The immunology of atopic dermatitis and its reversibility with broad-spectrum and targeted therapies

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1. To review the pathophysiologic mechanisms of atopic dermatitis (AD).
2. To identify the latest research regarding the development of therapeutic agents for AD.

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Atopic dermatitis (AD), the most common chronic inflammatory skin disease, is driven by both terminal keratinocyte differentiation defects and strong type 2 immune responses. In contrast to chronic plaque-type psoriasis, AD is now understood to be a much more heterogeneous disease, with additional activation of T_H22, T_H17/IL-23, and T_H1 cytokine pathways depending on the subtype of the disease. In this review we discuss our current understanding of the AD immune map in both patients with early-onset and those with chronic disease. Clinical studies with broad and targeted therapeutics have helped to elucidate the contribution of various immune axes to the disease phenotype. Importantly, immune activation extends well beyond lesional AD because nonlesional skin and the blood component harbor AD-specific inflammatory changes. For this reason, future therapeutics will need to focus on a systemic treatment approach, especially in patients with moderate-to-severe disease. (J Allergy Clin Immunol 2017;139:S65-76.)

Key words: *Atopic dermatitis, eczema, keratinocyte, immune, T helper cell, skin immune map, targeted therapy*

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease, with a prevalence of up to 7% in adults and up to 25% among children.[1-5] Characteristically, symptoms start within the first 5 years of life, and in adults the disease has generally been present for decades. Similar to psoriasis,[6,7] AD is now considered a primarily T cell–driven disease,[8,9] as proved by the clinical efficacy of broad T cell–targeting therapeutics, such as cyclosporine,

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Abbreviations used
AD: Atopic dermatitis
AMP: Antimicrobial peptide
CRTH2: Prostaglandin DP2 receptor
EASI: Eczema Area and Severity Index
FLG: Filaggrin
JAK: Janus kinase
OX40L: OX40 ligand
PDE: Phosphodiesterase
TSLP: Thymic stromal lymphopoietin

efalizumab, and alefacept.[10-12] Although the latter 2 are no longer available because of safety concerns, cyclosporine, oral glucocorticosteroids, and phototherapy (narrow-band UVB) are often used to treat moderate-to-severe disease.[13-15] However, cyclosporine and, even more so, glucocorticosteroids are not suitable for long-term use because of multiple side effects. Phototherapy is very time consuming and not feasible for most patients.[16] Therefore AD presents a large unmet need for both effective and safe therapeutics.[2] Although animal models have been instrumental in deciphering general components of cutaneous biology in health and disease, the complex interplay between immune mechanisms, skin barrier, and potential intrinsic and extrinsic triggers of disease are not well represented in a single animal model and thus need to be addressed and characterized in human subjects.[17,18]

One strategy that was instrumental in psoriasis to educate on disease pathogenesis and activated cytokines is through clinical trials with broad and specific immune antagonists coupled with tissue biomarkers.[19] Such an approach is also being successfully implemented in patients with AD.[20] Broad therapeutics, such as glucocorticosteroids, cyclosporine, topical calcineurin inhibitors, and narrow-band UVB, have suggested the immune nature of AD and indicated possible involvement of more than 1 cytokine pathway.[13,14,21,22] These studies not only provided final proof of the immune nature of AD but also of the pathogenic role of the T_H2 axis in this disease. Although increased IL-4 and IL-13 levels in patients with lesional and nonlesional AD were first described in 1994, it was not until recently that studies demonstrated the clinical efficacy of dupilumab, an IL-4 receptor antagonist, and conclusive clinical proof became available supporting the importance of the type 2 immune pathway in patients with AD.[23-26]

THE EMERGING IMMUNE MAP OF AD

Similar to psoriasis, which is centered around a T_H17/IL-23 axis, AD has been associated with activation of T-cell subsets.[27] Although AD seems to be unanimously characterized by a strong activation of T_H2 immune responses in lesional and even nonlesional skin,[20] the T_H22, T_H17/IL-23, and T_H1 cytokine pathways likely play a role in the disease, particularly in some AD subtypes.[8]

In acute lesions AD onset is characterized by profound increases of T_H2 levels (IL-4, IL-5, IL-13, IL-31, and CCL18) and T_H22 (IL-22 and S100A proteins) responses.[28,29] These mediators have been demonstrated to downregulate terminal differentiation genes and tight junction products, such as claudins, contributing to the barrier defect in patients with AD.[30-40] Recently, it has been demonstrated that group 2 innate lymphoid cells can also produce T_H2 cytokines. Although present at much lower frequencies than T cells, group 2 innate lymphoid cells have been found at increased levels in AD lesions compared with healthy control skin,[41-43] thereby possibly promoting T_H2 responses.[41,44]

Among T_H2 immune mediators, IL-4 and IL-13 have been demonstrated to play a key role in AD pathogenesis. Genetically, AD has been shown to be associated with IL-4 and IL-13 polymorphisms,[45-48] and eczema-like features can be induced in transgenic mice overexpressing these cytokines.[49-52] In human subjects mRNA *in situ* hybridization studies by Hamid et al[26,53] demonstrated increased levels of IL-4 and IL-13 in patients with both acute and chronic AD to a higher degree than IFN-γ. IL-4 decreases expression of multiple genes in the epidermal differentiation complex that regulates epidermal barrier function.[54] Keratinocytes differentiated in the presence of IL-4 and IL-13 exhibited significantly reduced filaggrin *(FLG)* gene expression, even in patients without *FLG* mutations.[38] Aside from *FLG*, loricrin and involucrin are also downregulated in lesional and nonlesional AD skin by IL-4 and IL-13, contributing to a defective skin barrier in patients with AD.[31] A compromised barrier allows penetration of bacteria and allergens in the skin, leading to infections and allergen sensitization, both of which are highly characteristic of AD.[31]

T_H2 polarization facilitates *Staphylococcus aureus* binding and colonization,[55,56] and IL-4 and IL-13 inhibit skin production of antimicrobial peptides (AMPs),[56] predisposing AD skin to *S aureus* infections,[57] which, in turn, further exacerbate skin inflammation and barrier defects.[58-62] Also, eczema vaccinatum, a disseminated viral skin infection that occurs in patients with AD after inoculation with vaccinia virus, has been demonstrated to depend on IL-4/IL-13 expression through AMP downregulation.[63] Mechanistically, it has been shown that IL-4 and IL-13 inhibit TNF-α– and IFN-γ–induced human β-defensin 3 through activation of signal transducer and activator of transcription 6 (STAT6) production in keratinocytes,[64,65] as well as TNF-α–induced cathelicidin production.[57] Despite the fact that IL-17 can be found in AD lesions, its antimicrobial effects (through upregulation of AMPs, such as human β-defensin 2, in keratinocytes) are inhibited when IL-4, IL-13, or both are present.[62] The fact that IL-4/IL-13–driven inflammation can truncate these key T_H1 (IFN-γ)– and T_H17 (IL-17)–dependent skin defense mechanisms in patients with AD, as well as the successful treatment of AD with dupilumab, which blocks receptor binding of both IL-4 and IL-13,[23-25] proves their central role in disease pathogenesis.

T_H17-associated molecules (IL-17A, peptidase inhibitor 3/elafin, and CCL20) are consistently upregulated in both patients with acute and those with chronic AD but at lower levels than in patients with psoriasis (compared with normal skin).[66,67] IL-17A could possibly contribute to the immune dysregulation in patients with AD by synergistically upregulating S100A7/8/9 together with IL-22.[68] The S100A proteins, which are highly upregulated in patients with AD, can act as both antimicrobial agents and inflammatory molecules.[69] There is also evidence that IL-17 can contribute to barrier abnormalities by downregulating *FLG* and affecting keratinocyte expression of genes associated with cellular adhesion.[34]

T_H2 and T_H22 responses are intensified in chronic AD lesions, with parallel activation of the T_H1 axis (IFN-γ, CXCL9, and CXCL10) rather than a "switch" to a T_H1-only signature.[66,70]