also T_H22 inflammation.[146] Innate immune cytokines, such as TNF-α and IL-1α, synergize with T_H2 cytokines to induce TSLP production by keratinocytes, which further stimulates migration of LCs to LNs and triggers naive T cells to become "proallergic." In turn, these proallergic T cells home to the skin, where they release T_H2 cytokines that further induce TSLP release from keratinocytes (Fig 2).[146]

T-CELL RESPONSES IN THE PATHOGENESIS OF ACD AND AD

New immune participants in ACD

The pathogenesis of ACD involves 2 main stages: the sensitization phase and the elicitation phase (Fig 2). During the sensitization phase, the haptens become immunogenic after binding to carrier proteins and activate keratinocytes to release inflammatory molecules, including TNF-α, GM-CSF, IL-1β, and IL-10. Activated LCs then migrate from the epidermis to the LNs that are draining the site of initial contact. In the LNs LCs present the peptides to naive T cells and activate $CD4^+$ and $CD8^+$ antigen-specific T cells. These effector T cells proliferate and enter the circulation and the site of initial epidermal exposure. The elicitation phase occurs on re-encounter with the allergen, during which the antigen-specific T cells home into hapten-exposed skin and induce an inflammatory cascade that leads to further cellular infiltration.[8]

T_H1 cells have been classically considered the primary effector cells of ACD because responses to haptens, such as nickel, were reported to be dominated by IFN-γ–producing cells, whereas T_H2 cells have been considered minor effectors.[150] Yet recent studies indicate that T_H2 cells participate in the development of contact hypersensitivity.[15,151,152] In most experimental systems the

majority of haptens, such as DNFB, trinitrochlorobenzene (TNCB), and oxazolone, induce a T_H1-dominant response, whereas only some, such as fluorescein isothiocyanate and trimellitic anhydride, induce T_H2-dominant responses.[153] However, in both IFN-γ– and IFN-γ receptor–deficient mice, TNCB and DNFB induced normal contact hypersensitivity reactions, whereas the contact hypersensitivity reactions were diminished in mice with deficient IL-4 and signal transducer and activator of transcription 6, T_H2-specific factors.[152,153] Also, although antigen-specific T-cell lines in mice expressed only T_H1 cytokines, transfer of these lines induced systemic contact dermatitis only on incubation and transfer with IL-4.[154] Recently, GATA-3 transgenic mice were exposed to nickel and 2,4,6-TNCB, both of which induced a T_H2-predominant response.[155]

Human data have also supported the role of T_H2 responses in patients with ACD. IL-4 has been detected in the dermis of some human ACD lesions.[156] Also, isolated nickel-specific T-cell clones from patients with ACD and PBMCs from patients with nickel-positive patch test results have demonstrated increased T_H2 responses, with induction of IL-4, IL-5, and IL-13 in addition to T_H1/IFN-γ responses.[15,157,158] The T_H2 responses correlated with patch test reactivity, with an increased number of subjects having increased levels of T_H2 compared with T_H1 cytokines.[15]

Lately, both murine models and human studies have also emphasized the potential role of T_H17 cells in the immunopathogenesis of ACD because the T_H17/IL-17 axis has become recognized as playing a role in the pathogenesis of many autoimmune diseases previously considered T_H1-mediated diseases.[159-161] Increased levels of cytokines favoring a T_H17 response (ie, IL-6)[162] and allergen-specific IL-17–producing T cells were found in sensitized mice.[163] In addition, IL-17–deficient mice showed decreased secretion of cytokines and chemokines, diminished hapten-specific $CD4^+$ T-cell responses, and reduced ear swelling.[164,165]

Furthermore, T_H17-associated mediators, such as IL-17A, IL-17F, IL-22, IL-23, CCR6, IL-22 receptor, and the T_H17 transcription factor retinoic acid–related orphan receptor γ, were shown to be produced by nickel-specific T cells isolated from patients with ACD[166] and were upregulated in ACD lesional skin and positive patch test biopsy speicmens.[153,167,168] In addition, nickel exposure was reported to induce production of IL-23 by keratinocytes, promoting a T_H17-mediated response, as detected by the presence of IL-17–producing T cells in peripheral blood from patients with nickel allergy.[168] The role of IL-17 in ACD lesions includes induction of keratinocyte release of cytokines and chemokines (ie, IL-8 and IL-6) and promotion of T cell–induced apoptosis of keratinocytes. Compared with T_H1, supernatants from IL-17–producing T cells were much more efficient in inducing ICAM-1 expression on keratinocytes and keratinocyte/T-cell adhesiveness *in vitro*.[169] Thus IL-17 might amplify the allergic reaction by enhancing the capacity of the recruited T lymphocytes to contribute to tissue damage. The significance of IL-17–producing cells in ACD lesions is emphasized by the correlation between the increase in IL-17–producing cells with the clinical manifestations of ACD,[170] as well as by their significant percentage (20%) among skin-infiltrating $CD4^+$ and $CD8^+$ T cells in contrast to their minor representation (only 1.5%) in regional LNs of allergen-primed mice.[153,163]

More recently, a particular role for IL-22, a member of the IL-10 cytokine family, which is produced by T_H22 and T_H17 T cells,[35,147] has been suggested in patients with ACD to nickel. In these patients significantly higher levels of IL-22 were detected in the serum compared with that seen in control subjects.[171] IL-22 cytokine levels have also been shown to be upregulated in inflamed skin of nickel-challenged allergic patients,[168] although its specific contribution to ACD reactions is not yet known.

Upregulated immune axes in patients with AD

The T_H2 axis is particularly upregulated in the acute phase of AD, with a partial shift to T_H1 during the chronic phase.[172] AD spontaneously develops in transgenic mice that overexpress T_H2 cytokines, demonstrating thickened epidermis and dermis, inflammatory cell infiltrates, and increased serum IgE levels.[173] In lesional AD skin, there are increased levels of T_H2 T cells and associated cytokines (IL-4, IL-5, and IL-13),[174] which are also upregulated in nonlesional AD skin[23] and correlate with disease severity.[175] IL-4 and IL-13 induce activated B cells to produce IgE, levels of which are increased in the sera of a majority of patients with AD.[176,177] Hence a predominant T_H2 response characterizes both lesional and nonlesional AD skin and is further induced by ubiquitous environmental agents, which permeate the damaged epidermal barrier. Associations between *FLG* null mutations and increased allergen-specific $CD4^+$ T_H2 cell responses[178] and an inverse correlation between claudin-1 expression and epidermal barrier function in nonlesional AD skin with levels of T_H2 biomarkers support the role of immune dysregulation in the disturbed barrier of patients with AD.[41]

A few studies have suggested that the T_H17 axis might be upregulated in acute AD skin lesions[179] and peripheral blood.[180] We found that the IL-23/T_H17 axis is reduced in chronic AD skin lesions.[181] T_H2 cytokines, such as IL-4 and IL-13, were shown to inhibit IL-17 production, which might contribute to the attenuated T_H17 pathway in chronic AD.[182] Still, the increased T_H17 responses in acute lesions might predispose to antigen activation of T_H2 responses in a disturbed barrier system.

Numbers of a newly identified T-cell subset, T22, which is composed of T_H22 and T_C22 cells, which produce a majority of the IL-22 in patients with AD, were found to be increased in patients with chronic AD.[35,147] Furthermore, the frequency of these cells was correlated with AD disease activity.[35] The discovery of this new subset of cells has led to a model in which AD is mediated by T_H2 and T_H22 cells. IL-22, along with other cytokines in the IL-20 family, participates in the disruption of the epidermal barrier because it inhibits terminal differentiation.[33,35,36,183] This cytokine might contribute to the pathogenesis of contact dermatitis reactions in patients with chronic AD.

CONCLUSION

The increased permeation of allergens in a disturbed barrier system, in conjunction with existing activation of innate immunity, increased access of surface antigens to LCs, and selective upregulation of the T_H2 adaptive immune response, might explain the increased prevalence of contact dermatitis in patients with AD. T_H17 activation in patients with acute AD and the upregulated T_H22 axis in patients with chronic disease might also contribute to the pathogenesis of ICD and ACD in these patients. In patients with AD, cutaneous contact with irritants and allergens leads to amplification of innate immunity and enhanced adaptive immune responses, including T_H2 and T_H17 in patients with acute

AD and T_H22 and T_H1 in patients with chronic disease. Just as innate immune activation stimulated by an irritant permits a lower threshold of ACD elicitation,[48,53,57,58] the amplified adaptive responses in lesional and nonlesional skin promote increased ACD and ICD in patients with AD.

What are the possible mechanisms for increased ACD reactions in patients with AD?

1. Increased antigen penetration in a setting of a physical barrier defect (eg, decreased lipid, filaggrin, and terminal differentiation protein levels)
2. Activation and/or increased cellular infiltrates of LCs or other immune cells in nonlesional AD skin
3. Increased innate immunity in nonlesional AD skin
4. Priming of T-cell reactions through high levels of IgE/FcεRI-mediated allergic reactions (FcεRI is highly expressed on LCs, inflammatory dendritic epidermal cells, and mast cells in patients with AD)
5. Altered cytokine milieu in patients with AD, which might be more permissive for the development of allergic reactions
6. A state of decreased tolerance or disturbed steady state in patients with AD, rendering them more susceptible to allergen challenge
7. Altered properties of keratinocytes, including increased production of TSLP or innate immune cytokines that directly or indirectly feed T-cell activation responses
8. Genetic background variability causing differential antigen responses in patients with AD (similar to the differential allergen reactions in various murine strains)[66]

Open questions

1. Why do different persons have different thresholds for ACD reactions? Does it mainly relate to differences in genetic background? Are environmental factors also playing an important role in determining differential susceptibility to allergic reactions?
2. Why do patients with AD have more allergic reactions? Are there differences between extrinsic and intrinsic AD with respect to the development of allergic reactions? If so, are these related to the high IgE production or other factors? Is there a correlation between the IgE level and occurrence of ACD reactions in patients with AD?
3. Are patients with AD who outgrow their disease still more susceptible to contact allergy and, if so, why?
4. Is tolerance affected/decreased in the context of AD? Does decreased tolerance in nonlesional AD skin contribute to the increased contact sensitization in patients with AD?
5. Are increased ACD reactions universal to conditions with barrier deficiency, such as AD and aging skin, or are they condition specific?
6. Are immune infiltrates of ACD reactions that evolve in nonlesional AD different from those in other conditions of abnormal barrier or healthy skin?
7. Will effective treatment in patients with AD reduce/affect ACD reactions of nonlesional AD skin?
8. What are the factors that promote or inhibit tolerance in healthy skin compared with conditions of barrier deficiency?
9. Is it possible to desensitize by means of oral/epicutaneous immunotherapy to contact allergens (similar to aeroallergens/food allergens)? If so, what is the best route by which to establish immune tolerance? Do different antigens necessitate different desensitizing approaches?

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