Advances in atopic dermatitis in 2015

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This review aims to highlight recently published articles on atopic dermatitis (AD). Updated are the insights into epidemiology, pathology, diagnostics, and therapy. Epidemiologic studies have revealed a positive correlation between AD and systemic conditions, such as rheumatoid arthritis, inflammatory bowel disease, and neonatal adiposity. Pathologic findings highlight the involvement of novel barrier factors (desmoplakin and claudin), novel immune cell subsets (pathogenic effector T_H2 cells and group 2 innate lymphoid cells), and differential skewing of helper T cells (eg, T_H17 dominance in Asians with AD). As diagnostics, noninvasive examinations of the transepidermal water loss of neonates, the density of epidermal *Staphylococcus* species, and the gut flora might prognosticate the onset of AD. As for therapy, various methods are proposed, including conventional (petrolatum and UV) and molecule-oriented regimens targeting Janus kinase, signal transducer and activator of transcription 3, extracellular signal-regulated kinase, sirtuin 1, or aryl hydrocarbon receptor. (J Allergy Clin Immunol 2016;138:1548-55.)

Key words: *Atopic dermatitis, filaggrin, biologics, cytokines, chemokines, thymic stromal lymphopoietin, chemoattractant receptor-homologous molecule expressed on T_H2 cells, petrolatum, ultraviolet B, sirtuin 1, aryl hydrocarbon receptor, Janus kinase, signal transducer and activator of transcription 3, extracellular signal-regulated kinase, pathogenic effector T_H2, T_H1, T_H2, T_H17, T_H22, transepidermal water loss, adiposity, JTE-052*

Abbreviations used

AD:	Atopic dermatitis
aOR:	Adjusted odds ratio
APT:	Atopy patch test
CLA:	Cutaneous lymphocyte antigen
CRTH2:	Chemoattractant receptor-homologous molecule expressed on T_H2 cells
FLG:	Filaggrin
GWAS:	Genome-wide association study
ILC:	Innate lymphoid cell
IRR:	Incidence rate ratio
KYNU:	L-kynureninase
OR:	Odds ratio
peTH2:	Pathogenic effector T_H2
RR:	Risk ratio
SCORAD:	SCORing Atopic Dermatitis
SNP:	Single nucleotide polymorphism
STAT:	Signal transducer and activator of transcription
TSLP:	Thymic stromal lymphopoietin

Atopic dermatitis (AD) is a chronic skin disorder characterized by pruritus and recurrent eczematous lesions accompanied by inflammation dominated with T_H2 cells in the acute phase.[1] The lifetime prevalence of AD has been increased in the past 3 decades, and it has plateaued at 10% to 20% in developed countries.[1] About 60% of patients with AD have symptoms during the first year of life, although they can start at any age.[1] According to the World Health Organization 2010 Global Burden of Disease survey, AD ranked first among common skin diseases with respect to disability-adjusted life-years and years lived with a disease.[1]

The pathology of AD is not fully understood. Currently, 2 major abnormalities are speculated to underlie the development of AD, namely epidermal barrier and cutaneous immune dysfunctions.[2] The strong correlation between filaggrin *(FLG)* mutations and AD indicates the prime importance of barrier dysfunction in the development of AD. On the other hand, because up to 60% of carriers of *FLG* mutations will not have AD, *FLG* mutations are neither necessary nor sufficient to cause AD.[1] Therefore abnormality with cutaneous inflammation might also play an important role in the pathogenesis of AD.

As described in the following sections, various immune cells, including T cells, B cells, and innate lymphoid cells (ILCs), are involved in the eczematous lesions of patients with AD. Consistently, the pivotal role of IL-4/IL-13–mediated T_H2-type inflammation was proved by using a randomized, placebo-controlled, dose-ranging phase 2b trial with dupilumab.[3]

AD is a complex disease influenced by genetic predisposition and environmental factors.[4] To develop novel effective treatments, we must understand the pathogenesis of AD in detail. Recent advances in AD, as highlighted here, will be instrumental in understanding AD and developing novel therapeutics for the disease (Table I) (Fig 1).[5-51] For comprehensive information on AD, readers are directed to recent reviews.[1,52-55]

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EPIDEMIOLOGY

Incidence of AD

A current trend in incidence rates of AD showed a stable transition in children born in Denmark from 1997 to 2011 or in Sweden from 2006 to 2010.[5] In this study the incidence rate ratios (IRRs) of AD among Danish children ranged from an IRR of 1.05 (95% CI, 1.01-1.08) in 1998 to an IRR of 1.06 (95% CI, 1.03-1.09) in 2011. In Swedish children IRRs of AD ranged from an IRR of 1.05 (95% CI, 1.00-1.10) in 2007 to an IRR of 0.99 (95% CI, 0.95-1.03) in 2010.[5]

Risk factors for AD

Early nutrition and adiposity were linked to development of AD. Risk factors for AD at 6 and 12 months of age were maternal atopy (adjusted odds ratio [aOR], 2.99; 99% CI, 1.35-6.59; $P = .004$) and fat mass of the 80th percentile or greater at day 2 (aOR, 2.31; 99% CI, 1.02-2.25; $P = .0090$).[6]

Interaction between AD and systemic disorders

Comorbidities of AD were assessed by a cohort study using data from German National Health Insurance beneficiaries aged 40 years or younger (n = 655,815) between 2005 and 2011.[7] Patients with AD (n = 49,847) were at increased risk for incident rheumatoid arthritis (risk ratio [RR], 1.72; 95% CI, 1.25-2.37) and inflammatory bowel disease (Crohn disease: RR, 1.34; 95% CI, 1.11-1.61; ulcerative colitis: RR, 1.25; 95% CI, 1.03-1.53),[7] but there was an inverse effect on type 1 diabetes (RR, 0.72; 95% CI, 0.53-0.998).[7]

In another study interferon-gamma receptor 1 (*IFNGR1*) polymorphism was correlated with the onset of eczema herpeticum in European American patients with AD.[9] Replication genotyping was performed on interferon pathway genes (interferon-gamma [*IFNG*], *IFNGR1*, interferon-alpha receptor 1 [*IFNAR1*], and interleukin 12 receptor subunit beta 1 [*IL12RB1*]) in independent samples of 219 European American and 333 African American subjects. The compared sequence was the 494 single nucleotide variants encompassing a total of 105 kb targeting the 4 genes and 2 kb both upstream and downstream. There were 6 rare *IFNGR1* missense variants. The 3 variants (V14M, V16I, and Y397C) conferred a higher risk for AD associated with eczema herpeticum. V14M and Y397C were confirmed to be deleterious, leading to partial *IFNGR1* deficiency. Seven common *IFNGR1* single nucleotide polymorphisms (SNPs), along with common protective haplotypes (2-7 SNPs), conferred a reduced risk of AD associated with eczema herpeticum ($P = .015$-$.002$ and $P = .0015$-$.0004$, respectively). Both SNP and haplotype associations were replicated in an independent African American sample ($P = .004$-$.0001$ and $P = .001$-$.0001$, respectively).

Interaction between AD and sleep disturbances

The pruritus associated with AD leads to sleep disturbances in children and adults.[10-12] Analyzed data were from 401,002 children and adolescents in 19 US population-based cross-sectional studies from the National Survey of Children's Health 2003/2004 and 2007/2008 and the National Health Interview Survey 1997-2013.[11] Children with eczema compared with those without eczema had a higher prevalence (10.7% [95% CI, 10.3% to 11.0%] vs 5.4% [95% CI, 5.3% to 5.5%]) and odds (1.52 [95% CI, 1.45-1.59]) of headaches.[11] Another data set was from 27,157 and 34,525 adults aged 18 to 85 years from the 2010 and 2012 National Health Interview Survey.[12] Adults with a history of eczema had higher odds of hypertension (aOR, 1.48; 95% CI, 1.18-1.85).[12] A concept of IL-1–mediated "inflammatory skin march" was proposed to explain the higher incidence of cardiovascular diseases in patients with AD and those with psoriasis.[8]

PATHOLOGY

Genetics of AD

A genome-wide association study (GWAS) identified novel genes with associations to AD: neuroblastoma amplified sequence *(NBAS)*, thymus-expressed molecule involved in selection *(THEMIS)*, GATA binding protein 3 *(GATA3)*, protocadherin 9 *(PCDH9)*, and S-phase cyclin A-associated protein in the ER *(SCAPER)* at odds ratios (ORs) of 2.947 (95% CI, 1.989-4.386), 2.193 (1.610-2.994), 1.946 (1.529-2.494), 2.655 (1.904-3.717), and 2.126 (1.594-2.841), respectively, in the sample containing 246 Korean children with AD and 551 Korean adult control subjects without a history of allergic diseases (Table II).[13,14] GWASs of the German population revealed novel loci, such as 2q24.3 (xin actin-binding repeat-containing protein 2, *XIRP2*) and 9p21.3 (doublesex and mab-3-related transcription factor-like family A1, *DMRTA1*), at ORs of 1.31 (95% CI, 1.15-1.48) and 0.77 (95% CI, 0.69-0.86), respectively, in the initial GWAS sample set consisted of 870 cases and 5293 control subjects (Table II).[14] Whole-exome sequencing was performed on Ethiopian patients with ichthyosis vulgaris and AD.[15] It revealed heterogeneity of the pathogenesis among Ethiopians. The transcriptome of AD predicted triggering receptor expressed on myeloid cells 1 (TREM-1) and IL-36 as candidate drug targets for AD.[16]

Severe dermatitis, multiple allergies, and metabolic wasting syndrome was found to be caused by mutations of not only desmoglein 1 but also desmoplakin.[17] Furthermore, claudin-1 polymorphism was associated with susceptibility to AD (aOR, 1.48; 95% CI, 1.04-2.12).[18] These observations reinforced the importance of heritable skin barrier defects on the pathogenesis of AD.

Susceptibility loci for the atopic march

AD in children is often followed by different allergic diseases, such as asthma and rhinitis, in sequence with IgE antibody responses against common environmental antigens. This phenomenon is called the atopic or allergic march.[56,57] A GWAS on infantile eczema followed by childhood asthma (12 populations, including 2,428 cases and 17,034 control subjects) identified 7 loci that were involved in the atopic march.[58] Two of them were specific for the combined eczema and asthma phenotypes, which were rs9357733 located in EF-hand domain (C-teminal)-containing protein 1 (*EFHC1*) on chromosome 6p12.3 (OR, 1.27; $P = 2.1 \times 10^{-8}$) and rs993226 between transmembrane and tetratricopeptide repeat containing 2 (*TMTC2*) and solute carrier family 6 member 15 (*SLC6A15*) on chromosome 12q21.3 (OR, 1.58; $P = 5.3 \times 10^{-9}$).[58] Additional susceptibility loci were *FLG* (1q21.3), interleukin 4 (*IL4*)/kinesin superfamily 3A (*KIF3A*) (5q31.1), adaptor-related protein complex 5 beta-1 subunit (*AP5B1*)/ovo-like 1 (*OVOL1*) (11q13.1), chromosome 11 open reading frame 30 (*C11orf30*)/leucine rich