New insights in the pathogenesis of atopic dermatitis

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Atopic dermatitis (AD) is characterized by skin barrier defects and increased interleukin (IL)-4/IL-13 expression. Recent evidence also suggests the involvement of innate immunity including Toll-like receptors, IL-33, IL-25, and innate lymphoid cells in the pathogenesis of AD. This article reviews these innate immune components and how they may become an integral part of prognostic factors and therapeutic targets in the treatment of AD.

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease of childhood. It affects up to 25% of children worldwide and 10–20% of children in the United States (1,2). AD is associated with food allergy, asthma, and allergic rhinitis. Patients with AD, particularly those with moderate to severe disease, are at increased risk for skin infections, sleep disorders, and psychosocial morbidities including depression and anxiety disorders (3,4). The cost of AD has been estimated to be as high as $3.8 billion per year in the United States (5). The cause of AD remains to be a subject of debate. Defects in the physical barrier of the skin have been proposed to play a primary role in the pathogenesis of AD (6). However, allergic inflammation, including increased expression of T helper (Th) 2 cytokines such as interleukin (IL)-4 and IL-13, may also induce skin barrier defects in AD (7). This review aims to summarize recent studies in the pathogenesis of AD.

FILAGGRIN MUTATIONS: EVIDENCE FOR PHYSICAL BARRIER DEFECTS AS A CAUSE OF AD

Filaggrin is an important skin barrier protein in the skin that functions in preventing water loss from the skin and intrusion by microbial pathogens and irritants (8). A breakdown product of filaggrin, natural moisturizing factor, acts in retaining moisture and further contributes to the hydration of the skin. Before the identification of filaggrin null mutations (*FLG*), decreased expression of filaggrin has been shown in AD (9). In 2006, Smith *et al.* and Palmer *et al.* identified *FLG* and showed significant association between *FLG*, ichthyosis vulgaris, and AD among European populations (reviewed in ref. 8). Since then, more than 30 independent studies worldwide have confirmed the association of *FLG* with AD. However, the majority of AD patients do not carry *FLG*. In children, *FLG* accounts for only 26.7% of the patients with AD, suggesting that other skin barrier genes, particularly those in the epidermal differentiation complex of chromosome 1q21, likely exist to account for the barrier defects in AD patients without *FLG* (10,11). Abnormalities in skin lipid composition (6), excessive serine protease activity (as illustrated by the ichthyosiform disease Netherton syndrome, which is caused by mutations in *SPINK5* that encodes for lymphoepithelial Kazal-type–related inhibitor) (6), claudins of tight junction (12), or suppression of skin barrier protein expression by inflammation (9) may constitute other causes of skin barrier defects in AD. Mouse model of *FLG* has shown that deficiency of filaggrin in the skin leads to increased Th2 response and increased total serum immunoglobulin E (IgE) (reviewed in ref. 8). Multiple clinical studies have associated *FLG* with IgE sensitizations, asthma, and food allergy (reviewed in ref. 8). Using tape stripping and measurement of the concentrations of cytokines in the stratum corneum using a Luminex-based multiplex system, AD patients with *FLG* were determined to have increased IL-1 expression in their stratum corneum, as compared to AD patients without *FLG* (13). However, the mechanism(s) how FLG leads to Th2 inflammation in AD lesions remains unclear. A more recent human study showed that there was no significant difference in the basal *ex vivo* peripheral blood mononuclear cells expression of interferon (IFN)-γ or IL-4 between healthy controls, AD patients with or without *FLG* (14). All subjects were then sensitized to a nonallergenic chemical, 2,4-dinitrochlorobenzene, by epicutaneous application of 2,4-dinitrochlorobenzene. The 2,4-dinitrochlorobenzene-specific T-cell expression of IFN-γ and IL-4 was then analyzed. Healthy subjects were found to have significantly higher long-term expression of IFN-γ, whereas AD patients were found to have significantly higher IL-4 expression. Interestingly, there was no significant difference in the IL-4 expression between AD patients with or without *FLG*. This study suggests that *FLG* alone may not account for the pathogenesis of allergic inflammation in AD.

KERATINOCYTE DYSFUNCTIONS IN AD

Keratinocytes, the key epithelial cells of the skin, are the primary cellular source of barrier deficiency in AD. In the past 10 years, there has also been progress in the understanding of keratinocytes in the immune dysregulation of AD. It has previously been shown that AD keratinocytes have an increased expression of granulocyte-macrophage colony-stimulating factor and TNF-α (15). Stimulated keratinocytes isolated from

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Received 13 April 2013; accepted 6 August 2013; advance online publication 18 December 2013. doi:10.1038/pr.2013.196

nonlesional skin of AD patients showed lower expression of human β defensin-2, an antimicrobial peptide that chemoattracts Th17 cells, as compared to that in healthy subjects and psoriasis patients (16). The lower antimicrobial peptide expression in AD lesions may contribute to the increased skin infections in these patients (17).

While the innate immune responses against microbial pathogens are downregulated in AD, there is an increased expression of thymic stromal lymphopoietin (TSLP), a pro-Th2 IL-7–like cytokine, in the keratinocytes of AD lesions (18). TSLP activates dendritic cells (DC) to produce chemokines such as thymus- and activation-regulated chemokine/chemokine (C-C motif) ligand (CCL)17 and macrophage-derived chemokine/CCL22, which leads to infiltration of Th2 cells in AD lesions (19). In a recent AD mouse model, TSLP was shown to activate cutaneous group 2 innate lymphoid cells (ILCs; **Figure 1**) (20). ILCs are characterized by their lymphoid morphology, but lack recombination-activating gene–dependent rearrangement antigen receptors and myeloid/dendritic cell markers (20). They are divided into three groups: group 1 ILCs are IFN-γ–producing cells that include natural killer cells; group 2 ILCs produce IL-13, IL-5, and/or IL-4; and group 3 ILCs produce IL-17 and IL-22 (21). Group 2 ILCs were shown to be significantly increased in human AD lesions, as compared to healthy skin (20).

IL-33 and IL-25 are two other cytokines that may activate group 2 ILCs (22). IL-33 is an IL-1–related cytokine that induces allergic airway inflammation in mice in the absence of T and B cells (23). In addition, IL-33 has been shown to downregulate serum-induced expression of human β defensin-2 in keratinocytes (24). Immunohistochemical staining showed an increased number of IL-33$^+$ cells among suprabasal keratinocytes and an increased staining of ST2, an IL-33 receptor, among dermal infiltrates in AD lesions (25). IL-25 increases the expression of IL-5 and IL-13 in TSLP-DC–activated T cells (26). Immunohistochemical staining showed increased IL-25$^+$ keratinocytes in AD lesions, as compared to nonlesional skin (27). There was also an increased infiltration of cells, which expressed IL-17Rh1, an IL-25 receptor, in AD lesions, as compared to nonlesional AD skin (27). However, the majority of IL-25 producers are likely DC, eosinophils, and basophils (26,27).

Current evidence suggests that tissue repair mechanisms may underlie the pathogenesis of allergic inflammation (28). Double-stranded RNA released from damaged epithelial cells may stimulate Toll-like receptor (TLR) 3, leading to the production of TSLP from keratinocytes (29). Deletion of a disintegrin and metalloproteinase 17 (*ADAM 17*), a transmembrane metalloproteinase that cleaves cell surface proteins and maintains barrier homeostasis, in murine keratinocytes has been shown to result in skin barrier defects and chronic dermatitis in mouse models (30,31). Epidermal and systemic levels of TSLP and IL-33 were found to be significantly elevated in these mice (31). Epidermal expression of IL-4 and IL-17 was also found to be increased in *ADAM17*-deleted mice (31). The absence of *ADAM17* in the mice results in a reduction of epidermal growth factor receptor and Notch signaling, which lead to increased expression of IL-33, and AP-1, TSLP, IL-4, and IL-13, respectively (30–32). However, increased expression of IL-17 is not a prominent feature of human AD lesions, but it is a characteristic of psoriatic lesions (33). In addition, homozygous mutation of *ADAM17* in human leads to the development of inflammatory bowel disease, psoriaform dermatitis, and recurrent *Staphylococcus aureus* skin infections (34). Further studies are needed on the role of *ADAM17* in AD.

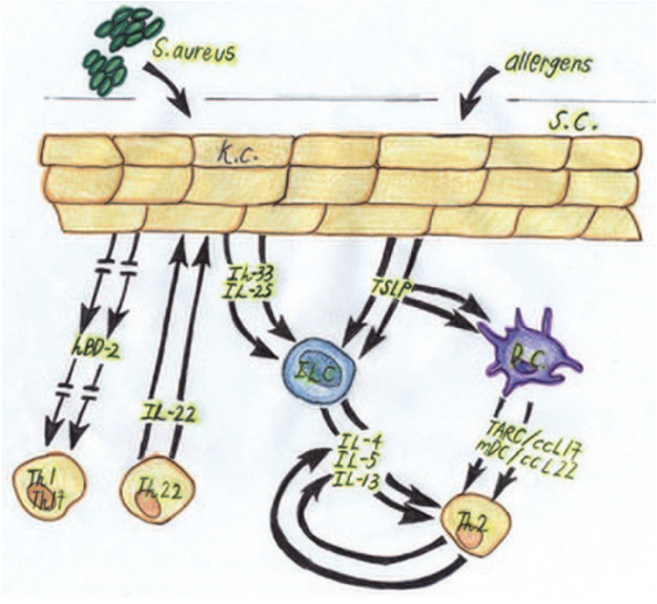

Figure 1. Cutaneous immune response in atopic dermatitis. CCL, chemokine (C-C motif) ligand; D.C., dendritic cells; hBD-2, human β defensin-2; ILC, innate lymphoid cells; K.C., keratinocytes; MDC, macrophage-derived chemokine; S.C., stratum corneum; TARC, thymus- and activation-regulated chemokine; TSLP, thymic stromal lymphopoietin.

ADAPTIVE IMMUNITY: PERPETRATOR OF PERSISTENT AND CHRONIC INFLAMMATION IN AD

The role of adaptive immunity in the cutaneous inflammation of AD has been well established. T-cell expression of IL-4, IL-5, and IL-13 is significantly upregulated in both acute and chronic AD lesions, as compared to nonlesional AD skin and healthy skin (35,36). Based on atopy patch testing using house dust mite allergens, a biphasic model of cytokine expression by T cells in AD was observed: an initial increase in the infiltration of IL-4$^+$ T cells into AD lesions, followed by infiltration of IFN-γ$^+$ T cells in the chronic phase (37). T-cell activities in AD are directed by specialized DCs in the skin including epidermal Langerhans cells and inflammatory dendritic epidermal cells. These cells have increased expression of high-affinity receptor for IgE (FcεRI), which captures allergens for antigen processing and presentation to Th2 cells (38,39). TLR-activated DC determines the type of T-cell response: activation of TLR4 on DC by microbial pathogens induces Th1 response, whereas activation of TLR4 on DC in the presence of TSLP or TGF-β and IL-6 promotes Th2 or Th17 response, respectively (40). Langerhans cells isolated from healthy human skin

induce T cells that produce less IFN-γ and IL-10, but more IL-4, IL-13, TNF-α, and thymus- and activation-regulated chemokine/CCL17 in the presence of TLSP (41).

IL-4 and IL-13 produced by Th2 have been shown to suppress filaggrin expression by keratinocytes (42). This is consistent with the clinical observation that filaggrin expression is significantly lower in the lesional AD, as compared to nonlesional AD skin (43). IL-4 and IL-13, together with TNF-α, also increase the expression of glucocorticoid-induced TNF receptor–related protein ligand in keratinocytes (44). Ligation of glucocorticoid-induced TNF receptor–related protein ligand on keratinocytes leads to the production of thymus and activation-regulated chemokine/CCL17, which further attracts Th2 cells to AD lesions. Cutaneous and systemic Th2 responses may amplify and maintain AD inflammation in a positive feedback mechanism (45). The absence of T-regulatory cells, and therefore a lack of suppression of cutaneous inflammation, may further contribute to the chronicity of AD (40).

Increased expression of IL-22 has been found consistently in both psoriatic and AD lesions (46,47). IL-22, together with Th2 cytokines and IL-31, may differentially induce keratinocyte differentiation proteins and epidermal hyperplasia (48). Its role in driving the development of psoriasis vs. AD may depend on the presence or absence of specific cytokines (49). More recently, Bromley *et al.* (50) showed that the chemokine (c-c motif) receptor 2–deficient mice which were injected intradermally with IL-23, a cytokine that increases the expression of IL-17 and IL-22 that characterize psoriatic lesions, developed skin lesions that resembled AD with elevated number of eosinophils and increased expression of IL-22, TSLP, and IL-4. The study did not find increased infiltration of Th2 cells in the lesions, suggesting that IL-22 may provide feedback to innate cells to increase allergic inflammation, rather than antimicrobial response, in chemokine (c-c motif) receptor 2–deficient mice. The role of chemokine (c-c motif) receptor 2 and IL-22 in human AD will require further studies. Both $CD4^+$ T cells, which were induced by Langerhans cells and dermal DC (51), and $CD8^+$ T cells, are the major contributors of IL-22 expression in AD lesions (47,52).

ROLE OF MICROBIAL PATHOGENS

S. aureus, Malassezia species, and *Candida albicans* are important triggers of cutaneous inflammation of AD (3,53,54). These microbial pathogens may induce host production of superantigen- or pathogen-specific IgE, which leads to basophil activation and histamine release (55). *S. aureus* cell wall products also bind to TLR, leading to the production of TSLP by keratinocytes (56). In addition to superantigens, *S. aureus* also produces α-toxin, which may be particularly virulent in filaggrin-deficient keratinocytes that lack sphingomyelinase, an enzyme that is required to cleave α-toxin receptor (57). α-toxin may also increase the risk of viral infections including herpes simplex virus and vaccinia virus in AD, resulting in eczema herpeticum and eczema vaccinatum, respectively (58).

The persistent colonization of *S. aureus* and Malassezia species may be influenced by epigenetics and microbiome, which are emerging areas of research in AD (59–61). The fungus *Malassezia furfur* has been shown to induce histone acetylation of antimicrobial peptide genes in keratinocytes (62). Bacterial components have been found in deeper skin compartments including the dermis, suggesting that the microbiome of the skin may extend beyond the skin surface (63). A mouse model showed that *Staphylococcus epidermidis* differentially upregulates the expression of IL-17 in the skin, rather than in the gut (64), suggesting a specific role of this bacteria in skin immunity. It has been shown that *S. epidermidis* may produce its own antimicrobial peptides that modulate the survival of other cutaneous microbial pathogens (65,66). More recently, Kong *et al.* (67) showed that increased bacterial diversity on typically affected skin areas of AD children was linked to treatments, whereas decreased bacterial diversity was associated with increased AD severity and flare. The decrease in bacterial diversity during AD flare corresponds to an increase in *S. aureus* and *S. epidermidis* sequences (67). Whether this increase in *S. epidermidis* during AD flare represents a compensatory and antagonistic mechanism against *S. aureus* will require further studies.

CLINICAL IMPLICATIONS AND CHALLENGES

In addition to therapeutic potential, studies of genetic, cellular, or cytokine markers may lead to early identification of different phenotypes of AD. This may be crucial in preventing morbidities such as infections, psychosocial issues, and respiratory allergies. Testing for these markers should be relatively simple (e.g., a blood test or noninvasive testing of stratum corneum) and inexpensive to be practical for clinical use. Elevated IgE have been associated with skin infections, respiratory allergy, and severity of AD (68,69). The presence and increased levels of specific IgE against microbial allergens correlate with AD severity (70,71). However, these markers tend to have a later onset (>3 y old) (72). Recent studies have associated *FLG* with AD severity, persistence, skin infections, and food allergy (8,73). Therefore, *FLG* may be a potential prognostic marker for clinical use. Genetic variations in TSLP are also a potential candidate for AD severity and herpes simplex virus infections (74). Further studies are also needed to delineate the pathways of innate immunity leading to the cutaneous inflammation of AD. The presence of early markers may allow for early intervention to prevent complications of AD. Mechanistic studies may also result in safer agents that target the innate immune response. An example is coal tar, which has long been known to be an effective treatment for AD (75). However, the potential carcinogenic effects and appearance of coal tar have hampered its clinical use in AD. More recently, it has been shown that coal tar may increase the differentiation of keratinocytes and expression barrier proteins including filaggrin via the activation of aryl hydrocarbon receptor (76). The study also showed that coal tar increased filaggrin expression in the keratinocytes of AD patients who were heterozygous for *FLG*. Further studies in this area may result in more effective and safer treatments for AD.

CONCLUSION AND FUTURE DIRECTIONS

It is now well established that skin barrier defects are one of the primary causes of AD. *FLG* is first genetic marker of barrier defects that have been confirmed in the pathogenesis of AD. More recently, it has been shown that copy number variations of filaggrin genes may result in lower filaggrin expression and confer a risk for AD (77). Further studies are needed to search for therapies that increase filaggrin expression in these patients. However, since the majority of AD patients do not carry *FLG*, the search for other causes of AD is needed. Genetic variations may exist in other skin barrier molecules or in the cutaneous immune response of AD. Molecular or cellular components for microbial sensing such as TLR (78–80), or skin tissue repair such as TSLP and ILC (28), deserve further studies. Prospective clinical studies are needed to correlate laboratory markers with development of moderate to severe AD and complications of AD. Studies on early implementation of anti-inflammatory therapies or barrier repair are needed for the prevention of AD complications.

ACKNOWLEDGMENTS

I wish to thank Rosemary Hernandez and Evelyn Ong for their assistance in the preparation of Figure 1.

STATEMENT OF FINANCIAL SUPPORT

None declared.

Disclosure: none.

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