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

TABLE I. Key advances in atopic dermatitis in 2015

Clinical or basic research concerns	Advances and observations
Epidemiology	
Incidence and risk factors	● The incidence rate of AD was stable in Denmark and Sweden, with one third of children being affected by AD at age 5 years.[5] ● Neonatal adiposity correlated with increased risk for AD during the first year of life.[6]
Interaction between AD and systemic disorders	● Patients with AD were at higher risk for RA and IBD.[7] ● IL-1–mediated "inflammatory skin march" was proposed to explain the cardiovascular events in patients with AD and those with psoriasis.[8] ● Eczema herpeticum in European American patients with AD was correlated with *IFNGR1* expression.[9]
Interaction between AD and sleep disturbances	● Nighttime exacerbation of AD disturbed circadian rhythms in children.[10] ● Childhood eczema was associated with headaches.[11] ● Eczema disturbed sleep and had higher odds for cardiovascular risk in adults.[12]
Pathology	
Genetics of AD	● GWAS on Korean children or German patients with AD revealed novel genes.[13,14] ● Whole-exome sequencing of Ethiopian patients with ichthyosis vulgaris and AD showed heterogeneous pathogenesis.[15] ● Transcriptome of AD predicted TREM-1 and IL-36 as candidate drug targets.[16] ● A novel mutation in desmoplakin caused SAM syndrome.[17] ● Claudin-1 polymorphism was associated with susceptibility to AD.[18] ● The skin immune reaction was altered in patients with AD.[19] ● Age and race affected immune response in patients with AD.[20-22]
Dysregulated T-cell immunity	● Skin-homing T cells exhibited a higher activation state in patients with AD and were skewed to T_H2/T_C2 and T_H22/T_C22 in correlation with disease severity.[23,24] ● Patients with AD harbored pathogenic effector T_H2 cells expressing CRTH2, HPGDS, and CD161 and producing IL-5/IL-13.[25] ● Activation of B cells varied more in patients with AD than in those with psoriasis.[26] ● Some patients with AD were sensitized to thioredoxin, an autoallergen.[27]
Innate immunity	● Initiation of murine AD-like dermatitis was dependent on IL-5–producing group 2 ILCs.[28] ● Human skin mast cells were the major source of IL-22 in patients with AD.[29]
Multiple roles of TSLP	● TSLP plays a role in T_H2 memory formation in mice.[30] ● Short and long forms of TSLP had anti-inflammatory and proinflammatory activity, respectively.[31]
Kynurenine	● Proinflammatory effects of kynurenine metabolites (3HAA and quinolinic acid) were shown.[32]
Diagnostics	
Prognostic examinations	● Measurement of TEWL on day 2 after birth reflected AD at 1 year of age.[33] ● Density of *Staphylococcus aureus* was associated with severity of AD.[34] ● Dysbiosis in *Faecalibacterium* species led to AD.[35]
Basic research on analytic tools for AD	● *In vitro* proliferation and cytokine production by $CD3^+CD4^+$ T cells did not suffice for evaluation of skin responses in patients with AD.[36] ● Laser capture microdissection–mediated fine analysis of the skin was useful.[37]
Therapy	
Avoidance of aeroallergens	● Avoidance of exposure to airborne allergens prevented worsening of AD.[38]
Prebiotics	● Prebiotics seemed to prevent early AD, but the effect was not sustained in infants at low risk of atopy.[39]
Recovery of the skin barrier	● Topical Janus kinase inhibitor improved skin barrier function in mice and engrafted human skin.[40] ● UVB was salubrious for the skin barrier.[41] ● Petrolatum induced beneficial molecular responses in the skin.[42] ● Decrease of FLG expression by TSLP was mediated by STAT3/ERK.[43] ● IL-33 downregulated FLG expression and impaired skin barrier.[44] ● SIRT1 promoted FLG expression through AhR in mice.[45] ● Levels of natural moisturizing factor correlated with morphology of corneocytes.[46] ● FLG mutations were not associated with allergen sensitization in adults without AD, intimating the importance of the concomitant presence of inflammation in this step.[47] ● AD augmented sensitization for peanut antigen in skin of patients with AD.[48]
Biologics	● Clinical trials for T_H2, T_H22, and IL-23/T_H17 are being pursued for AD.[49]
Novel targets	● Lidocaine increased the number of regulatory T cells and ameliorated Chinese patients with AD.[50] ● IL-25 inhibition might be applicable to AD.[51]

AhR, Aryl hydrocarbon receptor; *CRTH2*, chemoattractant receptor-homologous molecule expressed on T_H2 cells; *ERK*, extracellular signal-regulated kinase; *3HAA*, 3-Hydroxyanthranilic acid; *HPGDS*, hematopoietic prostaglandin D_2 synthase; *IBD*, inflammatory bowel disease; *RA*, rheumatoid arthritis; *SAM*, severe dermatitis, multiple allergies, and metabolic wasting; *SIRT1*, Sirtuin 1; *TEWL*, transepidermal water loss; *TREM-1*, triggering receptor expressed on myeloid cells 1.

repeat containing 32 (*LRRC32*) (11q13.5), and Ikaros family zinc finger protein 3 (*IKZF3*) (17q21).[58] This study showed the predominance of eczema-related loci for the atopic march, indicating the importance of skin care in children with an atopic diathesis.

Dysregulated T-cell immune balance

Altered or dysregulated balance of T-cell immunity was found in patients with AD (Fig 1).[19] Biopsy specimens from skin patch tested with common contact allergens (nickel, fragrance, and rubber) were obtained from 24 patients (10 patients with AD

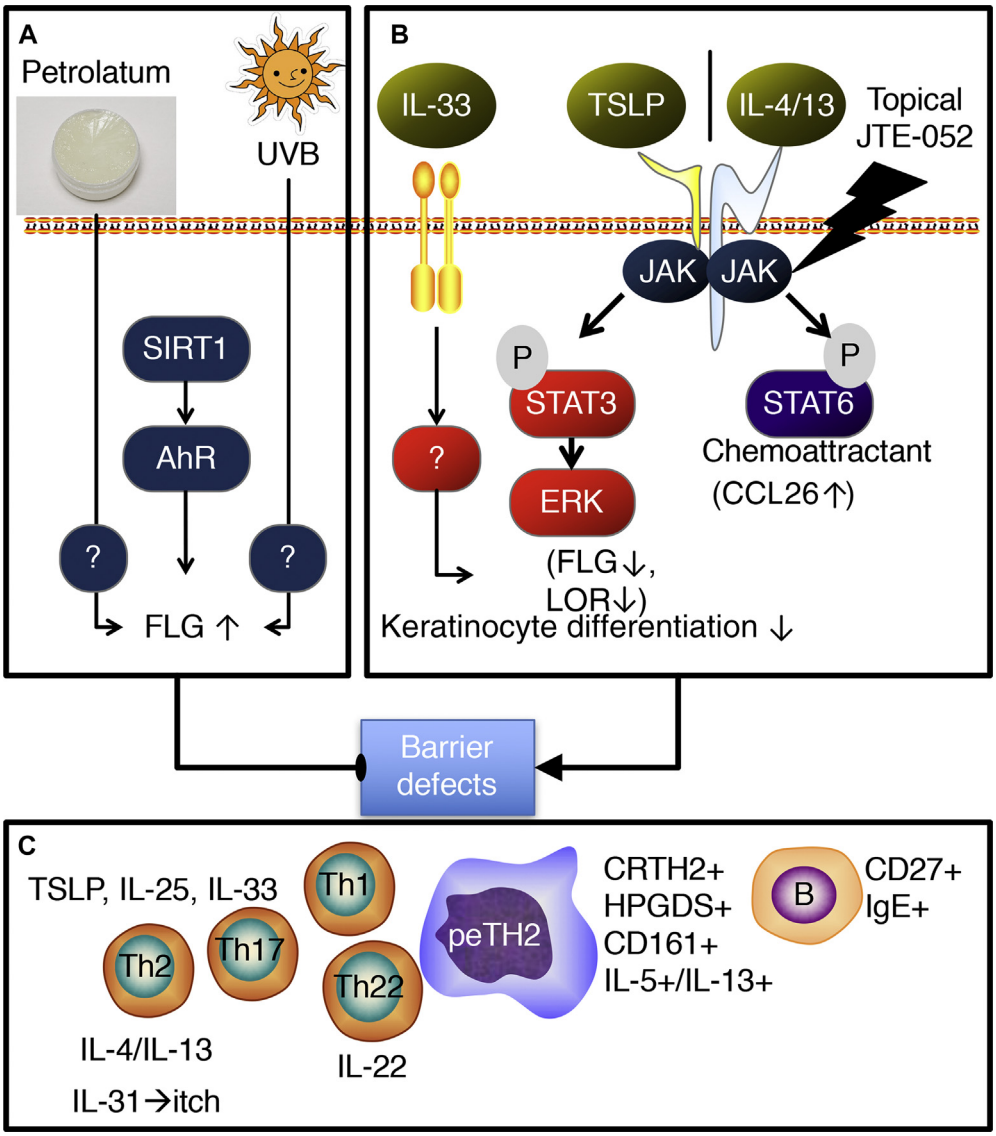

FIG 1. Pathogenesis of AD and therapeutic targets. Control of the skin barrier is critical for the treatment of AD. FLG and loricrin *(LOR)* are cardinal proteins that maintain the barrier. Thus checkpoints for FLG/LOR expression are targets for therapeutic approaches. **A,** Conventional regimens targeting FLG. Petrolatum, UVB, and sirtuin 1 *(SIRT1)* increase expression of FLG. The effect of SIRT1 is mediated by aryl hydrocarbon receptor (AhR). **B,** Drug targets for AD treatment. IL-33 reduces FLG expression through a pathway that is not well studied. Like IL-4 and IL-13, TSLP inhibits expression of FLG through the STAT3/extracellular signal-regulated kinase (ERK) pathway. Topical JTE-052, a Janus kinase inhibitor, effectively ameliorates dermatitis through inhibition of STAT3-mediated reduction of FLG and LOR, as well as STAT6-mediated production of the chemoattractant CCL26. **C,** Cytokines and lymphocytes involved in the pathogenesis of barrier defects and AD. Skin damages leads to activation of keratinocytes to produce IL-25, IL-33, and TSLP. Langerhans cells and dendritic cells are activated and induce production of IL-4 and IL-13 from T_H2 cells. T_H1, T_H17, and T_H22 cells appear and play pathogenic roles in the chronic stage of lesional skin in patients with AD. CRTH2-positive, hematopoietic prostaglandin D_2 synthase (HPGDS)–positive, $CD161^+$, $IL\text{-}5^+$, $IL\text{-}13^+$ peT_H2 cells, and IgE^+CD27^+ activated B cells also increase in the patients with AD.

and 14 patients without AD). Gene expression and immunohistochemistry studies revealed that allergic immune reactions were globally attenuated and differentially polarized (decreases in T_H1 and increases in T_H2/T_H17 products) in patients with AD.[19]

Aging and racial factors were shown to add complexity to the dysregulated immune response in patients with AD. Infants with AD showed increased T_H2 responses but lower IFN-γ responses compared with adults.[20] Also, early pediatric AD showed cutaneous lymphocyte antigen (CLA)-positive T_H2 cells, whereas adults with AD acquired T_H22 and T_C22 cells (a counterpart of T_H22 cells in $CD8^+$ T cells).[20] Asian patients with AD had increased T_H17 and T_H22 responses compared with white patients.[21] Asian patients with AD presented with a blended phenotype between that of European American patients with AD and those with psoriasis.[22] IL-17A might play a role in

TABLE II. List of novel genes associated with AD

Study	Genes (OR)
GWAS (Korean)[13]	*NBAS* (2.947), *THEMIS* (2.193), *GATA3* (1.946), *PCDH9* (2.655), *SCAPER* (2.126)
GWAS (German)[14]	*XIRP2* (1.31), *DMRTA1* (0.77)

inducing the T_H2-type immune response in Asian patients with AD, as shown in a murine model of AD.[59]

Skin-homing T cells exhibited a higher activation state in patients with AD compared with those in patients with psoriasis in the expression profiles of inducible T-cell costimulator and HLA-DR.[23] The expression of CD69 in skin-homing cells was negatively correlated with SCORing Atopic Dermatitis (SCORAD) scores.[23] This might be explained by a role of CD69 for T_H17 differentiation.[23] Skin-homing T cells were skewed to T_H2/T_C2 and T_H22/T_C22 but not T_H17/T_C17 cells in peripheral blood.[24] Positive correlations were found between frequencies of IL-13– and IL-22–producing $CD4^+$ and $CD8^+$ T cells.[24] The frequencies of IL-13–producing CLA^+ cells were correlated with IgE levels and SCORAD scores.[24] This indicates that severe AD is correlated with T_H2/T_H22 cells.

The human counterpart of the pathogenic effector T_H2 (peT_H2) cell subset was identified in patients with AD.[25] The peT_H2 cell is characterized by expression of hematopoietic prostaglandin D synthase, chemoattractant receptor-homologous molecule expressed on T_H2 cells (CRTH2), and CD161.[25] The peT_H2 cells produced greater amounts of IL-5 and IL-13.[25]

Activation of B cells varied more in patients with moderate-to-severe AD (n = 24; mean SCORAD score, 65) than in patients with psoriasis (n = 16; mean Psoriasis Area and Severity Index score, 16).[26] Higher frequencies of chronically activated $CD27^+$ memory B cells were observed in patients with AD.

Some patients with AD were sensitized to thioredoxin.[27] Thioredoxin seemed to function as a skin-associated autoallergen.[27] Thioredoxin induced IgE-dependent upregulation of IL-13 and impaired upregulation of IL-10 in sensitized patients with AD.[27]

Innate immunity

IL-5–producing group 2 ILCs initiated dermatitis in *Flg* mutant ($Flg^{ft/ft}$ BALB/c) mice.[28] This finding indicates group 2 ILCs might play a role in AD in human subjects. Human skin mast cells were shown to be the major producer of IL-22 in patients with AD or psoriasis.[29] Further studies are required to elucidate the importance of ILCs in the pathogenesis of AD.

Multiple roles of thymic stromal lymphopoietin

Thymic stromal lymphopoietin (TSLP) is one of the cytokines that promote T-cell maturation and activation of antigen-presenting cells. In accordance, TSLP was shown to play a role in T_H2 memory formation in mice.[30] Furthermore, TSLP was shown to activate signal transducer and activator of transcription (STAT) 3/extracellular signal-regulated kinase (ERK) and decreases expression of FLG in mice and human keratinocytes.[40,43] Importantly, the suppressive effect of TSLP on FLG expression was confirmed by the human skin engrafted on immunocompromised mice.[40]

It turned out that the short and long forms of TSLP differentially functioned in anti-inflammatory and proinflammatory ways, respectively.[31] The short form was expressed under steady-state conditions and reinforced the anti-inflammatory capacity of PBMCs and dendritic cells.[31]

Proinflammatory role of kynurenine metabolites

Kynurenine is a metabolite of tryptophan. Kynurenine is further degraded by L-kynureninase (KYNU) into 3-hydroxyanthranilic acid and quinolinic acid. These kynurenine metabolites were shown to induce inflammatory genes.[32] $KYNU^+$ cells were of myeloid origin and enriched in the inflammatory lesions of patients with psoriasis and those with AD.[32]

NOVEL DIAGNOSTIC TOOLS FOR AD

Prognostic examinations

A measure of transepidermal water loss on day 2 after birth reflected AD at 1 year of age.[33] Therefore evaluation of transepidermal water loss enables us to identify neonates with a high risk for AD. Such neonates should be treated with emollients and closely followed to prevent the onset of AD. The density of *Staphylococcus aureus* on the skin surface was proposed as another noninvasive prognostic examination. The density of *S aureus* on both lesional and nonlesional areas was correlated with SCORAD score (present severity) and Nottingham Eczema Severity Score (disease course severity) in patients with AD.[34] Furthermore, *Faecalibacterium prausnitzii*, an operational taxonomic unit (F06 in particular), was enriched in the gut microbiome of patients with AD ($P < .003$).[35] Thus evaluation of the gut microbiome can be another prognostic tool for AD.

Basic research on analytic tools for AD

The atopy patch test (APT) is used to evaluate non–IgE-mediated or T cell–mediated reactions in patients with AD. However, it was shown that an *in vitro* T-cell proliferation/cytokine production assay with $CD3^+CD4^+$ T cells did not correlate with the APT response.[36] This finding indicates an unidentified factor is involved in the APT. Further research is awaited. To analyze the epidermis and dermis separately, laser capture microdissection was applied to skin obtained from subjects with or without AD.[37] This method could identify changes in expression of IL-34 and claudin-4 and claudin-8 in the epidermis.[37] This research will lead to the development of robust diagnostic tools.

THERAPEUTIC APPROACHES

Avoidance of aeroallergens

The inflammatory effect of pollen was studied by using an environmental challenge chamber.[38] Pollen was shown to exacerbate AD by upregulating CCL17, CCL22, and IL-4 at exposed areas of the skin.[38] This study emphasizes the importance of avoiding exposures to aeroallergens. Covering the skin with clothes might be helpful to prevent worsening of AD.

TABLE III. Biologics for AD (adopted and modified from Noda et al[49])

Agent	Trade name	Target	Drug	Phase	Manufacturer	ClinicalTrials.gov
Dupilumab		IL-4Rα	mAb	III	Regeneron	NCT01949311
Ustekinumab	Sterala	IL-12/23p40	mAb	II	Janssen	NCT01806662
ILV-094 (fezakinumab)		IL-22	mAb	II	Pfizer	NCT01941537
CIM331		IL-31R	mAb	II	Chugai	NCT01986933
BMS-981164		IL-31	mAb	I	BMS	NCT01614756
Apremilast	Otezla	PDE4	Oral small molecule	II	Celgene	NCT02087943
QGE031		IgE	mAb	II completed	Novartis	NCT01552629
OC000459		CRTH2	Oral antagonist	II	Atopix	NCT02002208
AMG 157		TSLP	mAb	I completed	Amgen	NCT00757042
MK-8226		TSLPR	mAb	I	Merck	NCT01732510

CRTH2, Chemoattractant receptor-homologous molecule expressed on T_H2 cells; *PDE4*, phosphodiesterase 4; *TSLPR*, thymic stromal lymphopoietin receptor.

Prebiotics

Prebiotics are food ingredients that are conducive to the growth of beneficial microorganisms in the host. Prebiotics seemed to be preventive against early AD, but the effect was not sustained in infants at low risk of atopy.[39] In this study, prebiotic oligosaccharides were designed to mimic human milk oligosaccharides. The prebiotic formula group received a nonhydrolyzed cow-based formula supplemented with neutral short-chain galacto-oligosaccharides and long-chain fructo-oligosaccharides and specific pectin-derived acidic oligosaccharides up to age 12 months.[39]

Recovery of the skin barrier by FLG expression

Novel or conventional methods can increase FLG expression (Fig 1). The topical Janus kinase inhibitor JTE-052 inhibited STAT3 and increased FLG expression.[40] UVB stimulated expression of FLG through increased cutaneous vitamin D production.[41] Petrolatum induced beneficial molecular responses, including upregulation of FLG and loricrin.[42] The regulatory mechanism of FLG expression was heterogeneous. TSLP decreased FLG expression through the STAT3/extracellular signal-regulated kinase (ERK) pathway.[40,43] IL-33 also decreased expression of FLG through an unidentified signaling pathway.[44] Sirtuin 1 promoted FLG expression through activation of aryl hydrocarbon receptor, and the ligand for aryl hydrocarbon receptor restored FLG expression in mice.[45]

Natural moisturizing factor is a converted form of FLG. Levels of natural moisturizing factor correlated with the morphology of corneocytes.[46] Morphologic changes in corneocytes might explain the barrier defect in patients with AD. These findings are consistent with the observation that sensitization to peanut antigen was augmented in the skin of patients with AD.[48] However, FLG mutations were not associated with allergen sensitization in adults without AD.[47] This evidence indicates *FLG* mutations by themselves do not suffice to render the skin vulnerable to allergen sensitization. Also, the presence of concomitant inflammation might be required for the establishment of sensitization. Therefore inflammation must be controlled to prevent the onset of AD.

Biologics

Noda et al[49] reviewed the current state of biologics being pursued for AD (Table III). Dupilumab competitively binds to IL-4 receptor α and inhibits downstream signaling events induced by IL-4 and IL-13. Dupilumab achieved major improvement in disease activity and reduced levels of the T_H2 chemokines CCL17, CCL18, and CCL26, as well as certain T_H17/T_H22-related genes encoding S100A12 and elafin. These data support the centrality of T_H2 cells in the development of AD.

IL-31 is a T_H2 cytokine that promotes itch. Anti–IL-31 receptor (CIM331) and anti–IL-31 (BMS-981164) are being tested in clinical trials. Anti-TSLP ligand (AMG 157) and its receptor (MK-8226) are intended to block T_H2-promoting dendritic cell signaling. Ustekinumab (anti–IL-12/23p40) and fezakinumab (anti–IL-22) are being tested in patients with AD. Apremilast (an inhibitor for phosphodiestrase 4) is approved for the treatment of psoriatic arthritis and psoriasis. Phosphodiesterase 4 degrades cyclic AMP and reduces T-cell receptor–mediated T-cell activation and cytokine production. Apremilast has shown efficacy to AD in a preliminary study. OC000459 (an oral antagonist for CRTH2) has shown efficacy in patients with asthma, allergic rhinitis, and conjunctivitis. OC000459 is being tested for AD.

Further targets

IL-25 (an IL-17 family cytokine) induces T_H2 immune responses. Inhibition of IL-25 was beneficial in the nasal polyps of Asian patients with chronic rhinosinusitis.[51] Therefore IL-25 blockade might ameliorate AD. Lidocaine ameliorated Chinese patients with AD.[51] The mechanism of the improvement was attributed to the increased number of regulatory T cells.[50]

CONCLUSION

The quality of life of patients with AD is still far from satisfactory. At present, AD cannot be cured fundamentally, and the current treatments are limited to improve and control symptoms. Deeper understanding of the mechanism of barrier damage and immune dysregulation will lead to development of more specific regimens to control and prevent AD.

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