

Contrasting pathogenesis of atopic dermatitis and psoriasis—Part II: Immune cell subsets and therapeutic concepts

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Atopic dermatitis (AD) and psoriasis are among the most common inflammatory skin diseases. In the first part of this 2-part review, we discussed the similarities and differences between AD and psoriasis with respect to clinical features and pathology. The diseases are characterized by infiltration of skin lesions by large numbers of inflammatory cells; the second part of this review focuses on immune cell subsets that distinguish each disease and the therapeutic strategies that might be used or developed based on this information. We discuss the interactions among different populations of immune cells that ultimately create the complex inflammatory phenotype of AD and compare these with psoriasis. Therapeutic strategies have been developed for psoriasis based on the cytokine network that promotes inflammation in this disease. Antibodies against IL-12 and IL-23p40 antibody and antagonists of TNF are used to treat patients with psoriasis, and studies are underway to test specific antagonists of IL-23, IL-17, IL-17 receptor, IL-20, and IL-22. We discuss how these therapeutic approaches might be applied to AD. (*J Allergy Clin Immunol* 2011;■■■:■■■-■■■.)

Key words: Atopic dermatitis, psoriasis, pathogenesis, therapy

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

Atopic dermatitis (AD) and psoriasis are characterized by infiltration of skin lesions by large numbers of T cells, dendritic cells (DCs), and other inflammatory cells (see Fig 3 in part 1 of the review¹).²⁻⁷ We discuss the immune cells and factors that mediate the inflammation associated with AD (Fig 1).

T CELLS

Recruitment of T cells into the skin and their effector responses are considered to be key features in the pathogenesis of AD and psoriasis.^{4,8-10} In both diseases T cells that bear a specialized skin-homing receptor, the cutaneous lymphocyte antigen (CLA), are present in skin lesions. This antigen is defined by the mAb

Abbreviations used

AD:	Atopic dermatitis
AMP:	Antimicrobial protein
CLA:	Cutaneous lymphocyte antigen
CsA:	Cyclosporine A
DC:	Dendritic cell
DC-LAMP:	Lysosome-associated membrane glycoprotein, dendritic cell-specific
dDC:	Dermal dendritic cell
FDA:	US Food and Drug Administration
IDC:	Inflammatory dendritic cell
IDEC:	Inflammatory dendritic epidermal cell
LC:	Langerhans cell
MCC:	Mast cell chymase
mDC:	Myeloid dendritic cell
OX40L:	OX40 ligand
pDC:	Plasmacytoid dendritic cell
TIP-DC:	TNF and iNOS-producing dendritic cell
TLR:	Toll-like receptor
Treg:	Regulatory T
TSLP:	Thymic stromal lymphopoietin

HECA-452.¹¹ Most CLA⁺ T cells reside in normal skin, with only a small fraction in the peripheral circulation; AD and psoriasis involve expansion of CLA⁺ cell subsets.^{12,13} However, the diseases differ in the subset of immune cells that localize to inflamed skin and mediate their clinical differences.

T_H1 and T_H2 cells

Psoriasis and AD were considered to be opposing diseases in that one was believed to be mediated by T_H1 cells and the other by T_H2 cells, respectively (referred to as polarization of the T_H response). Distinct populations of T cells are defined by their unique patterns of cytokine production. T_H1 cells produce IFN- γ , whereas T_H2 cells produce IL-4, IL-5, and IL-13.^{7,14}

T_H2-associated cytokines regulate important barrier-related functions, such as epidermal cornification and production of antimicrobial proteins (AMPs; Fig 2, A).¹⁵⁻¹⁷ They also inhibit the production of major terminal differentiation proteins, such as loricrin, filaggrin, involucrin, and the AMPs Human Beta Defensin 2 and 3, which are associated with AD.^{15,17,18} However, overproduction of cytokines by T_H2 cells cannot account for the hyperplasia of epidermal keratinocytes observed in patients with chronic AD.¹⁹ The original hypothesis, that AD was mediated by T_H2 cell activity, was modified when the T_H17 and T22 cell subsets were associated with epidermal activation.^{20,21}

T_H17 cells

T_H17 cells produce IL-17 and IL-22.²² IL-17 is an important regulator of antimicrobial peptides in keratinocytes.^{14,23} T_H17

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Inflammatory Products of Leukocyte Infiltrates in AD Lesions					
Mast cell	Eosinophil	Dendritic cell	T _H 2	Inflammatory T _H 2	T _H 22
					
IL-5 IL-6 IL-4 IL-13 IL-31 GM-CSF Histamine PGD ₂ Tryptase	MBP PAF LKT IL-1 IL-3 IL-4 IL-5 IL-6 IL-10 GM-CSF TNF α Toxic O ₂ metabolites	CCL17 CCL18 CCL22 Eotaxin2	IL-4 IL-13 IL-5 IL-10 IL-31	IL-4 IL-5 IL-13 No IL-10	IL-22

FIG 1. Cellular and inflammatory factors in AD lesions. TSLP induction of T_H2 cells (proinflammatory) causes them to produce the cytokines IL-4, IL-5, IL-13, and TNF- α but not IL-10. The T_H22 subset of T cells produces only IL-22. MBP, Major basic protein; PAF, platelet-activating factor; PGD₂, prostaglandin D₂.

cells contribute to the pathogenesis of psoriasis, mediating neutrophil chemotaxis and increased production of antimicrobial peptides (Fig 2 B, and see Table I in part 1 of this review¹).^{24,25} However, until recently, their role in AD was not clear.

Immunohistochemical studies showed increased numbers of T_H17 cells in the peripheral blood of patients with acute AD²⁶ and in acute skin lesions.²⁷ However, T_H17 cell production of IL-17 was found to be reduced in patients with chronic AD compared with that seen in patients with chronic psoriasis (Fig 2, A).¹⁴ Moreover, a deficiency in AMPs was reported in patients with acute or chronic AD compared with that seen in patients with psoriasis.^{16,28-31} The relative deficiency in AMPs was proposed to account for the increased rate of infections among patients with AD in contrast to the decreased risk of infection in patients with psoriasis.^{3,14,29} This comparative downregulation of AMPs in patients with AD was proposed to result from the inhibitory effects of T_H2 cytokines.¹⁷ However, the relative hypoexpression of T_H17 in patients with AD and the fact that IL-17 induces production of AMPs by human keratinocytes indicate that the relative absence of T_H17 production of IL-17 in AD tissues might account for reduced AMP levels and a possible increase in the incidence of skin infection.¹⁴ In addition, cytokines produced by T_H2 cells (IL-4 and IL-13) inhibit IL-17 production from T cells, which further reduces T_H17 cell activity (Fig 2, A).³² This might explain the 20-fold difference in levels of *IL17* mRNA between skin lesions from patients with chronic AD and those with psoriasis¹⁴ compared with only a 2-fold difference in the number of T_H17 cells between lesions from patients with AD and those with psoriasis.²⁰ Although T_H17 cells might exist in AD skin lesions, they might not be activated or might be inhibited by T_H2 cytokines.

T22 cells and IL-20

Although T_H17 cells produce small amounts of IL-22, a new T-cell subset, T22 cells, has been identified that also produces IL-22; these cells produce most of the IL-22 detected in human skin.³²⁻³⁸ This T-cell subset includes CD4⁺ (T_H22) and CD8⁺ (T_C22) cells.²⁰ Production of IL-22 is used to define T22 cells, which, along with other cytokines in the IL-20 family, mediate epidermal hyperplasia and inhibit terminal differentiation.^{20,23,39-42}

The immune infiltrate observed in patients with chronic AD is primarily composed of T22 and T_H2 cells (Fig 2, A).²⁰ Numbers

of T_H22 and T_C22 cells were significantly increased in lesional skin from patients with chronic AD compared with those seen in patients with chronic psoriasis. Furthermore, numbers of T22 T cells correlated with disease activity; numbers of T_C22 cells had the highest level of correlation.²⁰ IL-22 and IL-20 have been proposed to mediate the pathogenesis of psoriasis and induce epidermal hyperplasia and hypogranularity.^{24,39,41,43}

The discovery of T_H22 and T_C22 cells has led to a model in which psoriasis is mediated by T_H1 and T_H17 cells and AD is mediated by T_H2 and T22 cells; T_H1 cells also contribute to the chronic phase of AD (Fig 2).

Regulatory T cells

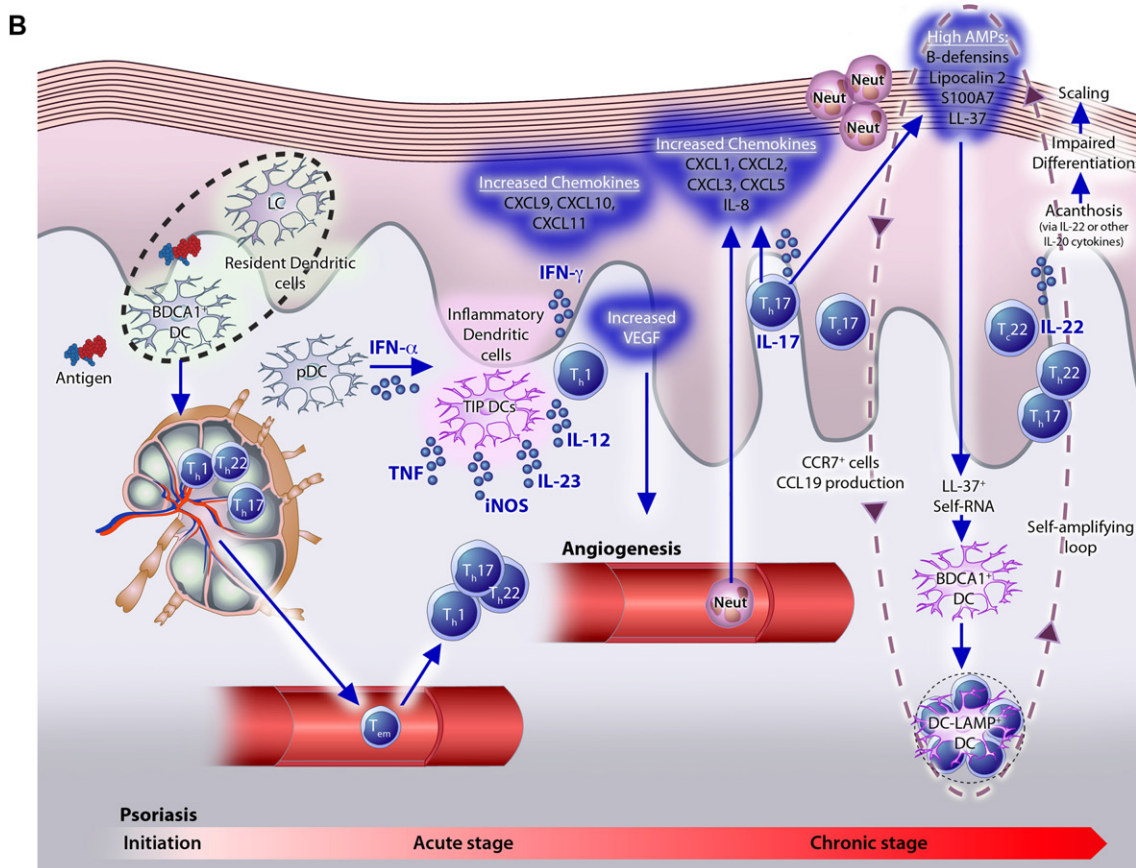
The role of regulatory T (Treg) cells in patients with AD remains to be clarified.^{44,45} In patients with psoriasis, Treg cells were reported to be both quantitatively and functionally deficient in the ability to suppress T-cell activation.⁴⁶ In patients with AD, these cells were shown to be increased in the circulation, and their levels were shown to correlate with disease activity.⁴⁷⁻⁴⁹ However, Treg cells were found to be decreased in AD skin, perhaps because of increased bacterial superantigens.^{50,51}

DCs

Langerhans cells (LCs) and dermal DCs (dDCs) were once recognized as the main DC subsets in human skin.^{52,53} However, psoriasis and AD are associated with additional types of DCs.

Numbers of myeloid (CD11c⁺) DCs (mDCs) are increased in chronic lesions of patients with AD and those with psoriasis and are comparable with T cells found in each type of lesion (Fig 2).^{2,6,7,9} mDCs represent the largest population of dDCs in both diseases, although other types of DCs exist, such as plasmacytoid DCs (pDCs; blood DC antigen-positive and CD123⁺ cells), which secrete IFN- α and are believed to mediate lesion formation in both diseases.^{2,6,54,55} Increased numbers of pDCs were measured in lesions from the skin of patients with chronic AD compared with lesions from patients with psoriasis and produce the inflammatory chemokine CCL22, which activates a T_H2 cell response.² Interestingly, pDCs also activate naive T cells to develop into T22 cells.³⁷

Inflammatory dendritic epidermal cells (IDECs) are a myeloid type of DC that have been detected in epidermal, single-cell



suspensions from patients with AD or psoriasis.^{56,57} IDECs resemble LCs but do not contain Birbeck granules. They are characterized by the following surface markers: CD11c, CD1a, HLA-DR, CD206 (macrophage mannose receptor), CD36, the high-affinity IgE receptor FcεRI, CD1b/c, and CD11b.^{56,57} IDECs do not express CD123, blood DC antigen 2, markers of T cells, B cells, natural killer cells, or monocytes (Lin[−] cells).^{56,57} Together with LCs that express FcεRI, IDECs are believed to contribute to activation of T-cell responses associated with AD.^{58,59} However, CD1a⁺ DCs have been detected in the dermis; these skin-derived cells have immunostimulatory effects.⁶⁰ It is not clear, however, whether CD1a⁺ IDECs are located only in the epidermis.⁶⁰ Skin samples from patients with AD contain many CD11c⁺ and CD1a⁺ cells that express IDEC-associated markers (CD206 and FcεRI) and, surprisingly, have a mainly dermal distribution; there are not a significant number in the epidermis.² Although these cells express the same surface markers as IDECs, because of their presence in the dermis, they are referred to as dDCs (Fig 2, A). dDCs express high levels of the receptor for thymic stromal lymphopoietin (TSLP), a cytokine that induces the T_H2 cell response (Fig 2, A).² Given their dermal location and their role in stimulating inflammatory responses, we propose renaming dermal IDEC-like cells “inflammatory DCs” (IDCs; Fig 2, A).²

In skin from patients with AD or psoriasis, IDCs produce a range of inflammatory chemokines (Fig 2). Skin lesions from patients with psoriasis contain IDCs that produce TNF-α and inducible nitric oxide synthase (called TNF and iNOS-producing dendritic cells [TIP-DCs]; Fig 2, B)⁶¹; TIP-DCs are not found in lesions from patients with AD.^{2,7,9,61} Instead, the IDCs found in lesions from patients with AD produce the chemokines CCL17, CCL18, and CCL22, which recruit T_H2 cells (Fig 2, A). The

TIP-DCs associated with psoriasis produce the inflammatory mediators IL-8, IL-1, signal transducer and activator of transcription 1, CCL20, IL-20, IL-23p19, and IL-12/IL-23p40, which mediate T_H1 and T_H17 cell responses (Fig 2, B, and see Table I in part 1 of this review¹).^{2,7,9,24}

A number of markers can be used to distinguish different subtypes of dDCs. dDCs that are CD11c⁺ and CD1c[−] are inflammatory dDCs, whereas those that express CD11c⁺ and CD1c⁺ are defined as resident dDCs (Fig 2, B).⁶² Other markers of inflammatory dDCs included TNF-related apoptosis-inducing ligand, Toll-like receptor (TLR) 1, TLR2, S100A12, and CD32. The distribution of these markers on various DC subsets and their immune stimulatory functions in patients with AD and other inflammatory diseases have not been determined (Fig 2, A).

It is not clear how LCs and IDCs contribute to the pathologic T-cell responses that promote AD. Both are antigen-presenting cells that express FcεRI and the TSLP receptor, which directly mediate mechanisms of skin inflammation in patients with AD (Fig 2, A).^{7,63} In contrast to LCs, which induce a T_H2 cell response on FcεRI ligation, IDEC-like cells promoted a T_H1 cell response with IFN-γ production *in vitro*.⁵⁴ Furthermore, epicutaneous sensitization with antigens on skin with a disrupted barrier has been associated with activation of LCs, leading to initiation of a T_H2 cell response.^{63,64} Recently, LCs were also shown to induce cells that produce IL-22, inducing a T22-type response.³⁶ LCs and dermal IDCs therefore each have different but important roles in the initiation and maintenance phases of AD.

Whereas IDCs promote T_H1 and T_H17 cell responses during the pathogenesis of psoriasis (Fig 2, B),^{7,9,24} it is possible that LCs promote T_H2 cell and T22 responses during the pathogenesis of AD (Fig 2, A).^{33,36} During the acute stages of AD, LCs, rather than dDCs, appear to stimulate T_H2 cell responses⁵²; dDCs induce

FIG 2. A, Initiation, acute, and chronic phases of AD. Defects in the epithelial barrier lead to penetration by epicutaneous antigens, which encounter LCs and induce T_H2 cells to produce IL-4 and IL-13. These cytokines induce IgE class switching and promote T_H2 cell survival. Numbers of T_H2 cells are increased during the acute and chronic stages of AD, and the cytokines they produce (IL-4 and IL-13) have direct effects on the epidermis, such as inducing keratinocytes to produce TSLP. IL-4 and IL-13 inhibit terminal differentiation and production of AMPs, leading to the disrupted epithelial barrier and increased rate of infection associated with AD. Cytokines and chemokines produced by T_H2 cells and DCs increase the number of eosinophils and mast cell precursors in the circulation. Numbers of CD4⁺ T_H22 cells and CD8⁺ T_C22 cells, which produce IL-22, are increased in skin lesions of patients with chronic AD compared with those seen in patients with psoriasis. Because IL-22 receptors are highly expressed by epidermal keratinocytes, increased expression of IL-22 in lesions from patients with chronic AD might account for defects observed in cornification and terminal differentiation, as well as epidermal hyperplasia and acanthosis. The disrupted skin barrier in patients with AD therefore results from the combined effects of T_H2 and T22 cells. LCs and pDCs have been proposed to activate T22 cells in the chronic stage of AD. Numbers of IDCs increase in the acute and chronic stages of AD and produce many inflammatory mediators, such as CCL17 and CCL18, that amplify T_H2 cell-mediated inflammation. TSLP, a keratinocyte-derived cytokine, can strongly activate DCs; TSLP-activated DCs activate T_H2 cells by expressing the surface ligand OX40L. OX40 is mainly expressed on T cells, whereas OX40L is mainly expressed by DCs, macrophages, and LCs. T_H2 cells secrete IL-4 and IL-13 but not IL-10. T_H17 cells and cytokines are downregulated in patients with AD compared with those seen in patients with psoriasis, possibly because of the inhibitory effect of the cytokines produced by T_H2 cells. IL-17 regulates AMP production; levels of AMP are reduced in patients with AD because of the suppressive effects of T_H2 cytokines and attenuation of T_H17 activation. **B**, Initiation, acute, and chronic stages of psoriasis. pDCs produce IFN-α, which induces maturation and differentiation of IDCs. Inflammatory mDCs produce TNF-α, inducible nitric oxide synthase (*iNOS*), IL-20, and IL-23, which induce T_H1 and T_H17 cell responses. The T_H1 cytokine IFN-γ induces keratinocytes to produce proinflammatory chemokines and increase production of vascular endothelial growth factor, which promotes angiogenesis. DC-derived IL-23 stimulates T_H17 and T22 cell production of IL-17 and IL-22. IL-17 induces keratinocytes to produce chemoattractants for T cells, neutrophils, and mononuclear cells. IL-22 and other IL-20 family cytokines promote epidermal acanthosis. IL-17 and IL-22 induce keratinocyte production of AMPs that include defensins, lipocalin 2, and LL-37/cathelicidin. LL-37 upregulation results in a self-amplifying inflammatory loop from LL-37/self-DNA complexes that stimulate pDC production of IFN-α and LL-37/self-RNA complexes that stimulate production of TNF, IL-6, and IL-23 by DCs and their maturation into DC-LAMP⁺ cells. DC-LAMP⁺ DCs colocalize with T cells in lymphoid structures that include CCR7⁺ cells and produce CCL19. *BDCA*, Blood DC antigen.

production of additional T_H2 cell chemoattractants, such as CCL17, CCL22, and CCL24.^{2,65} In the chronic phase of AD, the T_H2 response is activated (potentially mediated by LCs and pDCs),^{36,37} along with a T_H1 cell response believed to be induced by IDCs.^{5,66,67} Interestingly, numbers of LCs are increased in epidermal lesions from patients with AD compared with those from patients with psoriasis.²

MAST CELLS AND EOSINOPHILS

Mast cells and eosinophils often colocalize during the development of allergic or parasitic diseases. In patients with allergic diseases, mast cells might amplify IgE-mediated inflammation and eosinophil influx to tissues (Figs 1 and 2, A).⁶⁸

Mast cells have important roles in inflammation: they regulate eosinophil activation and recruitment. These potent granulated cells are often the first to respond to challenge with an antigen and initiate an immune response.^{69,70} They have FcεRI on their surface; cross-linking of FcεRI by surface IgE and antigen generates rapid release of inflammatory mediators (histamine, proteases, arachidonic acid metabolites [eg, prostaglandins and leukotrienes], and chemotactic molecules).⁷¹ Mast cells secrete multiple mediators that affect eosinophils (Fig 1), including IL-5, IL-6, IL-4, IL-13, TNF-α, GM-CSF, tryptase, eotaxins, RANTES, monocyte chemoattractant protein 1, and others.^{69,70} Mast cell-derived histamine, the proteinases tryptase and mast cell chymase (MCC), and other mast cell-derived inflammatory mediators, contribute to itching and inflammation in patients with AD.⁷² Whereas histamine mainly induces erythema and edema and is not likely to be a significant mediator of pruritus in patients with AD,⁷⁰ tryptase has pruritogenic activities, mainly through activation of proteinase-activated receptor 2.⁷⁰

The gene *MCC*, located on chromosome 14q11.2, has been associated with AD. MCC is a serine protease with chymotrypsin-like specificity. It is produced by mast cells and promotes inflammatory effects in association with histamine, including increased vascular permeability and regulation of active peptides.^{73,74} However, mast cells were not required for the development of disease in a murine model of AD induced by epicutaneous sensitization with antigen.⁷⁵

Increased numbers of mast cells were found to infiltrate skin lesions of patients with psoriasis.⁷⁶ In psoriatic lesions approximately 70% of mast cells are positive for IFN-γ, whereas in AD lesions only 10% of the mast cells are positive for IFN-γ.⁷⁷ During development of psoriasis, mast cells have been proposed to recruit neutrophils through production of TNF-α and IL-8. Mast cells and keratinocytes also induce angiogenesis by producing IL-8 and vascular endothelial growth factor.^{70,78}

AD is characterized by increased numbers of circulating eosinophils^{79,80} and dermal and epidermal infiltrates of eosinophils.⁸¹ Tissue and blood eosinophilia and increased serum levels of eosinophil granule proteins, such as eosinophil cationic protein, major basic protein, and eosinophil-derived neurotoxin, have been correlated with disease activity.^{72,82,83} Levels of the T_H2 cell cytokine IL-5, which promotes survival and mobilization of eosinophils, are increased in the sera of patients with AD and correlate with disease activity.⁸⁴ Although eosinophils might have important roles in AD pathogenesis, their exact mechanisms are not clear. Many cytokines assist in recruiting eosinophils to sites of inflammation (Fig 1), including the T_H2 cell cytokines IL-4, IL-5, and IL-13; the chemokines RANTES/CCL5 and eotaxins (eotaxin-1/CCL11, eotaxin-2/CCL24, and eotaxin-3/CCL26);

and adhesion molecules, such as the integrin β-subunit.⁸⁵ Only the eotaxins and IL-5 act solely on eosinophils. CCR3, which is present on all eosinophils, is the receptor for all eotaxins, as well as for RANTES/CCL5 and CCL13/monocyte chemoattractant protein 4.⁸ Interestingly, experiments in CCR3-deficient mice showed that although eosinophils and major basic protein were absent from the skin of mice that had been sensitized to ovalbumin, the mice still produced mast cells and expressed *IL4* mRNA. Therefore CCR3 is required for recruitment of eosinophils to sites of atopic inflammation but not mast or T_H2 cells.⁸⁶

The cytokine IL-31, which is produced by T_H2 cells, has been reported to induce severe itching and dermatitis in transgenic mice^{87,88} and was recently proposed to promote pruritus in patients with AD.⁸⁹ IL-31 is expressed by eosinophils and keratinocytes; activation with IL-31 promotes release of proinflammatory cytokines and chemokines, such as IL-1β, CXCL1, IL-8, CCL2, and CCL18, from these cells.⁸⁹

Unlike AD, numbers of eosinophils are not increased in the skin or peripheral circulation of patients with psoriasis.

KERATINOCYTES AND THE INFLAMMATORY RESPONSE

In skin from patients with AD or psoriasis, alterations in keratinocyte function not only cause the most visible alterations and symptoms, but keratinocytes also produce inflammatory factors that promote chronic, self-amplifying loops of immune activation.^{9,24,43,90} The epidermis functions as not only a physical barrier but also a chemical and immunologic barrier; it produces many inflammatory mediators, including cytokines, chemokines, S100 proteins, and AMPs.

Two examples illustrate the importance of epidermal keratinocytes in the pathogenesis of psoriasis. IL-17 induces keratinocytes to produce the AMP cathelicidin/LL-37, which forms a complex with DNA to activate pDCs^{91,92} to produce IFN-α, which leads to psoriasis.^{10,93} LL-37 can also complex with RNA. Interaction of RNA with LL-37 promotes maturation of mDCs into lysosome-associated membrane glycoprotein, DC-specific (DC-LAMP)⁺ cells (Fig 2, B). In the skin aggregates of DC-LAMP⁺ DCs can lead to chronic activation of T cells, and these aggregates are associated with active psoriasis (Fig 2, B). Keratinocytes also produce CCL20 on activation by IL-17 (or TNF-α); CCL20 attracts T_H17 cells and mDCs into specific regions of the skin.^{62,94} These mechanisms of inflammation are not likely to mediate the pathogenesis of AD because LL-37 and CCL20 are expressed at low levels.¹⁴ In patients with AD, production of AMPs by keratinocytes decreases, possibly in response to the T_H2 cell response; this decrease might account for the increased rate of infection associated with AD.^{16,28}

Keratinocytes have a smaller effect on immune responses during development of AD, but TSLP, which is produced at high levels by keratinocytes from patients with AD (but is not detected in normal skin), might initiate T_H2 polarization through an OX40-dependent mechanism that affects DC activity.⁹⁵⁻⁹⁸ Microbial products, physical injury, or inflammatory cytokines induce production of TSLP by human keratinocytes.⁹⁸⁻¹⁰⁰ DCs activated by TSLP become inflammatory, expressing OX40 (CD134) ligand (OX40L), which induces development of T_H2 cells (and expresses IL-4, IL-5, and IL-13 but not IL-10).^{95,101,102} TSLP also stimulates DCs to produce, among other inflammatory mediators, eotaxin-2/CCL24, macrophage-derived chemokine/CCL22, and

thymus and activation-regulated chemokine/CCL17.⁹⁵ TSLP also stimulates mast cells to produce IL-5, IL-6, IL-13, and GM-CSF; TSLP has synergistic activity with IL-1 and TNF- α to induce production of high levels of T_H2 cytokines by mast cells (Fig 2, A).⁹⁹ These cytokines and chemokines initiate and amplify allergic inflammation and induce eosinophils.^{95,103}

INNATE AND ADAPTIVE IMMUNITY AND DEFECTS IN THE EPIDERMAL BARRIER

Defects in immune and epidermal barrier function might have overlapping effects that contribute to AD and psoriasis.^{15,17} During the development of AD, the T_H2 cell cytokines IL-4 and IL-13 modify keratinocyte responses (Fig 2, A) and inhibit production of terminal differentiation proteins, including loricrin, filaggrin, and involucrin,^{15,17,18} and/or AMPs.^{16,17} Additionally, T22 cell production of IL-22 is upregulated in skin lesions of patients with AD compared with that seen in healthy skin; IL-22 inhibits terminal differentiation proteins and induces epidermal hyperplasia (Fig 2, A).²³ This cytokine might promote the epidermal effects of keratinocytes (ie, increased proliferation and inhibition of terminal differentiation) to lead to AD.¹⁰⁴

In contrast, skin lesions from patients with psoriasis express high levels of IFN- γ and IL-17, each of which induces distinct expression patterns of genes that regulate neutrophil chemotaxis, AMPs, and terminal differentiation of keratinocytes. These cytokines also synergize with IL-22 to regulate AMPs and genes that encode terminal differentiation factors, such as the S100 family proteins, and induce epidermal cell proliferation.²³ Because skin lesions from patients with AD and psoriasis have similar processes of regenerative growth, the differences in barrier alterations associated with each disease might result from the differences in cytokines associated with each disease (T_H1 and T_H17 cell responses mediate psoriasis, whereas T_H2 and T22 cell responses mediate AD); these differences might also affect keratinocyte differentiation.

In the skin of patients with AD, barrier defects might allow for epidermal penetration of epicutaneous antigens, which are processed by LCs in the epidermis. LCs might activate T_H2 and T22 cell responses, whereas the epidermal hyperplasia that develops in response to IL-22 might eliminate epidermal antigens more rapidly by means of faster turnover of keratinocytes. Hence, in patients with AD, immune activation might occur through the epidermis, resulting in a reactive epidermal response to the immune-derived cytokines. In contrast, psoriasis might involve dDCs that more effectively promote T_H1 and T_H17 cell responses, although LCs might also be important for activation of T22 cells.

THERAPEUTICS

Psoriasis is a useful model for studying targeted therapies for inflammatory diseases because areas of diseased skin can clearly be distinguished from normal skin using quantitative and qualitative biomarkers of epidermal hyperplasia. Furthermore, active psoriasis can be completely reversed, such that biopsy samples from treated lesions cannot be distinguished from those from normal skin. Treatment time is also short. Symptoms of the disease can usually be completely reversed within 8 to 12 weeks of treatment with drugs, such as cyclosporine A (CsA) or etanercept,¹⁰⁵⁻¹⁰⁷ or with less-specific approaches, such as ultraviolet (UV) B light.¹⁰⁸ Therapeutics for psoriasis have been developed

based on what is known about the cytokine-signaling pathways that promote the associated inflammation (Fig 2, B).^{9,24,90}

Antibodies to the shared p40 subunit of IL-12 and IL-23 and antagonists of TNF have been approved for the treatment of psoriasis and are used by many patients; many studies are underway to test more specific antagonists of IL-23, IL-17, the IL-17 receptor, IL-20, IL-22, and other cytokines.^{106,109-111} With this perspective, we will discuss existing and future therapeutic options for AD.

In patients with psoriasis, suppression of the immune system is associated with reversal of the abnormal epidermal barrier when treatment with specific immune antagonists is found to correct epidermal defects.^{108,112,113} Because epidermal hyperplasia and immune and epidermal barrier abnormalities are characteristics of AD and psoriasis, immune-based strategies that correct the epidermal defects in patients with psoriasis might be effective in patients with AD.^{105-108,112-114} It is important to establish the extent to which pathological features and biomarkers of AD can be reversed by effective treatment because the demonstration that psoriasis had a reversible phenotype and that specific biomarkers could distinguish active disease from background "nonlesional" skin greatly accelerated the testing of new therapeutics.

Therapeutics for AD

Despite the increasing worldwide incidence of AD and the substantial burden of the disease on patients and society, therapies for AD are limited because they were developed based on chance observations, with little understanding of their targets.^{5,79,115,116} This is in contrast to psoriasis, for which known molecular mechanisms of pathogenesis were used to develop specific targets.^{10,24,43,90} Several excellent articles review therapeutic approaches for AD.^{115,117-119} We summarize treatment strategies, the rationale behind their use, and experimental or potential therapeutic targets.

Treatment of AD is complex. In addition to treating existing disease, it is also important to instruct patients to avoid irritant factors and environmental allergens (food or inhalants) that can induce or exacerbate skin lesions.¹¹⁷

Therapy for AD consists largely of topical treatments with agents that restore barrier function, have anti-inflammatory effects, and suppress the immune response (Table I).^{115,117} The goals of therapy with barrier-restoring agents are to hydrate the skin, prevent transepidermal water loss, and suppress pruritus, which initiates the itch-scratch cycle.¹²⁰ These agents consist of emollients, lipid-based barrier repair formulations,¹²¹ and, for patients with severe exudates, wet wraps¹¹⁷; they are applied to the entire skin surface several times daily. Although clinical experience and a few randomized controlled trials indicate that these reagents reduce the need for steroid therapy (and help avoid its side effects), evidence for their efficacy is limited.^{117,122,123} In contrast, topical anti-inflammatory and immunomodulatory agents are used to treat only areas of visible disease; they are the mainstay of treatment for acute exacerbations and chronic disease.^{72,117} Topical corticosteroids are the first-line therapy and provide rapid relief of symptoms. However, these, and particularly potent steroids, should be used with caution, particularly in sensitive or intertriginous areas, because prolonged use can cause skin atrophy and tachyphylaxis.¹¹⁷

The topical calcineurin inhibitors pimecrolimus and tacrolimus are immune regulators that were approved for the treatment of

TABLE I. Available therapies and those in development for AD

Current therapies
Topical therapy
Barrier restorers
Moisturizers
Lipid replacement (particularly ceramides)
Wet wraps and occlusive dressing
Anti-inflammatory and immunosuppressive
Topical corticosteroids
Topical calcineurin antagonists
Tar preparations
Systemic
Antihistamines
Not effective
UV phototherapy
UVA/UVB
Narrow-band UVB
Psoralen plus UVA
UVA1
Broad immune suppressants
Systemic corticosteroids
CsA
Methotrexate
Mycophenolate mophetil
Azathioprine
Anti-infectives (topical or systemic)
Antibiotics
Antivirals
Antifungal
Bleach
Experimental therapies
Agents that target the innate immune system
Oral vitamin D supplementation
Probiotics
Topical protease inhibitors
Agents that target the adaptive immune system
Biologic therapies:
Reagents that target T cells (alefacept, efalizumab, withdrawn from market)
Antibody against IgE (omalizumab)
B-cell targeting (rituximab)
Anti-TNF reagents (etanercept, infliximab, adalimumab)
Restoration of balance between T _H 1 and T _H 2 cells (IFN- γ)
Target T _H 2 cells (anti-IL-4, anti-IL-13, anti-IL-5, and anti-IL-31)
Target TSLP or OX40
Target T _H 22 or T _C 22 cells (anti-IL-22)
Target multiple immune pathways (using anti-p40 to block T _H 1 and possibly T _H 22 cell responses)
Specific immunotherapy (target house dust mite-specific T and B cells)
Immunosuppressants
Janus kinase inhibitors to block γ_c signaling (IL-4 signal transduction)
Cytokines that promote T-cell differentiation and survival

eczema; their long-term efficacy has been demonstrated in placebo-controlled clinical trials.^{120,124} However, the US Food and Drug Administration (FDA) has warned about the risk for lymphoma and other cancers associated with prolonged treatment, which might limit their use, although there is no evidence for increased risk of malignancy from clinical trials.¹¹⁷

Tar preparations are also topical anti-inflammatory therapies for AD, although they are not popular because of their odor and dark-staining features.¹¹⁷ These immune modulators inhibit activation and release of cytokines from T cells, mast cells, and

LCs.¹¹² Antihistamines, which block the histamine receptor, are used as adjuncts to topical or systemic anti-inflammatory or immunosuppressant therapies to break the itch-scratch cycle.¹²⁵ Their role in controlling pruritus in patients with AD is controversial because many mediators besides histamine contribute to itching in patients with AD. It is likely that their sedative effects, rather than their histamine-blocking capabilities, provide the most relief to patients.¹²⁶

Patients with severe AD who do not respond to topical therapy are treated with a range of other modalities, most of which are not currently approved by the FDA for this indication. These include oral immunosuppressive drugs, such as corticosteroids, CsA, methotrexate, mycophenolate mofetil, and azathioprine, as well as phototherapy (Table I). Phototherapy is effective for treatment of patients with moderate-to-severe AD.^{127,128} It can be administered as UVA and UVB, narrow-band UVB, UVA1, or psoralen plus UVA for extensive disease.¹¹⁷ Phototherapy upregulates production of AMPs in patients with AD, which might prevent skin infections.^{128,129} However, the immunomodulatory effects of phototherapy for AD are largely unknown. In patients with psoriasis, narrow-band UVB phototherapy suppressed immunity and reversed epidermal hyperplasia.^{108,113} Psoralen plus UVA also had strong immunosuppressive effects in a murine model of psoriasis.¹³⁰

Patients with AD are more prone to bacterial, viral, and fungal infections that can cause disease exacerbation^{16,131}; patients with signs of these infections might require treatment with antistaphylococcal, antiherpetic, and antifungal agents (Table I).^{115,117,132,133} Bleach baths can decrease the severity of AD by reducing staphylococcal colonization^{134,135} but also possibly by altering the commensal flora that activate immune cells through TLR signaling. In patients with recalcitrant AD, systemic immunosuppressive therapies (eg, systemic corticosteroids, CsA, and methotrexate) provide a short-term solution to control inflammation (Table I).^{116,117,136,137} Therapy with systemic corticosteroids should be avoided, however, because patients have rebound effects when they discontinue therapy and the drugs have long-term side effects. Systemic corticosteroids should be given only in short courses to stop an acute exacerbation of AD.^{116,117}

As for patients with psoriasis,^{112,138} T cell-directed therapeutics, such as CsA^{117,139} or, more recently, efalizumab¹⁴⁰ and alefacept,¹⁴¹ are effective for treatment of patients with moderate-to-severe AD. This is not surprising because both diseases are associated with high numbers of CD3⁺ T cells (see Fig 3 in part 1 of this review¹).² Efalizumab, an immunosuppressive antibody against CD11a, has been withdrawn from European and US markets because of its association with progressive multifocal leukoencephalopathy. It is not clear whether immune suppressants have a benefit/risk profile sufficient to warrant their continuous administration to patients with AD. Although CsA has not been approved by the FDA for treatment of severe AD, it is effective in adults and children.^{137,142} CsA is a relatively safe treatment for 3 to 24 months for patients who have not responded to other approaches, such as topical therapies, phototherapy, and oral corticosteroids.^{136,137} Although CsA is widely prescribed for patients with severe AD, studies of its efficacy lack mechanistic information; its effects on skin lesions and disease activity have been documented by using the AD scoring index SCORAD. A few studies have correlated clinical activity with numbers of T cells in peripheral blood, levels of T-cell activation,^{143,144} levels of thymus and

activation-regulated chemokine (CCL17) or macrophage-derived chemokine/CCL22,^{145,146} or upregulation of Treg cells.¹⁴³ Interestingly, the clinical effects of CsA for AD were not associated with levels of IgE; levels of IgE were even reported to increase in a subgroup of patients.^{147,148} In patients with psoriasis, CsA has been shown to suppress the T_H1 and T_H17 cell responses that mediate pathogenesis.¹⁰⁷ Suppression of these immune pathways was linked to reversal of epidermal hyperplasia.^{112,138}

Antimetabolites, such as methotrexate and mycophenolate mofetil (Cellcept; Roche, Mannheim, Germany), have limited efficacy in patients with AD in whom other treatment strategies have failed.^{136,137,149} Several trials have reported that azathioprine is effective in treating moderate-to-severe AD.^{117,150} Immunosuppressive drugs, such as mycophenolate mofetil and azathioprine, inhibit T-cell and B-cell proliferation.¹⁵¹

Experimental therapeutics

The innate immune system is linked to barrier functions, and therefore therapeutic strategies that improve innate immunity might lead to barrier repair (Table I). In preliminary studies vitamin D3 supplements upregulated production of AMPs¹⁵²; these findings should be validated in patients with AD. Probiotics (cultures of commensal bacteria) might restore a healthy microbial balance to patients with AD and other inflammatory disorders. The hygiene hypothesis prompted studies of these bacteria and found that they had immunomodulatory properties.¹⁵³ However, a meta-analysis of trials of probiotics did not show that they benefitted patients with AD.¹⁵⁴ Because an imbalance of proteases has been proposed to contribute to AD, topical protease inhibitors are also being tested for treatment of AD, although there is no evidence for their benefit.¹¹⁷

Biologics that target adaptive immune responses have been tested in patients with AD that do not respond to other therapies (Table I).^{31,115,117} These include inhibitors of T cells, IgE, B cells, and T_H1 cytokines, as well as antagonists of T_H2 or proinflammatory cytokines.^{31,117} Biologics that target T cells, such as efalizumab and alefacept, have been approved for the treatment of psoriasis and shown to have some efficacy in patients with AD.^{141,155} Efalizumab and alefacept are effective in patients with psoriasis because they interfere with receptor-ligand interactions that activate T cells (eg, lymphocyte function–associated antigen 1–intercellular adhesion molecule 1 and lymphocyte function–associated antigen 3–CD2, respectively), but little is known about their mechanisms in patients with AD; they are thought to nonspecifically deplete T cells in the skin.^{141,155–157}

Although the role of IgE in the pathogenesis of AD is not clear, omalizumab, an mAb against IgE, has been tested. Although it is effective in treating patients with asthma, omalizumab was not observed to have effects in patients with AD, despite its ability to downregulate FcεRI on DCs.^{158,159} This finding indicates that levels of IgE increase after induction of the T_H2 cell response in patients with AD; this is in contrast to asthma, in which allergic inflammation has an important primary role in its pathogenesis. Although AD and asthma both belong to the group of atopic diseases, they have different mechanisms and thereby different therapeutic targets. The relative ineffectiveness of CsA in patients with asthma supports the concept that it is a primarily IgE-induced disease, whereas AD as mediated by T-cell responses.¹⁶⁰

Small studies of rituximab, an antibody against CD20 that depletes B cells, have had contradictory results in patients with

AD.^{141,161} Further studies are required to determine whether reagents that inhibit or deplete B cells might be used to treat AD.

Anti-TNF agents have been successful in treating psoriasis,^{162–164} probably because TNF and its synergistic interaction with IL-17 mediate pathogenesis.¹⁶⁵ Furthermore, TNF antagonists inhibit the pathogenic T_H1 and T_H17 cell responses that contribute to psoriasis.^{105,106} However, a pilot study of the effects of the TNF antagonist infliximab in patients with moderate-to-severe AD had disappointing results,¹⁶⁶ possibly because TNF-induced inflammatory responses have only a minor role in AD.^{165,167} Additional studies are needed to exclude the role of TNF in pathogenesis and identify other therapeutic targets. In patients with AD, it might be possible to restore the balance of T_H1 and T_H2 cell responses and lower IgE production by means of administration of recombinant IFN-γ. However, trials showed that IFN-γ therapy was effective in only a subset of patients and did not reduce levels of IgE.^{168,169} This observation, along with the lack of an effect of CsA and the ineffectiveness of IgE-directed therapies, indicated that increased levels of IgE are an effect, rather than a primary cause, of AD.

Cytokines produced by T_H2 cells inhibit production of AMP and terminal differentiation proteins. IL-4 promotes differentiation of T_H2 cells and IgE class switching by B cells; mutations in *IL4* and its receptor have been associated with AD. Therapeutic strategies that inhibit cytokines produced by T_H2 cells, particularly IL-4, might therefore have therapeutic effects in patients with AD (Table I). Because IL-4 and IL-13 signal through a common receptor, IL-4RA, targeting this receptor might reduce the response to both cytokines.

An inhibitor of IL-4 receptor signaling (pitrakinra/pascolizumab) that competitively binds to IL-4RA to inhibit binding of IL-4 and IL-13 has shown efficacy in trials of patients with asthma^{165,170,171} but has not been tested in patients with AD.¹¹⁷ We are not aware of reports of the efficacy of IL-13 antagonists in patients with AD. Another cytokine produced by T_H2 cells, IL-5, induces eosinophil differentiation, activation, mobilization, and survival. Eosinophils are important mediators of the inflammatory process in AD, and therefore reagents that block IL-5 might be developed as therapeutics. However, mepolizumab, a fully humanized mAb against IL-5, reduced blood and tissue eosinophilia but did not have clinical effects in patients with AD.^{172,173} Mepolizumab reduced the numbers of eosinophils in patients with asthma, but it had no effect on T-cell responses,^{165,174} arguing against its role in the treatment of AD. IL-31 is a cytokine produced by T_H2 cells that is believed to promote itching in patients with AD; therapeutics that disrupt its activity are being developed.¹¹⁷

TSLP and OX40 mediate signaling by DCs that promotes T_H2 cell responses and are highly upregulated in atopic skin. Reagents that target these molecules might be developed to treat patients with AD (Table I). Numbers of T22 cells, which produce IL-22, are increased in patients with chronic AD, indicating that IL-22 might be a therapeutic target for chronic-phase AD. Because levels of IL-17 are increased in patients with acute AD, whereas IL-22 and IFN-γ levels are upregulated in patients with chronic-phase AD, reagents against IL-12 and IL-23, such as anti-p40 (ustekinumab [Stelara]; Centocor Ortho Biotech, Inc, Horsham, Pa), might be effective in reducing numbers of T_H17 cells in patients with acute-phase AD and T_H1 and T22 cells in patients with chronic AD (Table I).

Several reports indicate the efficacy of allergen-specific immunotherapies, such as immunotherapy for house dust mite

antigen, in patients with AD.^{117,175,176} This treatment was proposed to induce Treg cells; increase levels of allergen-specific IgG4, IL-10, and TGF- β ; and inhibit T_H2 cell responses.^{117,175,176} Interestingly, a randomized study showed that reduced exposure to allergens significantly decreased the risk of AD in children.¹⁷⁷ A model in which childhood exposure to allergens determines the risk for AD requires validation in large controlled trials with extended follow-up periods.

CONCLUSION

Psoriasis develops through well-understood mechanisms and has many treatment options, including targeted biologics with proved efficacy, whereas our understanding of AD's pathogenesis and treatment is limited. AD and psoriasis are characterized by equally complex immunologic interactions, but broad-spectrum agents that inhibit production of T_H2 cytokines and chemokines might be the best therapeutic approach for AD. Strategies that include a combination of more than 1 biologic agent or a biologic agent that targets more than 1 immunologic factor or cell type (eg, anti-p40, which inhibits T_H1, T_H17, and T22 cells) might be the best approach to treating AD. Gaining a better understanding of the pathogenesis of AD will lead to development of more efficient treatment strategies for patients.

IMPORTANT QUESTIONS ABOUT PSORIASIS AND AD

Immune mechanisms

1. Is AD initiated by an increased response by T_H2 cells or reduced response by T_H1 cells? What are the roles of T cells and DCs in determining whether the response is mediated by T_H1 or T_H2 cells?
2. Patients with AD do not have adequate T_H1 cell responses. Is this because of exposures to specific antigens or bacteria or lack of exposure?
3. What is the role of T_H17 and T22 cells in disease induction? Do T22 cells have an active role in induction of disease (acute stage), or do they function only in perpetuating the disease (chronic stage)?
4. Does AD develop because of defective central and peripheral tolerance mechanisms or through loss of balance between T_H1 and T_H2 cell-mediated immune responses to epicutaneous antigens in the neonatal period?
5. Is the hygiene hypothesis (both versions of this hypothesis) right? The alternative to the hygiene hypothesis might be that the balance in T_H1 and T_H2 cell-mediated responses is affected by alterations in the presentation of epicutaneous antigens and bacteria to the immune system because of genetic factors that cause barrier defects.
6. Can chronic AD be managed safely and effectively with systemic immune-modifying drugs, similarly to psoriasis?
7. Is AD a primarily T_H2 or T22 cell-mediated disease, and how might changes to one response affect the other?
8. Are intrinsic and extrinsic AD similar in terms of basic immunologic mechanisms?
9. Can the concept of atopy be applied to skin and airway inflammation, or do these diseases have different mechanisms of pathogenesis?
10. If therapeutics that target T cells, such as CsA, are effective in patients with AD and less effective in those with asthma, whereas omalizumab (an antibody against IgE)

is effective in treating asthma but not AD, does this mean that AD is a T cell-mediated disease (and that an increase in IgE is a secondary effect), whereas asthma is a B cell-mediated disease?

11. Because psoriasis and AD appear on different skin regions, at least initially, are there regional variations in T_H1, T_H2, and T_H17/22 immunity in the skin?

Epidermal mechanisms

1. Are there differences in the severity or features of disease between patients with variants in filaggrin that affect its expression or function and subjects who do not have variants that affect filaggrin's activity?
2. To what extent does correct cornification depend on expression of filaggrin? In models filaggrin initiates a complex process that results in differentiated corneocytes and correct deposition of lipids. Can defects in lipid synthesis¹²¹ affect the function of filaggrin?
3. How is it possible to compensate for defects in filaggrin's function in that AD symptoms can subside in subjects with mutations in filaggrin?

Disease models

1. What is the best animal model for AD? Should the models be developed based on characteristics of epidermal disease, differences in the immune response, or both?
2. Given the recent ability to discriminate and classify cases of AD versus psoriasis based on genomic features,¹⁸ can similar criteria be applied to determine the ability of model systems to reproduce skin diseases that are mediated by imbalances in T_H1 versus T_H2 cell responses, such as AD and psoriasis?

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