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The Skin as a Route of Allergen Exposure: Part I. Immune Components and Mechanisms

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Abstract

Purpose of Review—To highlight recent contributions in the literature that enhance our understanding of the cutaneous immune response to allergen.

Recent Findings—Defects in skin barrier function in infancy set the stage for the development of atopic dermatitis (AD) and allergy. Both genetic and environmental factors can contribute to damage of the stratum corneum (SC), with activation of specific protease enzymes under high pH conditions playing a key role. Immune cells and mediators in the dermis and epidermis impair SC repair mechanisms and support allergy development. In barrier-disrupted skin, type 2 innate lymphoid cells (ILC2s), mast cells (MCs), and basophils have been shown to promote AD and pathogenic Th2 responses in murine models.

Summary—Skin barrier disruption favors induction of systemic Th2-associated inflammatory pathways. A better understanding of the ontogeny and regulation of these complex networks in infant skin is needed to guide future strategies for allergy treatment and prevention.

Keywords

Atopic dermatitis; Epicutaneous allergy; Detergent; Cutaneous sensitization . Skin

Anna R. Smith and George Knaysi contributed equally to this work.

Compliance with Ethical Standards

Conflict of Interest Drs. Smith, Knaysi, Wilson, and Wisniewski declare no conflicts of interest relevant to this manuscript.

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Introduction

Diverse immune responses occur through skin in response to environmental antigens; the quality of the immune response depends on the integrity of the skin barrier, qualities of the antigen itself, and characteristics of the cellular networks present in the skin at the time of allergen contact. Allergic immune responses, defined classically by the induction of antigen-specific Th2 cells and specific IgE antibody production, involve activation of the adaptive arm of the immune system during allergen exposure. Nickel and poison ivy are examples of contact allergens that sensitize through skin (inducing mixed T cell responses, but not IgE antibody production) because their low molecular weight and chemical reactivity towards host proteins convert these otherwise innocuous compounds into hapten-protein complexes (antigens) that induce migration of dendritic cells (DCs) to skin draining lymph nodes where the adaptive immune response is activated upon antigen presentation to T cells. Downstream signaling leads to infiltration of skin by inflammatory cells (eosinophils, mast cells, basophils) that mediate clinical symptoms of skin erythema and pruritus [1]. While clearly the mechanism of contact hypersensitivity to haptens is distinct from IgE-mediated responses to other allergens, murine models of contact allergy have hinted at the Th2-promoting properties of skin barrier disruption for over a decade [1]. In contrast to low molecular weight contact allergens (<500 Da) [2]; water-soluble cat, dust mite, or peanut allergens (particle sizes range from 5000 to 100,000 Da) [3, 4] are theoretically too large to bypass the cutaneous permeability barrier [5]. To explain this size discrepancy, it is now evident that skin barrier defects are the driver of allergen exposure through skin. Our current understanding of the mechanisms of allergen responses through skin is pieced together from epidemiologic studies, experiments in animal models, and translational studies in patients who suffer from AD. The objectives of this article are to review what is known about the skin as an immune organ and to integrate current knowledge regarding the relationship between skin barrier disruption and epicutaneous mechanisms of allergen sensitization.

The Role of Skin in Allergy

Atopic dermatitis is a common inflammatory skin disease characterized by severe pruritus and the predisposition towards development of IgE antibodies against food and inhalant allergens. The skin of patients with AD contains high expression of IL-4 [6], IL-33 [7, 8], and thymic stromal lymphopoietin (TSLP) [9–12], hallmark cytokines associated with Th2 inflammation. The causal role of allergen as the driver of AD has been debated for over a decade [13]; prevailing theories consider both skin barrier defects and cellular immune deviations as contributors to increased sensitization to environmental allergens in AD [14]. More simply said, allergen exposure without both barrier disruption and involvement of adaptive immune recognition is not sufficient to elicit an allergic response [15], and allergen avoidance in the absence of preventing skin barrier disruption is unlikely to protect against allergy [16]. The public health importance of pinpointing the causal factors in AD is further demonstrated by the strong association between onset of AD in infancy and future development of food allergy [17] and asthma [18, 19]. Given the innumerable studies that have identified interesting relationships between cutaneous immunity and allergens that may be relevant to food allergy and asthma, an in-depth discussion of every study is beyond the scope of this review. Rather, the focus will be on studies that identify novel aspects of the

skin barrier that may inform the immune response to food and environmental allergens. The first mechanistic implication of the role of skin in allergy development was the identification of deficiencies in the key epidermal barrier protein, filaggrin, among patients with AD. Filaggrin defects were later correlated with disease severity and allergen exposure through skin [20]. Non-invasive biomarkers of skin barrier integrity and epidermal permeability, such as transepidermal water loss (TEWL), have expanded our understanding of the relationship between the skin barrier and allergy development. Kelleher and colleagues reported that higher TEWL at 2 days of life predicted the development of atopic dermatitis in infants by 12 months [21]. Infants with high TEWL at 2 days of life also exhibited higher rates of IgE-positive food allergy at 2 years of age even in the absence of clinically apparent AD [22••]. At the epidemiologic level, these associations confirm that defects in the skin barrier in early life set the stage for allergy development.

Th2 Immune Activation by Skin Allergens

The anatomic properties and localization of immune cells that mediate Th2 responses in skin are gleaned from in situ examination and flow cytometry analysis of cells extracted from healthy and human skin with AD. Migration and other functional characteristics of these cells have mainly been studied in animal models. In this section, we highlight some of the key cell types that support a pathogenic role for Th2 responses to cutaneous allergens.

Skin Dendritic Cells

Skin DCs are at the interface of innate and adaptive immunity, anatomically positioned to acquire environmental antigens and equipped to direct heterogeneous T cell effector functions. Diverse skin DC types have been described in healthy and inflamed human skin [23–25]. It is important to emphasize that in healthy skin, epidermal Langerhans cells and dermal DCs are abundant in an inactive or immature state and play key roles in normal immune surveillance. Activated inflammatory dendritic epithelial cells (IDECs), TNF and iNOS-producing DCs (Tip-DCs), and plasmacytoid dendritic cells are identified only in inflamed skin and are thought to mediate allergic responses to skin antigens [23]. Langerhans cells (LCs), identified by the C-type lectin receptor, CD207/ langerin, and Birbeck granules, are present in all layers of the viable epidermis [26•]. The number of epidermal LCs was found to increase or decrease in AD versus healthy epidermis, dependent on disease severity and treatment with topical steroids or calcineurin inhibitors [27]. FcεRI, the high affinity IgE receptor, has been theorized to play a role in antigen-uptake and facilitated antigen presentation by LCs based on observations of higher FcεRI surface expression on LCs in AD skin [28–30]. However, the involvement of FcεRI on LCs in humans is likely limited to inflamed skin with underlying skin barrier abnormalities. This view is supported by recent microscopic in situ examination of LCs from AD subjects, showing differential anatomical localization of FcεRI and langerin on the LC surface. Based on these observations, LC uptake of surface antigens by langerin (located on the apical surface of dendrites), but not FcεRI (located on the basal surface), was posited to occur through the epidermal tight junction barrier [26•]. IDECs reside in the lower layers of the epidermis in patients with AD and are absent in healthy epidermis [28]. High surface expression of thymic stromal lymphopoietin receptor (TSLPR) confers this DC subset with

Th2 priming properties [25, 31–33]. Unlike activated LCs which extend their dendrites vertically through intact tight junctions, IDECs extend dendrites horizontally across the lower layers of the epidermis [26•]. Dermal DCs (DDCs) are localized below the epidermal basement membrane, but display no exclusive marker comparable to langerin or Birbeck granules for LCs. In murine models of contact allergy, dermal DCs migrate preferentially to the paracortex of lymph nodes adjacent to B cell follicles, where they are better positioned than LCs to stimulate B cells [23]. In AD skin, a subset of DDCs that resemble IDECs, including surface expression of TSLPR and production of similar pro-inflammatory cytokines, have been termed inflammatory dendritic cells (iDCs) [34]. DC expression of Toll-like receptors (TLRs) is another critical determinant of downstream T cell responses. Patterns of surface and endosomal TLR expression on human skin DCs vary by subset and activation status [23, 24] and differ in adult compared to neonatal skin [35]. The ontogeny of functional skin DC subsets in relation to allergy remains enigmatic. Differences in DC characteristics between healthy adult, infant, and inflamed AD skin suggest potentially divergent roles in responsiveness to skin allergens, but the precise mechanisms remain elusive at this time.

Skin T cells

Tcells are abundant in healthy skin where they reside below the epidermal-dermal barrier at a density of 1×10^6 T cells/cm² [36]. In response to prolonged allergen challenge via patch occlusion with allergen extract, T cells migrate from the dermis and infiltrate the epidermis along with other inflammatory cell types [37]. Using ex vivo and in situ methods, diverse effector T cell types have been described in adult AD, including Th1, Th2, Th22, and Th17 [38]. The key role of Th2 cells (important in the secretion of IL-13 and IL-4) in AD skin was confirmed in recent clinical trials where blocking the common receptor for IL-13 and IL-4 (IL-4R α) resulted in significant improvement in the inflammatory profile of lesional skin that paralleled clinical improvement of disease in adults with severe AD [39]. In addition to having increased Tcells numbers in their skin, patients with AD also have higher frequencies of skin-trafficking activated effector T cells in blood [40, 41]. Surface expression of the skin homing receptor, cutaneous lymphocyte antigen (CLA), is a feature of skin-resident T cells [36] and also a marker for ex vivo characterization of skin-trafficking T cells from blood. Co-culturing peripheral blood T cells from patients with AD with allergen has shown increased Th2-like (IL-4+) allergen-specific T cells within the CLA+ subset skin homing T cells [42]. In young children with AD, Th2 (CD4+IL-13+) cells were the dominant cell type within skin homing T cells in peripheral blood, compared to adults with AD where Th1 and Th22 cell types were predominant [41].

Innate Lymphoid Cells

Type 2 innate lymphoid cells (ILC2s) constitute 5–10% of CD45+ cells in healthy dermis where they are posited to play key roles in immune regulation and wound healing [43, 44]. Despite phenotypic and developmental similarities with T cells including expression of CLA, skin ILC2s have distinct surface markers, exhibit distinct migratory patterns, and constitutively express IL-13 [43]. ILC2s do not express cell lineage markers associated with lymphocytes or other leukocytes. They are defined within lineage negative cells by expression of CD25 (IL-2R α), ST2 (IL-33R), and CD127 (IL7R α) [45]. Constitutive

production of IL-13 was shown to suppress IgE-dependent cytokine release from skin mast cells in mice in an IL-7-dependent manner [46•], giving ILC2s a potentially important regulatory role in inflamed skin. ILC2 cell numbers are increased in the dermis and epidermis in AD [45] and after intraepidermal injection of house dust mite (HDM) allergen ILC2s increased at the site of allergen exposure [47]. In response to skin barrier disruption, keratinocyte-derived cytokines activate ILC2s via binding with surface receptors for IL-25, TSLP, and IL-33, resulting in enhanced IL-5 and IL-13 production [43]. In contrast, binding of the intercellular adhesion protein, E-cadherin, to the surface of ILC2s was shown to inhibit IL-5 and IL-13 production [47]. Clarifying the role of ILC2 cells in allergen-exposed skin is particularly relevant to AD where skin barrier dysfunction has been associated with decreased E-cadherin levels [47].

Mast Cells and Basophils

By virtue of their localization in human skin and ability for cutaneous allergens to cross-link FcεRI, mast cells and basophils are major sources of histamine and vasoactive mediator release triggered by skin allergens [48, 49]. While controversial as to whether basophils function as professional antigen-presenting cells (APCs) [50], they are a major source of innate IL-4 production and can promote the development of Th2 cells via either direct or indirect effects. Cutaneous uptake of papain, a natural protease allergen homologous to the major dust mite allergen, Der p 1, by mouse DCs caused co-migration of basophils with DCs and T cells to lymph nodes, in a manner dependent on production of the basophil chemotactic cytokine, CCL7/MCP-3 [51]. In mice epicutaneously sensitized to ovalbumin (OVA), basophil recruitment was dependent on TSLP production in response to skin barrier disruption, and TSLP-elicited basophils promoted antigen-specific Th2 responsiveness [52]. Early murine models depleted of mast cells implicated a similar role, without a clear mechanism, for mast cells in supporting cutaneous Th2 responses [53]. Most recently, a novel pathway involving IL-33 and mast cells was described in which the systemic recall response to cutaneous allergen exposure was mediated by keratinocyte-derived IL-33-effects on mast cells [54]. Barrier-disrupted mouse skin produces IL-33 and supported the development of allergen-specific IgE antibodies in response to epicutaneous OVA allergen; similar to previous observations of Th2 skewing mediated by skin barrier disruption and TSLP [11, 12]. In parallel, systemic IL-33 release by damaged keratinocytes resulted in mast cell migration to the gut and enhanced antigen-driven IgE-dependent MC degranulation upon oral challenge with OVA. Supporting the critical role of IL-33, anaphylaxis was blocked by treating mice with an IL-33 receptor antagonist prior to oral challenge and could not be restored in mice lacking IL-33 receptor [54]. Using bone marrow-derived mast cells, previous groups showed that IL-33-stimulated mast cell signaling promotes expansion of T regulatory (Treg) cells in an IL-2-dependent fashion [55]. Given these findings came from in vitro work, the IL-33/Th2 pathway may be confined to tissue-resident mast cells. The most consistent observation from multiple murine studies is that cutaneous sensitization with food allergens through barrier-disrupted skin, but not oral exposure, results in expansion of intestinal mast cells and systemic increases in Th2 cytokines [52, 54, 56]. Though limited by the constraints of modeling mechanisms of epicutaneous allergy development in mice, these results are provocative in their suggestion that damaged keratinocytes regulate both cutaneous and systemic responses to allergen in a basophil and mast cell-dependent manner

(Fig. 1). Together, these recent studies support the pathogenic involvement of diverse Th2-promoting cells in skin.

Skin Barrier to Allergen

Stratum Corneum

The outermost stratum corneum (SC) layer of skin is a dual compartment of corneocytes and lipid-rich extracellular lamellar matrix that form the main protective barrier against environmental allergens and TEWL. Tape-stripping is a common method used to remove layers of the stratum corneum to allow for increased allergen penetration to underlying immune cells in animal and human models of allergy. When the stratum corneum is disrupted by tape-stripping, allergen-exposed human skin becomes more susceptible to inflammation [57] and demonstrates increased TEWL [58]. In this section, we will explain why the integrity of the SC is inversely related to susceptibility to epicutaneous allergen sensitization and how Th2-promoting cells decrease SC integrity.

SC formation over viable epidermis is the final step in keratinocyte differentiation and skin barrier formation (Fig. 2). In the process of cornification, basal keratinocytes differentiate and morphologically transform in a programmatic fashion from epidermal stem cells until they become essentially apoptotic keratinocytes that are highly specialized to retain skin moisture and maintain an optimal surface pH for the function of surface enzymes [59]. The cornified envelope is formed from the dense packing of keratin filaments by filaggrin and covalent cross-linking of structural proteins (e.g., involucrin, loricrin) by transglutaminases during the transition of granular to cornified keratinocytes. Intercellular attachments between corneocytes are formed by assembly of adhesion proteins (e.g., desmoglein, desmocollins, plakoglobin, desmoplakin) into modified desmosomes, termed corneodesmosomes. Skin proteases, such as stratum corneum chymotryptic enzyme (SCCE), eventually degrade these intercellular corneodesmosome attachments, allowing cells to detach (desquamate). The processes of cornification and desquamation are highly regulated by the activity of specialized proteases and protease inhibitors [60], including lymphoepithelial Kazal-type 5 serine protease inhibitor (LEKTI) and skin-derived antileukoprotease (SKALP) [61]. During the final stages of cornification, lamellar bodies release stored lipids, anti-microbial peptides, proteases, and antiproteases onto the skin surface [20]. The by-products of filaggrin proteolysis further contribute to the normal functioning of the skin barrier. As filaggrin is broken down into its amino acid constituents, glutamine is converted to natural moisturizing factor (NMF) which maintains corneocyte hydration, flexibility, and detachment [62]. A wide variety of defects in SC structural proteins, proteases, and antiproteases have been linked to the development of AD [63, 64]. Patients with inherited defects in the serine protease inhibitor kazal-type-5 (*SPINK 5*) gene are deficient in the protease inhibitor, LEKTI, resulting in unrestricted serine protease-dependent degradation of lipid-processing enzymes and early degradation of corneodesmosome attachments [65]. Patients with defects in the *filaggrin* (*FLG*) gene demonstrate diminished keratohyalin granules in the stratum granulosum, abnormal cornified envelope formation, reduced corneocyte hydration, and increased skin pH [20]. Patients with *FLG* null mutations also demonstrate evidence of higher systemic absorption of environmental toxins, such as

phthalates (plasticizers in many consumer products), presumably through their skin [66]. In patients without inherited defects in filaggrin, age and exogenous stressors decrease filaggrin expression, including environmental exposures (e.g., low humidity, sun exposure, skin irritants), microorganisms (e.g., HPV), and topical exposures (e.g., dithranol and corticosteroids) [20].

The skin's acidic surface pH, termed the acid mantle, is a key factor that regulates the activation of enzymes that control the integrity of the skin barrier through cornification and desquamation. Alkaline pH soap (pH >7) use is associated with decreased corneocyte adhesion and increased TEWL, in part, because of its pH effects on filaggrin expression [67–69]. Among 40 infants aged 2 weeks to 16 months, washing skin with alkaline soap (pH 9.5) caused decreased epidermal lipid content and increased skin pH (by 0.45) compared to prior to bath [70, 71]. In line with the pH dependency of keratinocyte enzymes like filaggrin, increased skin pH can result in skin barrier defects comparable to subjects with inherited FLG-loss-of-function mutations [72]. In a feed-back cycle, decreased filaggrin expression further impairs skin's acid mantle formation because one of the filaggrin break-down products, *trans*-urocanic acid (*t*-UCA), plays a major role as a natural acidifier of stratum corneum [73]. In the absence of sufficient FLG-derived *t*-UCA or other natural acidifiers, the resulting alkaline skin surface environment promotes serine protease activation and premature break-down of corneodesmosome attachments, a driver for skin barrier break-down and increased allergen penetration [64]. This final step of corneodesmosome break-down is likely a common event by which many genetic defects and environmental exposures mediate skin barrier break-down and enhanced cutaneous allergen exposure [60, 74].

The competence of the SC is also dependent on the abundance of ceramides and equal ratios of free fatty acids (FFAs) and cholesterol that form the lamellar membranous matrix that seals connections between corneocytes. Ceramide accounts for about half of the lipids in SC and is synthesized by ceramide synthase 3 (CerS3). Patients with decreased ceramide production due to *CerS3* deficiency demonstrate scaling skin, hyperkeratosis, and repeated skin infections owing to enhanced epidermal penetration by fungal organisms [75]. Beyond the SC, further transcellular movement of antigens is blocked by intercellular tight junctions (TJs) between keratinocytes. TJs are formed by TJ proteins (claudins, occludin, cingulin) expressed by keratinocytes in the stratum granulosum (Fig. 2). The “tightness” of TJ structures is dynamically regulated to address physiologic needs and by environmental factors [76]. In patients with inherited defects in the major TJ protein claudin 1, odds of lifetime AD were 2.61 ($P = 0.008$) times higher compared to unaffected children [77]. Openings in sweat glands or hair follicles provide a possible portal for allergen penetration as ostia range from 0.5 to 50 μm [77]; however, as pores comprise 0.1% of the total skin surface, they are thought to be irrelevant [2]. Hence, structural proteins, lipid matrix formation, protease regulation, and acidic pH are critical parts of a healthy SC and alterations in any of these aspects can result in skin barrier disruption and enhance susceptibility to environmental allergens.

Damage and Repair of the Stratum Corneum

Importantly, any perturbation of the SC initiates a rapid repair process in the underlying epidermis. But, in patients with AD, this process is often dysregulated and results in further skin barrier dysfunction. In response to environmental damage, keratinocytes become the very source of pro-inflammatory cytokines (IL-33, TLSP) required for induction of the Th2 responses discussed above. In a complex and vicious cycle, memory T and other immune cells responding to keratinocyte signaling infiltrate skin and secrete pro-inflammatory cytokines that worsen skin barrier defects by impairing normal keratinocyte differentiation and SC repair. As one example, incubation of human-derived epithelial keratinocytes with IL-31 downregulated expression of the genes for filaggrin processing and desmosome formation, and resulted in enhanced penetration of timothy grass pollen allergen (Phl p 1) [78]. IL-31-induced interference with the SC permeability barrier was abrogated by pre-treatment with anakinra (IL-1R antagonist), implicating a novel pathway by which T cell or MC-derived IL-31 regulate SC integrity through downstream IL-1 signaling [78]. This pathway for allergen exposures is particularly relevant in established AD, where keratinocyte IL-31 receptor expression is increased compared to healthy skin []. Through similar mechanisms, other cytokines, including IL-4, IL-13, IL-17A, IL-22, IL-25, and TNF- α , also impair SC repair through downregulation of filaggrin and NMF in skin, independent of *FLG* mutation status [20] (Fig. 1).

Infant Skin Barrier and Effects of Washing

The process of cornification of epidermal keratinocytes occurs continuously in human epidermis, starting from 23 weeks of fetal gestation throughout life [62]. Compared to adult skin, infant skin is characterized by a thinner SC [80–84]. There is conflicting data regarding the kinetics of SC maturation and TEWL over the first year of life: some studies have found that TEWL at birth is within range of TEWL for healthy adults (4–6 g/m²/h) [85], while others have found that this maturation can take 2–4 weeks or longer [86–88]. Normalization of TEWL may directly relate to acidification of newborn skin which has a neutral pH at birth. The pH lowers significantly during the first 1–4 days of life and continues to decrease throughout the child's first 3 months as the enzymes required to produce acidic components become activated [80, 89, 90]. Restoring the skin's acid mantle through application of acidic treatments has been proposed as a strategy for repairing the SC and combating inflammation caused by disruption [69].

A unique feature of newborn skin is the presence of vernix caseosa, a mixture of immature corneocytes and sebaceous gland secretions extruded from hair follicles, that coats the fetus skin by 28 weeks gestation [62]. When the vernix is retained on the skin after birth, compared to vernix removal within 30 min of birth, there is significantly higher skin hydration and lower skin pH at 24 h of life [91]. One pilot study comparing a liquid detergent cleanser and pure water found that they were equally mild, as judged by skin pH, skin hydration, and TEWL [92]. Other studies suggest that bathing infants with water alone, but not mild liquid detergent cleanser, causes decreased SC moisture content [93]. Mild liquid cleansers have been shown to maintain skin hydration and acid pH [93, 94]. However, specific ingredients in detergents have been linked to loss of skin barrier integrity and/or development of cutaneous inflammation. As one example, sodium laureth sulfate (SLS) was

shown in adults to increase TEWL and inflammatory cytokine expression, particularly IL-6 and TNF- α , as well as IL-1 β , IL-2, and GM-CSF to a lesser degree [95–99]. In adult volunteers exposed to water (vehicle) and 1% SLS under occlusive patch tests for 24 h, skin biopsies performed 6 h post-exposure, compared to water-exposure alone, were associated with decreased expression of profilaggrin, kallikrein-7 (KLK-7), and kallikrein-5 (KLK-5)—key proteins involved in the desquamation process [100]. In the same subjects, most keratinocyte differentiation markers and corneodesmosome degradation enzymes normalized 7 days after SLS, suggesting the ability of healthy skin to recover from the immediate effects of detergent exposure [100]. We also know that the application of daily emollients to infant skin is protective against AD [101, 102] and may involve upregulation of key epidermal barrier proteins [103]. However, the potential effects of applying other skin products on barrier integrity and susceptibility to environmental allergen exposure among at-risk infants are incompletely understood.

Conclusion

As outlined here, several lines of evidence support the view that skin barrier disruption, caused by inherited defects or acquired from exogenous factors, is critical for cutaneous IgE-mediated allergen sensitization. Only a single study has reported that a food allergen (peanut) could cause sensitization in a mouse model lacking barrier disruption [104]. Thus, while there is clearly an important role for inflammatory cells and mediators that bias towards Th2 responses and IgE class switch, we posit that these pathways only become operational in the setting of a dysfunctional skin barrier. A major shortcoming in the field involves the limitations of studying natural immunity through skin using murine models. In addition, given that the neonatal period appears to be a developmental window for allergy prevention, further research is needed to clarify the ontogeny of cutaneous immune networks in newborn skin. Based on our current paradigm, the cutaneous route of allergen exposure is a critical determinant of systemic immunity. Therefore, advancements in this area of research are pivotal for the development of novel strategies that might mitigate pathogenic cutaneous responses to environmental allergens.

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Abbreviations

AD	Atopic dermatitis
AMP	Anti-microbial peptide
APC	Antigen-presenting cell
CerS3	Ceramide synthase
CLA	Cutaneous lymphocyte antigen
DC	Dendritic cell

DDC	Dermal dendritic cell
FFA	Free fatty acids
FLG	Filaggrin
HDM	House dust mite
HPV	Human papilloma virus
iDC	Inflammatory dendritic cells
IDEC	Inflammatory dendritic epithelial cell
ILC2	Type 2 innate lymphoid cell
KLK-5	Kallikrein-5
KLK-7	Kallikrein-7
LC	Langerhans cell
LEKTI	Kazal-type 5 serine protease inhibitor
LPS	Lipopolysaccharide
MC	Mast cell
MDDC	Monocyte-derived dendritic cell
NMF	Natural moisturizing factor
OVA	Ovalbumin
PAR-2	Protease-activated receptor-2
SC	Stratum corneum
SCCE	Stratum corneum chymotryptic enzyme
SKALP	Skin-derived antileukoprotease
SLS	Sodium laureth sulfate
SPINK 5	Serine protease inhibitor kazal-type-5
TER	Transepithelial resistance
TEWL	Transepidermal water loss
Tip-DCs	TNF and iNOS-producing DCs
TJ	Tight junction
TLR	Toll-like receptor
Treg	T regulatory cell

TSLP	Thymic stromal lymphopoietin
TSLPR	Thymic stromal lymphopoietin receptor
t-UCA	Trans urocanic acid

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- Of importance

- Of major importance

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Fig. 1.

Selected pathways linking skin barrier disruption to allergen entry and pathogenic Th2 responses. Filaggrin deficiency states, inherited or acquired, disrupt skin's normal acid pH. Alkaline pH conditions support upregulated protease activity and degradation of inter-corneocyte attachments (corneodesmosomes) in a protease-dependent manner. In this way, barrier disruption leads to allergen entry and release of pro-inflammatory cytokines (IL-25, IL-33, TSLP) by damaged keratinocytes. Basophils, mast cells, inflammatory dendritic cells (*iDCs*—inflammatory dermal dendritic cells; *IDECs*—inflammatory dendritic epithelial cells), and type 2 innate lymphoid cells (ILC2s) are poised to respond to these keratinocyte signals and support pathogenic Th2 responses in skin

Fig. 2.

The skin barrier to allergen is regulated by the programmed production of key structural proteins, lipids, and enzymes by keratinocytes undergoing epidermal differentiation. Skin barrier function is dependent on self-renewal of the skin's acid mantle (acidic pH), inter-corneocyte connections, and lipid matrix