

Contrasting pathogenesis of atopic dermatitis and psoriasis—Part I: Clinical and pathologic concepts

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Atopic dermatitis and psoriasis are 2 of the most common inflammatory skin diseases. They are similar in that they are complex inherited diseases involving genes that encode immune components and structural proteins that regulate differentiation of epidermal cells. Each disease is characterized by proliferation of epidermal keratinocytes and abnormal cornification or terminal differentiation in the epidermis; skin lesions contain immune infiltrates of T cells, dendritic cells, and other types of leukocytes. We review similarities between the diseases and differences in epidermal barrier defects and immune cells. We also propose mechanisms of pathogenesis based on differences in the balance of immune cell subsets that could cause the phenotypes that distinguish these diseases. The first part of this 2-part review focuses on the clinical and pathologic features of the diseases; the second part discusses differences in immune cell subsets between atopic dermatitis and psoriasis and recent therapeutic strategies. (*J Allergy Clin Immunol* 2011;■■■■:■■■■-■■■■.)

Key words: Atopic dermatitis, psoriasis, pathogenesis, therapy

This is part 1 of a 2-part review. Part 2 can be found in the June 2011 issue of the JACI.¹

Atopic dermatitis (AD) and psoriasis are 2 of the most common inflammatory skin diseases. Although they are believed to be mediated by different subsets of T_H cells (T_H1 vs T_H2), they have many similar features (Table I). We review pathogenesis and therapeutic approaches for AD using psoriasis as a point of reference. Psoriasis is similar to AD in its immune and barrier (epidermal) defects, but studies of immune-targeted therapeutics established it as a primarily immune-mediated disease that alters epithelial biology, causing keratinocyte proliferation and barrier defects.²⁻⁴ AD, particularly in its chronic phase, shares many characteristics with psoriasis, including epidermal hyperplasia, altered terminal

Abbreviations used

AD: Atopic dermatitis
CE: Cornified envelope
DC: Dendritic cell
EDC: Epidermal differentiation complex gene
FLG: Filaggrin gene
LCE: Late cornified envelope gene
SC: Stratum corneum
Treg: Regulatory T

differentiation of keratinocytes, and infiltrates of T cells and dendritic cells (DCs).^{5,6} AD might therefore be an immune-mediated disorder, with secondary barrier defects; the order of events in its pathogenesis must be resolved.^{7,8}

There are 2 forms of AD: 80% of AD cases are extrinsic and characterized by high IgE levels and eosinophil numbers in the peripheral circulation; the remaining 20% of patients have intrinsic AD, with normal IgE levels and eosinophil numbers.⁹ Because little is known about the immune abnormalities and genetic factors that mediate intrinsic AD, this review is focused on extrinsic AD.

EPIDEMIOLOGY

AD has a prevalence of up to 3% among adults and up to 25% among children.^{10,11} Approximately 85% of cases begin during early childhood (early-onset AD; Table I), although adult-onset AD also occurs. Whereas symptoms of early-onset AD usually improve during adolescence, as many as 33% of cases persist into adulthood. Nearly 80% of the children with AD also subsequently have asthma or allergic rhinitis later in life, which is commonly referred to as the atopic march or atopy.¹²

The prevalence of AD has increased 2- to 3-fold during the last century in industrial countries but remains much lower in agricultural areas. This has led to the hygiene hypothesis, in which the lack of the environmental stimuli required to activate a strong T_H1 response in early childhood results in continuous activation of the proallergic T_H2 response, which eventually leads to atopy.¹³⁻¹⁵ This model led to attempts to activate a T_H1 response in infants with atopy with the goal of rebalancing T_H1 and T_H2 immune responses, but this approach was not effective in reducing atopy.¹⁶

By contrast, psoriasis has an estimated worldwide prevalence of 2%.^{4,17} Interestingly, unlike AD, its incidence has not changed significantly in the last decades.¹⁶ Psoriasis commonly starts later in life, during adolescence or early adulthood, and does not usually improve with age (Table I). Psoriasis is associated with psoriatic arthritis but not atopy (Table I).^{4,18}

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TABLE I. Clinical, histologic, and immunologic differences between AD and psoriasis: differences in the clinical features of AD and psoriasis (A), differences in histology between AD and psoriasis (B), differences in immune infiltrates in lesional skin of patients with AD versus psoriasis (C), and differences in numbers of circulating leukocytes between patients with AD versus those with psoriasis (D)

AD	Psoriasis
A. Clinical features	
85% onset before age 5 y	Onset in adolescence or early adulthood common
Common association with asthma/atopy	Not associated with asthma/atopy
Oozing, “wet” skin lesions in acute stage, with crusting and serous exudate	Dry lesions
Not well demarcated from uninvolved skin	Sharply demarcated stable plaques
Face and flexors usually affected	Scalp and extensors (knees and elbows) often involved
Fine white scale (adherent)	Thick, silvery-white scale (nonadherent)
Prominent itch with excoriations	Rarely itchy
Lichenification evident in chronic stage from itch-scratch cycle	Very thick plaques caused by heavy scale accumulation
Pink to dull-red plaques	Bright-red plaques
Frequent impetiginization	Impetigo not evident
Viral dissemination common (eczema herpeticum)	No risk for viral dissemination
B. Histology	
Barrier defect: decreased cornification, decreased expression of terminal differentiation proteins, decreased lipids	Increased cornification, increased expression of terminal differentiation proteins, decreased lipids in intracellular space of SC
Spongiosis and vesicle formation in acute/subacute stages	No spongiosis seen, small pustules, Kogoj and Munro microabscesses
No neutrophils in epidermis	Accumulation of neutrophils in epidermis
Increased eosinophil and mast cell numbers in dermis	No eosinophils and mast cells
Orthokeratosis is typical	Parakeratosis is prominent and might be confluent
Hypogranulosis, sometimes absent granular layer	Hypogranulosis, granular layer might be completely absent with confluent parakeratosis
Rare thinning of suprapapillary plates	Thinning of suprapapillary plates
Few blood vessels in dermal papillae	Dilated tortuous vessels in dermal papillae
Evidence of vasodilation but no angiogenesis	Vasodilation and angiogenesis well documented
High frequency of bacterial colonization	Low frequency of bacterial colonization
C. Lesional immune infiltrates	
T _H 2/“T22” polarization (Tc22>Th22); lower T _H 1 component in chronic disease	T _H 1/T _H 17 polarization with T _H 22 present
Attenuated T _H 17 pathway	Increased T _H 17 pathway
Reduced antimicrobial axis	Increased production of antimicrobial agents
Inflammatory DCs in dermis > epidermis producing CCL17, CCL18, and CCL22	Inducible nitric oxide synthase, TNF- α , and IL-23 producing inflammatory DCs in dermis
D. Leukocytes in circulation	
T _H 2 > T _H 1 and T _H 17	Increased T _H 1, T _H 17 and T _H 22
Increased IgE levels and eosinophil numbers in circulation	Normal IgE levels and eosinophil numbers
IgE autoantibodies correlated with disease activity	Autoantibodies uncommon

CLINICAL AND HISTOLOGIC CHARACTERISTICS

Although AD and psoriasis are clinically different, their chronic stages have many histologic similarities, including increased epidermal hyperplasia and infiltrates of large numbers of T cells and DCs (Table I).^{5,6} Genomic studies have shown that genes that regulate proliferation of epidermal cells are upregulated in both diseases.^{5,19}

AD is characterized by highly pruritic, eczematous (wet) erythematous plaques with excoriated papules, crusts, and serous exudate, most commonly on flexural areas and the face (Table I).^{11,20} Erythematous plaques and scales also develop in patients with psoriasis, but features of the scales differ between diseases (Fig 1 and Table I).

Psoriasis is characterized by well-demarcated, dry, bright-red plaques with thick, nonadherent, silvery-white scales, usually on extensor surfaces and the scalp (Fig 1). Nail changes (pits, oil spots, or onycholysis) are characteristics of psoriasis.²¹ Unlike the intractable pruritus that develops in patients with AD, psoriasis is often not itchy (Table I).^{4,22} However, a subset of patients

with psoriasis have lesions that look like eczema: they do not have the typical, heavy scaly characteristics of psoriasis. Histologically, these cases might represent psoriasiform dermatitis, possibly an eczematous variant, and patients with this variant can complain of itching. Conversely, a subset of patients with AD have plaque-type psoriasiform lesions.

Whereas new psoriatic lesions usually appear similar to chronic lesions, AD has distinct acute and chronic stages. During the acute stage (varies in definition, ranging from a few hours to a few days), the skin lesions are bright-red oozing lesions with serous exudate. During the chronic stage, the lesions become pink to dull-red, lichenified plaques (Fig 1 and Table I). AD skin lesions are prone to bacterial impetiginization and viral infections (eg, eczema herpeticum), but these are not features of psoriatic lesions (Table I).²³⁻²⁵

The diseases share barrier abnormalities, although there are differences (Fig 2, A).¹⁹ AD skin lesions have reduced terminal differentiation of keratinocytes, decreased cornification, and reduced levels of lipids.^{19,26-28} In contrast, psoriatic lesions have increased cornification and expression of terminal differentiation



FIG 1. Different skin features of AD and psoriasis. Although erythematous plaques develop in patients with either disease, their quality and scale vary. Psoriasis is characterized by well-demarcated, dry, bright-red plaques with thick, nonadherent, silvery-white scales, usually on the extensor surfaces. AD lesions are dull-red lichenified plaques, with nonadherent white scales appearing mostly on flexor areas.

proteins, with reduced lipids in the intracellular spaces of the stratum corneum (SC; Table I).^{19,24,29,30}

Histologic analysis of acute AD tissue samples shows acute eczematous dermatitis with a highly spongiotic epidermis, whereas that of chronic AD tissue samples shows a resemblance to psoriasis and a hyperplastic epidermis with much less spongiosis (Fig 2 and Table I).^{11,19} Although AD is characterized by increased numbers of eosinophils and mast cells, psoriasis is associated with accumulation of neutrophils in the epidermis and formation of Kogoj and Munro microabscesses (Table I).^{4,31} Although hyperkeratosis is a feature of both diseases, patients with AD primarily have orthokeratosis, which is defined as an absence of nuclei from the SC cells. Patients with psoriasis, on the other hand, have prominent and, at times, confluent parakeratosis (ie, keratinization characterized by retention of nuclei in the SC; Fig 2 and Table I).^{11,30,31} Hypogranulosis commonly develops in both diseases, but AD ranges from hypogranulosis to a normal granular layer (Fig 2). Although both diseases are characterized by vasodilation, angiogenesis (new vessel growth) occurs only in patients with psoriasis (Table I).³²⁻³⁴

SKIN-SPECIFIC AND SYSTEMIC IMMUNE RESPONSES

AD and psoriasis are characterized by infiltration of the skin with T cells and dermal DCs (Fig 3), but different subsets of each cell type are associated with each disease (Table I).^{5,31,35} Differences in types of T-cell infiltrate could account for the decreased expression of antimicrobial proteins in patients with AD compared with psoriasis and the increased susceptibility to infections (Table I).^{6,23,25,36,37} Likewise, subsets of circulating leukocytes, levels of IgE, and autoantibodies are different in each disease (Table I).³⁸⁻⁴²

GENETICS

AD and psoriasis are familial diseases based on analyses of twins and families^{4,11,31,43-46}; they are genetically complex, are

multifactorial, and do not follow a Mendelian pattern of inheritance. About 33% of patients with psoriasis have a family history, whereas the percentage is much higher for patients with AD.³¹ A recent twin study determined that 82% of AD risk is determined by genetic factors and 18% by environmental factors.⁴⁷

Table II lists AD- and psoriasis-associated genes that have been identified in 2 or more studies. These genes encode factors in the adaptive and innate immune system and proteins that regulate terminal differentiation of keratinocytes (Table II). The genes most consistently associated with each disease encode factors with functional relationships to the disease that could be linked to immune and barrier defects.^{44,46,48-50} AD was associated with cytokines and chemokines expressed by T_H2 cells, such as *IL4*, *IL4RA*, *IL13*, and *RANTES/CCL5*, whereas psoriasis was associated with cytokines linked to T_H1 and T_H17 cells, such as *IL12B*, *IL23A*, and *IL23R* (Table II). Genetic association studies support a role for a number of genes that encode factors in the innate immune system in patients with AD that might have a role in susceptibility to infections, such as *NOD1*, *NOD2*, *TLR2*, *CD14*, and *DEFB1* (Table II). Psoriasis was associated with the innate immune response genes *TNFAIP3* and *TNIP1*, which participate in TNF signaling and regulation of the transcription factor nuclear factor κ B.^{49,51} Psoriasis and AD have been associated with genes encoded by the epidermal differentiation complex (EDC) locus on chromosome 1q21; variants in genes at this locus (*SPINK5*, loricrin [*LOR*], and involucrin [*IVL*]; filaggrin [*FLG*] in AD) could lead to alterations in terminal differentiation of keratinocytes.^{52,53} Deletion of the genes late cornified envelope 3B (*LCE3B*) and *LCE3C* in the EDC increases the risk for psoriasis.^{54,55}

Loss-of-function mutations in the gene *FLG*, which encodes the intermediate-filament protein filaggrin, were found in 10% to 50% of patients with AD, with regional variations.⁵⁶⁻⁵⁹ In contrast, mutations in *FLG* are not believed to determine susceptibility to psoriasis.⁶⁰ However, loss of filaggrin function cannot entirely account for the epidermal barrier defects that arise in patients with AD because these mutations are found in subjects who do not have AD (*FLG* is also associated with ichthyosis vulgaris), and some individuals with the mutations develop AD and then later recover from the disease. Other genetic factors are involved because in some populations only 10% of patients with AD carry the mutation.^{26,61,62}

CELL BIOLOGY

AD is a multifactorial disease that arises from complex interactions between genetic and environmental factors, as well as features of immune cells, IgE production, and skin cells.^{23,45,63} The etiology of AD is not fully understood. There are 2 models of pathogenesis.²⁰ In an outside-in model genetic defects that affect the cornification process result in abnormal skin cell proliferation and differentiation, allowing its penetration by large immunogenic proteins and subsequent immune activation.^{26,28} In an inside-out model activation of T_H2 cells and the T22 pathway result in reactive epidermal hyperplasia.^{23,64,65}

In the outside-in model barrier dysfunction is the main culprit. The model is supported by the association of AD with mutations in *FLG* and abnormal synthesis of lipids in affected and unaffected AD skin.^{26,28,66} Some patients with AD have an abnormal nonlesional phenotype,⁶⁷⁻⁶⁹ but it is not clear whether these patients express functional forms of filaggrin.

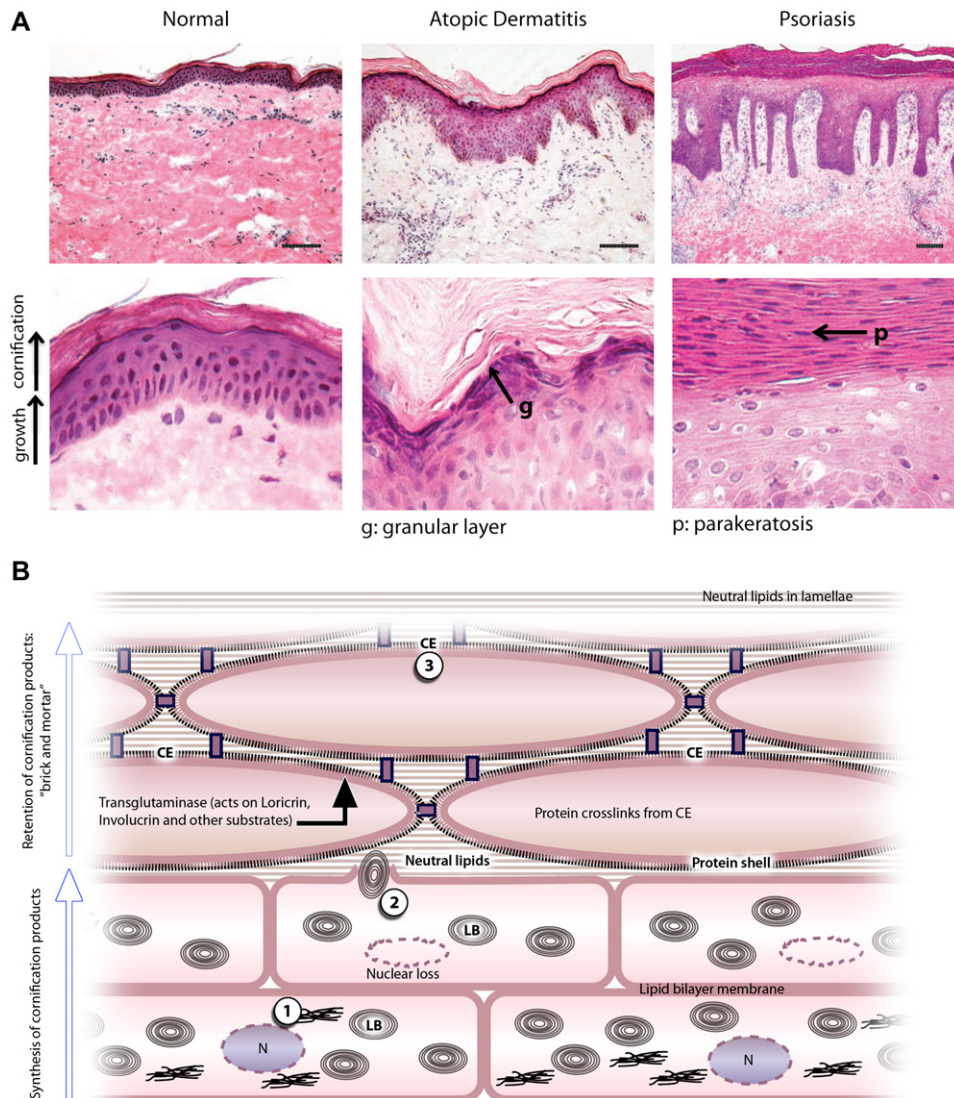


FIG 2. **A**, Normal skin growth and differentiation patterns compared with those of patients with AD and psoriasis. Whereas the epidermis of patients with AD and psoriasis had marked hyperplasia and hyperkeratosis, few distinctive features are shown. In patients with AD, there is a visible granular layer, whereas patients with psoriasis lack this layer. Additionally, patients with AD have orthokeratosis, whereas those with psoriasis have parakeratosis. **B**, Formation of the epidermal barrier and the basis for barrier disruption in patients with AD. Psoriasis and AD are characterized by disrupted terminal differentiation of keratinocytes in lesional skin. (1) In the process of terminal differentiation of keratinocytes in normal skin, filaggrin, an intermediate-filament protein that regulates differentiation of the epidermis, creates a template for the assembly of the CE. Neutral lipids are contained by lamellar bodies (2). Within the SC, a brick-and-mortar structure, the keratin is encapsulated within a protein shell, the CE, created by cross-linked proteins (3).

DISRUPTION OF THE EPIDERMAL BARRIER

Psoriasis and AD are characterized by disrupted terminal differentiation of keratinocytes in lesional skin.^{19,28,29,70,71} It is necessary to understand how terminal differentiation of keratinocytes creates a skin barrier to understand the physiological relevance of this alteration. The SC is the outermost layer of the skin: it forms a permeability barrier that consists of multiple layers of flattened, enucleated (orthokeratotic) corneocytes surrounded by multiple lamellae that contain neutral lipids, including ceramides, cholesterol, and free fatty acids.^{28,30,72,73} Within the SC, the keratin is encapsulated in a protein shell named the cornified envelope (CE). The CE is 15 to 20 nm thick and

composed of structural proteins and a specialized lipid layer.^{29,30} The structural proteins that comprise the CE include loricrin (small proline-rich proteins) and involucrin; these are cross-linked by disulfide bonds and γ -glutamyl-lysine bonds through the action of transglutaminases. This cross-linking makes the CE an insoluble structure.^{28,30}

Specialized proteins, particularly corneodesmosin, have an important role in corneocyte cohesion.^{29,30} During the process of final terminal differentiation or cornification, keratin filaments are aggregated into tight bundles by filaggrin (Fig 2, B).²⁸⁻³⁰ This promotes the flattening of the keratinocytes into their characteristic shape in the SC (Fig 2, B). Filaggrin is therefore a key protein

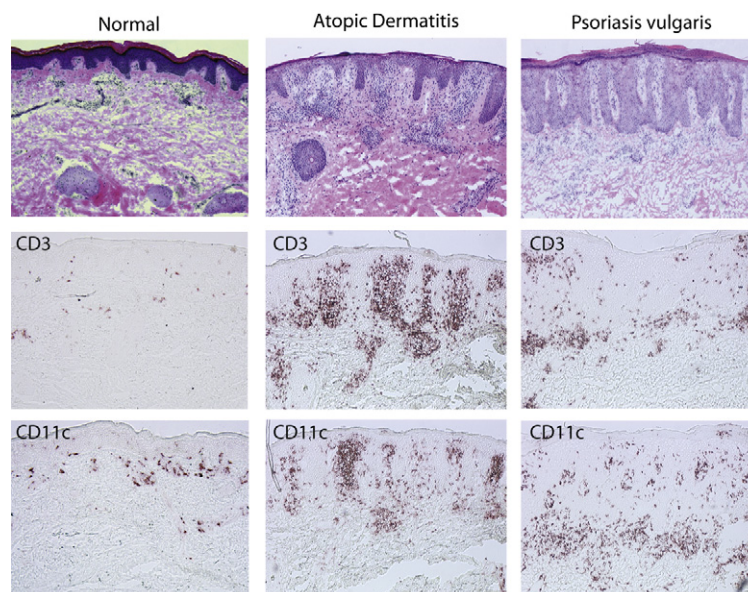


FIG 3. Histologic differences between normal skin, AD skin, and psoriatic skin by means of staining with hematoxylin and eosin and immunohistochemistry staining for T cells (CD3) and myeloid DCs (CD11c). Although more evident in patients with psoriasis, both diseases result in a hyperplastic epidermis, with a marked infiltrate in the superficial dermis. Both diseases are characterized by large infiltrates of T cells and DCs, as seen with CD3 and CD11c immunohistochemistry staining, respectively.

in epidermal differentiation, creating a template for the assembly of the CE. Furthermore, filaggrin metabolites act as osmolytes, drawing water into the SC and promoting its hydration.^{28,29}

The SC has been conceptualized as a brick-and-mortar structure in which the noncontinuous, mainly proteinaceous corneocytes (bricks) are embedded in a continuous specialized matrix of lipids (mortar). These lipids provide a barrier against water, whereas terminally differentiated keratinocytes (or corneocytes) protect against mechanical or chemical injury (Fig 2, B).^{29,34,72} Most SC lipids are derived from the contents of the lamellar bodies formed in the keratinocytes of stratum spinosum and granulosum (the uppermost layers of the still-viable epidermis). Through secretion of lamellar bodies at the interface between the stratum granulosum and the SC, these lipids are enzymatically cleaved to generate free fatty acids and ceramides.^{26,29,34} These components fuse together to form the characteristic continuous lamellar bilayers that allow the SC to prevent water loss through the epidermis (Fig 2, B).^{26,28,29}

Barrier defects in patients with AD and psoriasis

The chronic stages of AD and psoriasis are characterized by scaly erythematous plaques (Fig 1); biopsy analysis of skin reveals large amounts of epidermal hyperplasia (Fig 2, A). It is sometimes a challenge to differentiate between these diseases.^{5,6} However, the epidermal hyperplasias observed in patients with AD and psoriasis have major differences. Although the diseases each have defects in regenerative epidermal growth and maturation responses based on similar levels of epidermal hyperplasia and expression of keratin 16, they have different expression patterns of genes that control terminal differentiation of the epidermis.¹⁹ In patients with AD, there are defects in expression of a large set of genes that encode factors that control terminal differentiation and cornification (loricrin, filaggrin, involucrin, and

TABLE II. Genetic and pathogenic factors associated with AD and psoriasis

Adaptive immune response genes	
Atopic dermatitis	Psoriasis
<i>IL4</i>	<i>HLA-C/PSORS1/CCHCR1</i>
<i>IL4RA</i>	<i>IL12B (p40)</i>
<i>IL13</i>	<i>IL23R</i>
<i>CMA1</i> (mast cell chymase)	<i>IL23A</i>
<i>IL18</i>	<i>IL4/IL13</i>
<i>RANTES (CCL5)</i>	
Innate immune response genes	
Atopic dermatitis	Psoriasis
<i>NOD1, NOD2</i>	<i>TNFAIP3</i>
<i>TLR2</i>	<i>TNIP1</i>
<i>CD14</i>	
<i>DEFB1</i>	
Terminal differentiation genes	
Atopic dermatitis	Psoriasis
<i>SPINK5</i> (serine protease inhibitor, chromosome 5q32)	<i>LCE3B</i>
<i>FLG</i> (2 null mutations; most consistently associated)	<i>LCE3C</i>
<i>LOR</i> and <i>IVL</i> (chromosome 1q2116)	

All genes in this table were replicated in more than 1 study. The genetic associations for both diseases are divided according to adaptive immune response genes, innate immune response genes, and genes of terminal differentiation.

periplakin) compared with expression seen in patients with psoriasis. Ultrastructural analysis showed that AD lesions have reduced compaction of corneocytes and levels of intercellular lipids, as well as disruption of the CE and degradation of corneodesmosomes. The entire terminal differentiation program is therefore defective in patients with AD but accelerated in patients with psoriasis.¹⁹ These findings do not tell us whether AD arises through an inside-out or outside-in pathway, but they raise question of

whether the models could be reconciled by a link between immune and barrier dysfunctions.

Mutations in *FLG*

AD is associated with defective expression of functional filaggrin by keratinocytes, supporting the barrier (outside-in) model.^{26,28,56,74} Ten percent to 50% of patients with AD have 1 of 2 loss-of-function mutations in *FLG*.^{26,56,75} Although filaggrin deficiency is believed to cause defects in the permeability barrier, the cellular basis for these abnormalities has not been determined.⁵⁶ Mice that express low levels of filaggrin have flaky skin on their tails, and the barrier abnormality reduces the threshold for an inflammatory response to topical irritants and allergens.⁷⁶ Loss of filaggrin from human skin alters the shape of corneocytes, perhaps disrupting extracellular lamellar organization and the overall barrier.^{28,56} It was proposed that in patients with AD, barrier disruption could lead to inflammation through activation of IL-1 and other factors in the innate immune system, as well as increased skin penetration by antigens that selectively activate T_H2-mediated adaptive immune responses.²⁸ The first mechanism (barrier disruption) is supported by experiments in which the SC was disrupted with tape stripping, which caused rapid increases in levels of IL-1 and other innate cytokines.⁷⁷ Barrier disruption also induced epidermal hyperplasia.^{34,78} The second part of the outside-in hypothesis, namely that antigen exposure through a defective barrier will promote T_H2 immune activation, does not have as much experimental support. Exposure to topical antigens has been shown to generate nonselective T_H1, T_H2, and T_H17 cell responses in mice.⁷⁹

It is not clear that defects in filaggrin function or the barrier itself are the primary cause of AD. Mutations in *FLG* are found in only 10% to 50% of patients with AD, and those that carry the mutation eventually recover from the disease.⁸⁰ Furthermore, *FLG* mutations are also associated with ichthyosis vulgaris, and therefore altered filaggrin function can result in different phenotypes.^{61,81} Patients with AD have a broad range of barrier defects; many of the proteins that regulate terminal differentiation are also affected (eg, loricrin, involucrin, periplakin, and transglutaminase), indicating a reactive epidermal response to an immune stimuli.¹⁹ Topical inhibitors of calcineurin can partially correct the barrier abnormality, and gentamicin can partially restore filaggrin production, indicating a reactive barrier defect to an immune abnormality.^{23,82}

INSIDE-OUT MODEL: IMMUNE ALTERATIONS IN PATIENTS WITH AD

In the first working model of AD, IgE was believed to be the key mediator, and therefore the disease was grouped with atopy, such as asthma, allergic rhinitis, and hay fever (all have increased production of IgE against allergens). In this model of AD, B cells produced increased levels of IgE against various antigens after their inhalation, ingestion, or entrance through the epidermis. The receptor for IgE (FcεRI) is present on surfaces of mast cells and basophils; IgE binding to this receptor causes release of histamine and vasoactive factors that mediate allergic inflammation.^{58,83-86} Eosinophils are also involved in the development of subsequent allergic reactions that contribute to tissue damage.⁸⁷

There is evidence that autoreactive IgEs develop in patients with AD and might be associated with disease severity.³⁸⁻⁴¹ The

prevalence of IgE sensitization to self-antigens among patients with AD ranges from 8.7% to 29%. Recombinant human self-antigens with high levels of homology to environmental allergens bind IgE from sera of patients with AD; they also induce immediate type I hypersensitivity reactions in skin from only patients sensitized to the corresponding homologous environmental allergen. Several self-antigens have been described, such as *Homo sapiens* IgE-binding self antigens (Hom s) 1, 2, 3, and 5.³⁸⁻⁴¹

There are at least 2 mechanisms by which autoreactive IgE might lead to the development of AD. First, autoallergens might bind to IgEs that are cross-linked to effector cells, leading to release of inflammatory factors and immediate-type allergy symptoms. Second, autoreactive T cells might become activated by IgE-mediated presentation of autoallergens or by non-IgE-dependent mechanisms. Autoantibodies have been detected in patients with psoriasis, including antinuclear antibodies, antibodies to small nuclear and cytoplasmic ribonucleoproteins, and antibodies to epidermal cells.⁸⁷ However, these were not found to have a role in the pathogenesis of psoriasis.

With discovery of distinct subsets of T_H cells, namely T_H1 and T_H2 cells, a T_H2 cell-based model has emerged for pathogenesis of allergic inflammation. In this model T_H2 cells become activated, produce cytokines (eg, IL-4, IL-5, IL-10, IL-13, and IL-31), and promote antibody responses that include IgE isotype switching and mast cell and eosinophil differentiation and activation.^{13,86} T_H2 cell activation in patients with AD would account for the increased levels of IgE observed because IL-4 and IL-13 regulate IgE class switching.^{13,84,88} In this model T-cell products recruit and activate mast cells and eosinophils, but there is no direct reorganization of tissue structure in the skin.

There are several observations that argue against IgE as the mediator of AD pathogenesis. Signal transducer and activator of transcription 6-deficient mice that express transgenic IL-18 develop AD-like lesions despite the absence of IgE and production of high levels of IL-18.⁸⁹ Furthermore, patients with severe AD who are treated with the T-cell suppressant cyclosporine A recover from the disease, despite unchanged and even increased levels of IgE.^{90,91} Clinical trials of recombinant IFN-γ for severe AD improved symptoms in a subset of patients without changes in IgE levels.^{16,92} Finally, omalizumab (an mAb against IgE) induces downregulation of IgE and FcεRI on DCs in patients with AD but does not decrease disease activity.^{93,94} Omalizumab was effective in trials of asthmatic patients, indicating a role for IgE in asthma but not AD.⁹⁵ However, other small studies have indicated that omalizumab is effective in treating AD.^{96,97} Further studies of the role of IgE in AD are needed: IgE levels are higher in patients with AD, and therefore it might be more difficult to neutralize the antibody and reduce symptoms of AD.

It is possible that T_H2 cells mediate pathogenesis of AD and that high-level production of IgE occurs after production of IL-4 by activated T_H2 cells.^{11,20,23,98} This model is supported by the large numbers of T_H2 cells detected in the skin of patients with AD and the large increases in expression of T_H2 cytokines. Patients with mild-to-moderate and moderate-to-severe AD respond to topical and oral therapies, respectively, that inhibit T-cell activity, such as pimecrolimus and tacrolimus (topical) and cyclosporine A (oral calcineurin inhibitor). Antagonists of T cells, such as alefacept and efalizumab, reduced symptoms of AD in patients.^{82,99,100} Unfortunately, these studies evaluated mostly clinical parameters and lacked mechanistic analyses, such as measurements of T-cell markers before and after

treatment; such studies are needed to correlate T-cell suppression with clinical response. However, a few studies have shown that topical^{99,101} or systemic¹⁰² reagents that target T-cell activity reduce production of T_H2-associated cytokines.

T_H2 POLARIZATION AND THE HYGIENE HYPOTHESIS

AD and psoriasis are characterized by chronic inflammation of the skin, with large infiltrates of T cells, which is considered to be a pathogenic element of both diseases (Fig 3).^{2,5,31,103} Historically, AD has been associated with a T_H2 cell-mediated immune response (production of IL-4, IL-5, and IL-13), whereas psoriasis has been associated with a T_H1 cell-mediated immune response (production of IFN- γ and IL-2).^{3,22,23,31,104} The discovery of new subsets of immune cells has expanded models of pathogenesis beyond T_H1-mediated versus T_H2-mediated disease, although the hygiene hypothesis is associated mainly with these immune subsets.

Epidemiologic studies have associated children in Western countries with reduced exposure to bacteria compared with children in other areas, with increases in the severity and prevalence of AD.^{13,14,23,105} These findings support a hygiene hypothesis in which low levels of exposure to bacteria during childhood reduce activation of T_H1 cells, leading to expansion of the T_H2 cell population and diseases such as AD. Many studies support this model.^{13,106,107} Also, lack of exposure to bacteria prevents activation of regulatory T (Treg) cells, which also promotes T_H2 cell-mediated immune responses.^{13,14,108-110} Although pathogenesis of AD might involve T_H2 cell activation and defects in the population of Treg cells, this mechanism has also been proposed to account for the uncontrolled activation of T_H1 cells in patients with psoriasis.¹¹¹ Defective Treg cell function could be important for both diseases, although it seems unlikely that it is sufficient to increase activation of T_H2 cells to the levels observed in patients with AD.

In an extension of the hygiene hypothesis, vaccination during infancy might affect the risk for atopy. Vaccines that promote T_H1 cell responses, such as BCG, or T_H2 cell responses, such as pertussis or measles, could increase or decrease T_H2 cell-mediated inflammation and increase the risk for disorders such as AD.¹¹²⁻¹¹⁴ The effects of infant vaccination on development of the T_H1 and T_H2 cell-mediated immune responses are controversial and require much further study.¹¹²⁻¹¹⁵

The hygiene hypothesis proposes that lack of exposure to environmental antigens leads to reduced T_H1 cell-mediated immunity and thereby increased activation of T_H2 cells. Genes associated with AD can also influence T_H2 cell activity and increase IgE production to specific antigens. Delayed maturation of T_H1 cells in children at high risk for atopy was associated with attenuated memory T_H2 cell responses to diphtheria and tetanus vaccines, reduced humoral immune responses to pneumococcal vaccine, reduced capacity to generate stable memory T_H1 cells that recognize the BCG vaccine, and increased susceptibility to severe infection with respiratory syncytial virus.^{112,114} Studies in mice indicated that the increased susceptibility to infection with respiratory syncytial virus resulted from an initial T_H2 cell-mediated host adaptive immune response in the postnatal period that prevented development of an effective memory T_H1 cell response against reinfection. The immunomodulatory effects of vaccines and pathogens are affected by genetic variants; different

populations, such as Africans and Scandinavians, have different immune responses to vaccines.^{112,114} However, childhood vaccines are not believed to promote allergy: vaccinated children might actually be better protected against the development of atopy.^{113,114}

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