Cellular and molecular immunologic mechanisms in patients with atopic dermatitis

Thomas Werfel, MD,[a] Jean-Pierre Allam, MD,[b] Tilo Biedermann, MD,[c] Kilian Eyerich, MD, PhD,[c] Stefanie Gilles, PhD,[d] Emma Guttman-Yassky, MD, PhD,[e] Wolfram Hoetzenecker, MD,[f] Edward Knol, PhD,[g] Hans-Uwe Simon, MD, PhD,[h] Andreas Wollenberg, MD,[i] Thomas Bieber, MD, PhD, MDRA,[j,k] Roger Lauener, MD,[j,l] Peter Schmid-Grendelmeier, MD,[j,m] Claudia Traidl-Hoffmann, MD,[d,j] and Cezmi A. Akdis, MD[j,n] *Hannover, Bonn, Munich, and Augsburg, Germany; New York, NY; St Gallen, Bern, Davos, and Zurich, Switzerland; and Utrecht, The Netherlands*

Atopic dermatitis (AD) is a complex skin disease frequently associated with other diseases of the atopic diathesis. Recent evidence supports the concept that AD can also recognize other comorbidities, such as chronic inflammatory bowel or cardiovascular diseases. These comorbidities might result from chronic cutaneous inflammation or from a common, yet-to-be-defined immunologic background leading to immune deviations. The activation of immune cells and their migration to the skin play an essential role in the pathogenesis of AD. In patients with AD, an underlying immune deviation might result in higher susceptibility of the skin to environmental factors. There is a high unmet medical need to define immunologic endotypes of AD because it has significant implications on upcoming stratification of the phenotype of AD and the resulting targeted therapies in the development of precision medicine. This review article emphasizes studies on environmental factors affecting AD development and novel biological agents used in the treatment of AD. Best evidence of the clinical efficacy of novel immunologic approaches using biological agents in patients with AD is available for the anti–IL-4 receptor α-chain antibody dupilumab, but a number of studies are currently ongoing with other specific antagonists to immune system players. These targeted molecules can be expressed on or drive the cellular players infiltrating the skin (eg, T lymphocytes, dendritic cells, or eosinophils). Such approaches can have immunomodulatory and thereby beneficial clinical effects on the overall skin condition, as well as on the underlying immune deviation that might play a role in comorbidities. An effect of these immunologic treatments on pruritus and the disturbed microbiome in patients with AD has other potential consequences for treatment. (J Allergy Clin Immunol 2016;138:336-49.)

Key words: *Atopic dermatitis, skin barrier, filaggrin, T_H2, IL-4, IL-13, IL-31, IgE, innate, adaptive, skin*

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The 3rd Global Allergy Forum was a "think tank" conference held in July 2015 in Davos, Switzerland. The 3rd Global Allergy Forum was initiated and supported by the Christine Kühne-Center for Allergy Research and Education.[1] This review highlights the results of a discussion of a working group of experts from the field of immunodermatology with the aim to define future research avenues in patients with atopic dermatitis (AD).

From [a]the Division of Immunodermatology and Allergy Research, Department of Dermatology and Allergy, Hannover Medical School; [b]the Department of Dermatology and Allergy, Rheinische Friedrich Wilhelm University, Bonn; [c]the Department of Dermatology and Allergy, Technical University of Munich; [d]the Institute of Environmental Medicine, UNIKA-T, Technical University Munich and Helmholtz Zentrum München, Augsburg; [e]the Laboratory for Investigative Dermatology, Rockefeller University, and the Department of Dermatology and the Laboratory for Inflammatory Skin Diseases, Icahn School of Medicine at Mount Sinai, New York; [f]the Department of Dermatology/Allergology, Cantonal Hospital St Gallen; [g]the Departments of Immunology and Dermatology/Allergology, University Medical Center Utrecht; [h]the Institute of Pharmacology, University of Bern; [i]the Department of Dermatology and Allergy, Ludwig-Maximilians-Universität, Munich; [j]the Christine Kühne-Center for Allergy Research and Education, Davos; [k]the Department of Dermatology and Allergy, University of Bonn; [l]Children's Hospital of Eastern Switzerland, St Gallen; [m]the Allergy Unit, University of Zurich; and [n]the Swiss Institute for Allergy and Asthma Research (SIAF), University of Zurich, Davos.

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Corresponding author: Thomas Werfel, MD, Division of Immunodermatology and Allergy Research, Department of Dermatology and Allergy Hannover Medical School, Carl-Neuberg-Strasse 1, 30625 Hannover, Germany. E-mail: Werfel.Thomas@MH-Hannover.de.

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Terms in boldface and italics are defined in the glossary on page 337.

Abbreviations used

AD: Atopic dermatitis
AMP: Antimicrobial peptide
CNF: Cutaneous nerve fiber
DC: Dendritic cell
FLG: Filaggrin
HDM: House dust mite
ILC2: Type 2 innate lymphoid cell
TRP: Transient receptor potential
TSLP: Thymic stromal lymphopoietin

IS AD LIMITED TO THE SKIN OR IS IT A SYSTEMIC DISEASE?

The question of whether AD is a systemic disease can be answered by using epidemiologic data and systemic biomarkers of the disease. Concerning epidemiology, it is broadly accepted that AD is associated with other atopic diseases, namely allergic rhinoconjunctivitis, allergic bronchial asthma, and food allergy. Here, sequential disease development is called the atopic march.[2-5] Recently, other comorbidities of AD have been the focus of epidemiologic studies.[6] These studies report that AD is negatively correlated with different entities of cancer.[7,8] The systemic T_H2-dominated immunity in patients with AD is associated with ulcerative colitis, a chronic inflammatory bowel disease that is corroborated by the common hallmarks of T_H2 immunity and an impaired epithelial barrier.[9] Moreover, AD has been shown to be associated with a negative correlation with type 1 diabetes in at least 2 studies.[10,11]

However, the findings of positive correlations of AD with ***T_H1*** diseases and negative correlations with ***T_H2*** diseases are not clear. Recently, an increased risk of AD has been described in Taiwanese patients with type 1 diabetes.[12] Moreover, a positive correlation has recently been found for patients with AD with rheumatoid arthritis, a disease considered to be T_H1/***T_H17*** associated.[11] Similar to psoriasis, adults with AD have an increased risk of cardiovascular disease, heart attack, and stroke.[13] Recent data from a Danish study suggest that the higher incidence of adverse cardiovascular outcomes in patients with severe AD can be explained by an increased burden of comorbidities and detrimental lifestyle behavior.[14]

Taken together, these observations argue for the fact that AD is mainly a T_H2-driven systemic disease rather than inflammation limited to the skin. In line with this hypothesis, several T_H2-associated serum biomarkers correlate with disease severity, therapeutic response, or both, among them ***CCL17***, ***IL-31***, and ***eosinophil cationic protein*** (ECP).[15-17]

GLOSSARY

ACTINOBACTERIA: A phylum of gram-positive bacteria with high guanine and cytosine content in their DNA. Although understood primarily as soil bacteria, they can be more abundant in fresh water. Actinobacteria is one of the dominant bacterial phyla and contains one of the largest bacterial genera, *Streptomyces* species, as well as *Corynebacterium and Propionibacterium* species.

BACTEROIDES: A genus of gram-negative obligate anaerobic bacteria. *Bacteroides* species are non–endospore-forming bacilli and can be either motile or nonmotile, depending on the species. *Bacteroides* species membranes contain sphingolipids and meso-diaminopimelic acid in their peptidoglycan layer.

BIRBECK GRANULE: Cytoplasmic organelles with a central linear density and a striated appearance solely found in Langerhans cells.

CCL17 (Cys-Cys LIGAND 17): An antimicrobial cytokine that displays chemotactic activity for T lymphocytes but not monocytes or granulocytes. The product of this gene binds to the chemokine receptors CCR4 and CCR8 and plays important roles in T-cell development in the thymus, as well as in trafficking and activation of mature T cells.

$CD8^+$ T CELLS: T lymphocytes that kill virus-infected and cancer cells or damaged cells. $CD8^+$ T cells express T-cell receptors that can recognize a specific antigen bound to the class I MHC molecule of an infected cell and ultimately kill the target cell.

CD11b: A receptor for complement (C3bi), fibrinogen, or clotting factor X (also referred to as integrin alpha M), which mediates inflammation. In human subjects CD11b is strongly expressed on myeloid cells and weakly expressed on natural killer (NK) cells and some activated lymphocytes, as well as on microglia in the brain. In mice the CD11b antigen is expressed on monocytes/macrophages and microglia. To a lower extent, it is expressed on granulocytes, NK cells, $CD5^+$ B-1 cells, and subsets of dendritic cells.

CD11c: A type I transmembrane protein (also referred to as integrin, alpha X [complement component 3 receptor 4 subunit]) found at high levels on most human dendritic cells but also on monocytes, macrophages, neutrophils, and some B cells that induces cellular activation and helps trigger neutrophil respiratory burst.

DAMAGE-ASSOCIATED MOLECULAR PATTERN: Host molecules that can initiate and perpetuate a noninfectious inflammatory response.

DERMATOPHAGOIDES FARINAE: A house dust mite known to elicit an allergic response that is more common in drier areas. The European house dust mite *(Dermatophagoides pteronyssinus)* and the American house dust mite *(Dermatophagoides farinae)* are 2 different species but are not necessarily confined to Europe or North America.

ECZEMA HERPETICUM: An eruption caused by viral infection, usually with herpes simplex virus (HSV). This extensive cutaneous vesicular eruption arises from pre-existing skin disease, usually atopic dermatitis (AD). Children with AD have a higher risk of eczema herpeticum, in which HSV type 1 (HSV-1) is the most common pathogen. It is commonly caused by HSV-1 or HSV-2. A similar skin disease can also be caused by coxsackievirus A16 or vaccinia virus.

EOSINOPHIL CATIONIC PROTEIN (ECP): A protein released during degranulation of eosinophils that is related to inflammation and asthma because in these cases there are increased levels of ECP in the sputum and bronchoalveolar lavage fluid.

FcεRI: The high-affinity receptor for the Fc region of IgE, an antibody isotype involved in allergic disease and parasitic immunity, that is constitutively expressed on mast cells and basophils and inducible in dendritic cells (mainly atopic dermatitis) and in eosinophils.

FIRMICUTES: A phylum of bacteria, most of which have a gram-positive cell-wall structure but have recently been defined as a core group of related forms called the low-G+C group in contrast to the Actinobacteria. They have round cells, called cocci (singular coccus), or rod-like forms (bacillus), such as *Staphylococcus* species.

INDOLEAMINE 2,3-DIOXYGENASE 1: Indoleamine 2,3-dioxygenase is an immune checkpoint molecule in the sense that it is an immunomodulatory enzyme produced by some alternatively activated macrophages and other immunoregulatory cells (also used as an immune subversion strategy by many tumors).

IFN-γ: A cytokine critical for innate and adaptive immunity against viral, some bacterial, and protozoal infections. IFN-γ is produced predominantly by natural killer (NK) and NKT cells as part of the innate immune response and by $CD4^+$ T_H1 and $CD8^+$ cytotoxic T-lymphocyte effector T cells once antigen-specific immunity develops.

IL-4: A cytokine that induces differentiation of naive T_H0 to T_H2 cells and class-switching of IgE in B cells. IL-4 subsequently produces additional

IL-4 in a positive feedback loop. IL-4 is a ligand for the IL-4 receptor that also binds to IL-13, which might contribute to many overlapping functions of this cytokine and IL-13.

IL-5: A major maturation and differentiation cytokine expressed by T_H2 cells, type 2 innate lymphoid cells, and eosinophils in mice and human subjects. IL-5 has been shown to play an instrumental role in eosinophilic inflammation in patients with allergic diseases.

IL-6: Implicated in a wide variety of inflammation-associated disease states, this cytokine is involved in maturation of B cells and has been shown to be an endogenous pyrogen capable of inducing fever in patients with autoimmune diseases or infections.

IL-13: A cytokine produced primarily by T_H2 cells that is involved in several stages of B-cell maturation and differentiation and is critical to the pathogenesis of allergen-induced asthma but operates through mechanisms independent of IgE and eosinophils.

IL-22: A cytokine with important functions in host defense at mucosal surfaces, as well as in tissue repair. It is unique in that it is produced by immune cells, including T_H cell subsets and innate lymphocytes, but acts only on nonhematopoietic stromal cells, in particular epithelial cells, keratinocytes, and hepatocytes.

IL-23: A cytokine secreted by activated dendritic cells and macrophages, IL-23 functions in innate and adaptive immunity to regulate T_H17 function and proliferation. In addition, this cytokine induces $CD8^+$ memory T cells to proliferate and produce IL-17. As such, IL-23 has been described as a key cytokine controlling inflammation in peripheral tissues.

IL-25: A cytokine that shares sequence similarity with IL-17 and has been shown to be a proinflammatory cytokine favoring the T_H2-type immune response. IL-25 can induce nuclear factor κB activation and stimulate IL-8 production.

IL-31: A cytokine from the IL-6 family of cytokines that is expressed on activated T_H2 cells and believed to play a role in the promotion of allergic skin disorders and itch and regulation of other allergic diseases, such as asthma.

IL-33: A member of the IL-1 family that potently drives production of T_H2-associated cytokines.

INNATE LYMPHOID CELLS (ILCs): Innate immune cells that belong to the lymphoid lineage but lack a B- or T-cell receptor and thus cannot respond in an antigen-specific manner. ILCs are a recently described group of cells with physiologic functions analogous to those of helper T cells and cytotoxic natural killer cells. They have a role in protective immunity and the regulation of homeostasis and inflammation, and their dysregulation has been shown to lead to immune pathology, such as allergy and autoimmune disease.

LANGERHANS CELLS (LCs): Dendritic cells (antigen-presenting immune cells) of the skin and mucosa containing large organelles called Birbeck granules. They are present in all layers of the epidermis, except the stratum corneum, which protects against infections, and are most prominent in the stratum spinosum.

MicroRNAs: Small noncoding RNA molecules (containing about 22 nucleotides) found in plants, animals, and some viruses that function in RNA silencing and posttranscriptional regulation of gene expression.

NLRP3 INFLAMMASOME: Assembly of the NLRP3 inflammasome complex activates caspase-1 and mediates the processing and release of the leaderless cytokine IL-1β, thereby serving a central role in the inflammatory response and in diverse human diseases.

PATHOGEN-ASSOCIATED MOLECULAR PATTERNS: Molecules associated with groups of pathogens that are recognized by cells of the innate immune system. These molecules can be referred to as small molecular motifs conserved within a class of microbes.

PROTEOBACTERIA: A major group (phylum) of gram-negative bacteria. They include a wide variety of pathogens, such as *Escherichia*, *Salmonella*, *Vibrio*, *Helicobacter*, *Yersinia*, and many other notable genera.

T_H1 CELLS: A lineage of $CD4^+$ effector T cells that promote cell-mediated immune responses and are required for host defense against intracellular viral and bacterial pathogens. T_H1 cells secrete mainly IFN-γ, IL-2, and TNF-α/β. These cytokines promote macrophage activation, nitric oxide production, and cytotoxic T-lymphocyte proliferation, leading to the phagocytosis and destruction of microbial pathogens. Exaggerated T_H1 responses have been found to be associated with autoimmune diseases, including rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, and type 1 diabetes.

T_H2 CELLS: A distinct lineage of $CD4^+$ effector T cells that secretes IL-4, IL-5, IL-9, IL-13, and IL-17E/IL-25. These cells are required for humoral immunity and play an important role in coordinating the immune response to large extracellular pathogens.

T_H17 CELLS: A subset of activated $CD4^+$ T cells that are responsive to IL-1 receptor 1 and IL-23 receptor signaling. They are regulated by the IL-6/signal transducer and activator of transcription 3/retinoic acid–related orphan receptor γt lineage control and produce the cytokines IL-17A, IL-17F, IL-17AF, IL-21, IL-22, IL-26 (human), GM-CSF, macrophage inflammatory protein 3α, and TNF-α. T_H17 cells act as a bridge between adaptive and innate immunity, where they promote neutrophil activation, immunity to pathogens, and inflammation.

T_H22 CELLS: A subset of T cells that produce the cytokine IL-22 that express the skin-homing chemokine receptors CCR4 and CCR10, reside in the normal skin, and are enriched in the lesional skin of inflammatory skin diseases, indicating the importance of IL-22 in skin homeostasis and pathogenesis of skin diseases.

THYMIC STROMAL LYMPHOPOIETIN: A cytokine that stimulates the maturation of T cells through activation of antigen-presenting cells, such as dendritic cells and macrophages.

TNF-α: Secreted primarily by macrophages, this cytokine's primary role is the regulation of immune cells. Moreover, it is involved in the regulation of a wide spectrum of biological processes, including cell proliferation, differentiation, apoptosis, lipid metabolism, and coagulation.

TOLL-LIKE RECEPTORS: A class of proteins usually expressed in sentinel cells, such as macrophages and dendritic cells, that recognize structurally conserved molecules derived from microbes. Once these microbes have breached physical barriers, such as the skin or intestinal tract mucosa, they are recognized by Toll-like receptors (TLRs), which activate immune cell responses. The TLRs include TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, TLR10, TLR11, TLR12, and TLR13, although the latter 2 are not found in human subjects.

TYPE I INTERFERON: A subgroup of interferon proteins that help regulate the activity of the immune system. All type I interferons bind to a specific cell-surface receptor complex known as the IFN-α receptor (IFNAR) that consists of the IFNAR1 and IFNAR2 chains. They are responsible for inhibition of viral replication inside cells in addition to several cellular regulatory roles.

TYPE 2 INNATE LYMPHOID CELLS (ILC2s): Innate lymphoid cells capable of producing the T_H2 cytokines IL-4, IL-5, IL-9, and IL-13 in response to helminth infection that have been implicated in the development of allergic lung inflammation. They require IL-7 for their development, which activates 2 transcription factors required by these cells: retinoic acid–related orphan receptor α and GATA3.

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Differences in cytokine patterns in the nonallergic variant are discussed below in the context of endotypes in patients with AD. In addition, many intracellular molecular mechanisms, including ***microRNAs***, play a role in pathogenesis, emphasizing the complexity of the disease with a systemic immune/inflammatory dysfunction and its interaction with skin keratinocytes.[18,19]

COMPARATIVE FINDINGS IN PATIENTS WITH AD AND PSORIASIS

Similar to psoriasis, AD skin lesions show epidermal hyperplasia, T-cell and dendritic cell (DC) infiltrates, and increased production of inflammatory mediators.[20-22] However, a strong negative correlation and antagonistic clinical course were observed with the T_H17-driven disease psoriasis, and the latter can even be treated with the ***IL-4***–targeting T_H17-driving cytokine ***IL-23***.[23-26] In patients with psoriasis, increasing knowledge of inflammatory pathways led to bedside-to-bench pathogenic dissection and translational testing of therapeutics, with psoriasis being considered perhaps the best model of translational medicine in the field of dermatology. These therapeutic developments helped cement psoriasis as a T_H17/IL-23 and ***TNF-α***–associated disease with multiple approved biological medical products and many more in early- or late-phase clinical trials.[21] The growing mechanistic understanding of AD, clinical subclassifications, and better resolution of tissue inflammation with specific compounds antagonizing AD mediators are leading to a similar translational revolution in patients with AD.

In addition, these developments are guiding a paradigm shift in the interpretation of disease pathogenesis and further accelerating the development of new therapeutics.[27,28] These studies, as well as studies with broad immune suppressants,[27-30] also identified biomarkers of therapeutic response that are currently implemented in clinical trials. These trials will not only inform about key disease features but also shed light on differences and similarities in therapeutic responses between various AD endotypes.

IMMUNOLOGY OF ENDOTYPES IN PATIENTS WITH AD

Although AD is primarily defined by clinical criteria,[31] it is recognized as a complex disease with several distinct variants distinguished based on age of onset, race, acute versus chronic course, therapeutic response, and infectious or allergic/irritant triggers.[21,32-36] In addition to some differences in clinical characteristics (eg, pediatric vs adult AD), it is now established that various AD subtypes can also be distinguished based on their molecular and cellular characteristics.[37-39]

For a personalized medicine approach that can be implemented in future therapeutic trials and treatment schemes for AD, it is important to define AD endotypes.[34] In addition to the clinical phenotype, future stratifications of patients with AD should also account for differing immune polarizations and genotypes of skin barrier proteins, such as filaggrin (FLG). An early distinction relates atopy-related and unrelated AD: 80% of patients with AD manifest with high levels of serum IgE and a strong atopic background. Patients with the nonallergic variant of AD have normal levels of IgE but can still exhibit specific IgE against microbial and other antigens.[40] Different endotypes of AD have been recently proposed in a recent PRACTALL document, such as type 2 immune response and non–type 2 immune response AD, with a combination of T_H1-, T_H17-, and ***T_H22***-driven inflammation, as well as epithelial dysfunction.[41]

Biomarker-based studies suggest that various AD phenotypes are associated with distinct patterns of activation (or suppression) of polar immune axes and corresponding tissue responses.[37-39] Cytokine activation patterns were shown to differ in patients with extrinsic and intrinsic (ie, allergic and nonallergic) AD. Although both subtypes showed similar T_H2 activation regardless of IgE status, patients with intrinsic AD exhibited significantly higher activation of the T_H17/IL-23 and T_H22 axes and related keratinocyte products (eg, S100As) in skin tissues. These data suggest the potential for similar therapeutic responses to T_H2-targeting therapeutics, with possible higher responses to IL-17/IL-23 and ***IL-22*** antagonism in patients with intrinsic AD.[38] Of note, similar responses to dupilumab, an anti–IL-4 receptor antibody suppressing the T_H2 pathway, were observed in patients with both intrinsic and extrinsic AD.[27] Ongoing and future clinical trials with IL-17–, IL-23–, and IL-22–targeted treatments (eg, anti–IL-22/ILV-094 and anti–IL-23p40/ustekinumab) should clarify differences in therapeutic responses between these subtypes.

Population studies suggested that AD among different races (eg, Asian and African American subjects) might have phenotypic differences.[42-44] Prominent T_H17 activation has been observed in the blood of Asian patients with AD, and increased IL-17 staining was found in acute AD skin lesions.[45,46] The molecular Asian AD phenotype was described to present a mixed phenotype between European/American patients with AD and psoriasis, with highly atypical features for AD, such as parakeratosis, and a unique cytokine profile featuring simultaneous activation of the T_H2 and T_H17 axes.[39] The more "psoriasiform" phenotype of Asian patients with AD provides a rationale for including IL-17/IL-23–targeting therapeutics that are successfully used or tested in patients with psoriasis in the treatment of AD. The relative pathogenic contribution of the T_H2 and T_H17 axes in Asian patients remains to be determined through clinical trials with selective antagonists against these pathways.

A recent phase II study with ustekinumab, an antibody directed to the common p40 chain of IL-12 and IL-23, showed clear molecular effects in patients with AD. However, clinical outcomes were not significant from profound improvements in the placebo arm, which might have been due to background use of topical glucocorticosteroids.[47]

COMPARATIVE FINDINGS ON IMMUNE PARAMETERS IN CHILDHOOD VERSUS ADULT AD

Although there is increasing prevalence of AD in adults,[43,48] the pediatric population has the highest prevalence (15% to 25%) worldwide. Most children with early AD presentation in infancy will outgrow their disease before adolescence,[33] but 25% or more (often those with more severe AD) will persist into adulthood.[33,48] Thus it is important to define differences and similarities between early pediatric AD and chronic disease in adults, as well as factors that determine disease persistence. A recent publication[37] sheds light on mechanisms involved in initiation of AD in children. Although AD is established in adults as a disease with polarized T_H2 and T_H22 cytokine activation in both skin and blood,[36,49,50] early-onset AD begins as a T_H2 disease. Furthermore, in early pediatric AD the T_H2 imbalance is confined to skin-homing (cutaneous lymphocyte antigen–positive) T-cell subsets. In adults T-cell activation extends into systemic/cutaneous lymphocyte antigen–negative and ***$CD8^+$ T cells***, as well as into IL-22–producing T cells. These data provide critical insights to understand initial pathogenic mechanisms in patients with early AD and direct novel treatments toward children.[37] Additionally, early-onset AD showed very low T_H1 activation. Thus the reduced counterregulation by T_H1 T cells in children

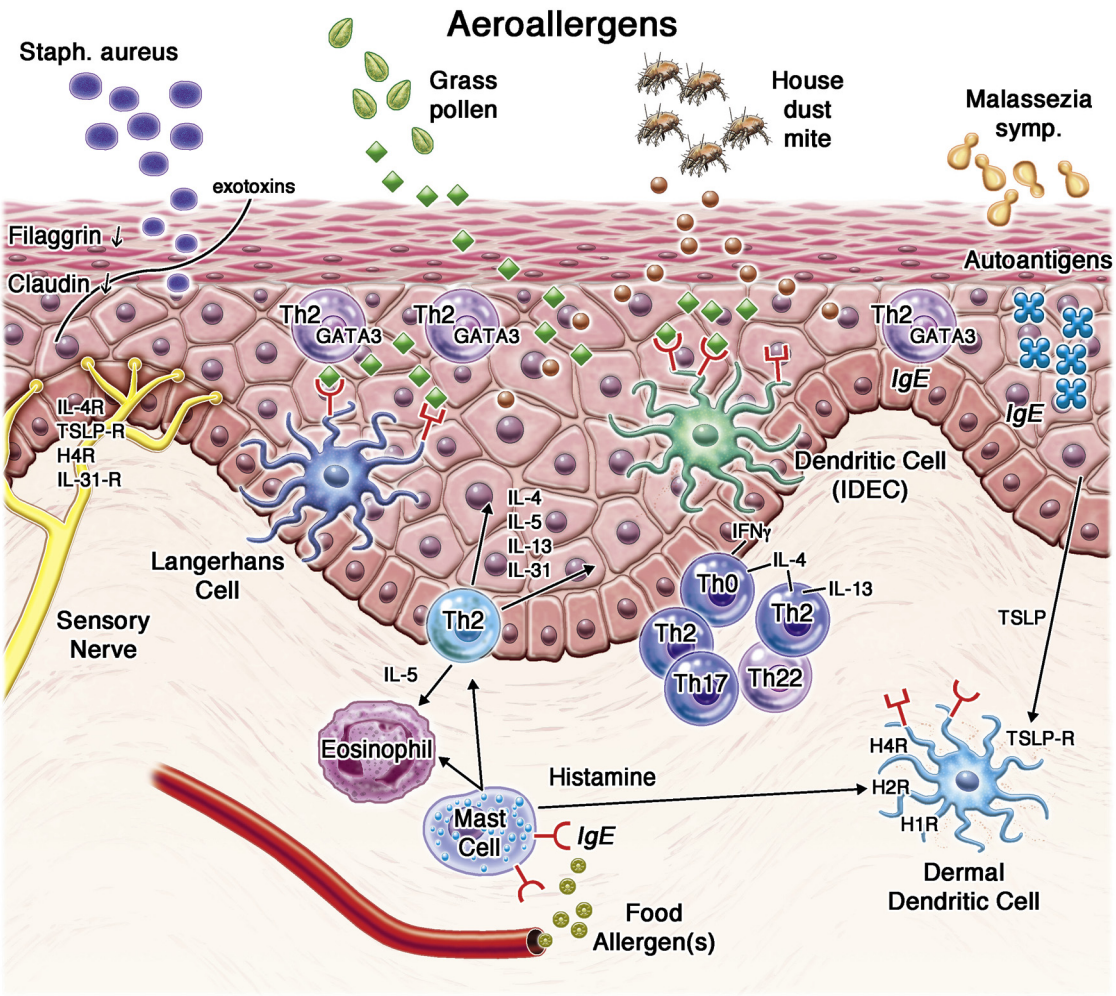

FIG 1. Selected cellular and molecular pathways in lesional skin of patients with AD. A defective skin barrier caused by genetic factors and inflammatory influences facilitates the penetration of irritants, microbial products, and allergens. T_H2-like lymphocytes dominate in the acute phase and are also present in the chronic phase of AD. Other T-cell subpopulations (T_H1, T_H17, and T_H22) are detectable in the skin as well, and other cell types, such as inflammatory dendritic cell populations and eosinophils, are found in increased numbers in lesional skin. Selected inflammatory mediators and their receptors are shown, some of them serving as target molecules in novel therapeutic approaches.

might allow excess T_H2 development in early-onset AD (Fig 1). Future studies should assess the contribution of changes in T_H1/T_H2 ratio and other regulatory elements in allowing disease persistence to adult AD.

THE MICROBIOME IN PATIENTS WITH AD

The skin is colonized by myriads of microorganisms shortly after birth, which total approximately 10^{10} bacteria covering the whole skin.[51,52] These skin-associated microbial populations have become a major research interest because the microbiome closely interacts with the local immune system in health and disease. The majority of bacterial species on the skin are classified into 4 phyla (ie, ***Actinobacteria***, ***Firmicutes***, ***Bacteroides***, and ***Proteobacteria***).[53] Interestingly, the skin microbiota differs greatly between the topographic locations "moist, dry, or sebaceous," supporting the concept of cutaneous habitats determining microbe composition by the cutaneous milieu.[52] At moist areas, *Staphylococcus* and *Corynebacterium* species are abundantly detectable, whereas sebaceous sites harbor mostly propionic bacteria. However, it should be noted that approximately 50% of the sequence reads in skin swabs do not map to any of the reference genomes or cannot be assigned a function on the basis of known genes, leaving large amounts of skin microorganisms unclassifiable.[52] In addition to the well-known coincidence of lesional atopic skin with *Staphylococcus aureus* colonization, detailed skin analyses have extended these findings by showing a general loss of microbial diversity during acute flares in patients with AD. Diversity is restored after successful anti-inflammatory treatment.[54] This is in line with other studies showing that atopic subjects had lower environmental biodiversity in the surroundings of their homes and significantly lower generic diversity of Gammaproteobacteria on their skin compared with healthy subjects.[55] In addition, aberrant interactions between gut microbes and the intestinal immune system have been implicated, such as the association of enrichment of a major gut species *Faecalibacterium prausnitzii* with AD.[56] In addition, the severity of AD was shown to inversely correlate with intestinal microbiota diversity and

butyrate-producing bacteria.[57] Overall, these findings raise the question of whether an altered microbial diversity in patients with AD is a cause or merely a consequence of skin inflammation.

Data from animal studies recently showed a loss of microbial diversity with abundant *S aureus* colonization in mouse models of skin barrier disruption.[58,59] Those mice ultimately had a T cell–driven skin inflammation that resembles that of human AD. In contrast, antibiotic treatment fully restored cutaneous bacterial diversity, with subsequent healing of the eczema. These data indicate that the skin's microbiome might play an important role in the development and promotion of T cell–driven skin inflammation in AD. We are just at the beginning of understanding the complex interactions between skin-associated microbial populations and the local immune system. However, it might be intriguing to manipulate the diversity of the microbiome as part of a prophylactic and therapeutic approach in the management of AD.[60]

DEVIATION OF THE INNATE IMMUNE SYSTEM IN PATIENTS WITH AD

Both the diversity of the microbiota on the skin and *S aureus* overgrowth are sensed and regulated by the innate immune system. One important group of regulators are antimicrobial peptides (AMPs) produced by the skin and bacteria to stabilize bacterial communities and prevent and fight infections.[61] Compared with T_H1- and T_H17-associated inflammation, T_H2-associated inflammation in patients with AD does not upregulate some (but not all) AMPs based on T_H2 cytokine–mediated suppression.[62,63] AD skin lesions harbor staphylococci as predominant bacteria, and the failure in AMP regulation might contribute to the loss of diversity of cutaneous microbiota.[54] Among other stimuli, this leads to a predominance of ***Toll-like receptor*** 2 ligands on AD skin.[64] As a response to environmental signals, epithelial ***IL-25***, IL-33, and ***thymic stromal lymphopoietin*** (TSLP) are upregulated. These epithelial cytokines are associated with accumulation of ***type 2 innate lymphoid cells*** (ILC2s), which are discussed to play a role in AD. They express skin-homing receptors and infiltrate the skin after allergen challenge, where they produce the type 2 cytokines ***IL-5*** and ***IL-13***.[65] In addition, ILC2 accumulation in patients with AD might influence DCs to further T_H2 phenotypes in T cells.[66] Importantly, DCs under the influence of T_H2 cytokines also lose the potential to produce anti-inflammatory IL-10 in response to bacteria, which in animal models turned self-limited dermatitis into chronic cutaneous inflammation.[67,68] Innate sensing of potent Toll-like receptor 2 ligands further boosts inflammation, upregulating innate cytokines, such as ***IL-6***,[69] a cytokine that, if targeted by blocking antibodies in patients with AD, leads to AD resolution but also susceptibility to infection.[70] IL-6 in patients with AD induced by *S aureus* products might in part be responsible for the T_H17-associated signatures in patients with AD and has systemic consequences, among them the induction of myeloid-derived suppressor cells (MDSCs), which, when recruited to the skin in an attempt to terminate inflammation, lead to suppression of anti-infective immune responses, allowing, for example, herpes viruses to spread.[69] Thus a large part of the deviation of the innate immune system in patients with AD can be interpreted as secondary to a weak epidermal barrier and a predominant T_H2-associated inflammation. Because the epidermal barrier is also negatively regulated by many T_H2 cytokines,[71] therapeutically blocking the T_H2 bias with drugs, such as dupilumab, will also correct much of the deviation of the innate immune system found in patients with AD, such as AMP inhibition and suppression of microbe-induced IL-10 responses. As a consequence, T_H2 blockade will also correct the loss of microbiota diversity on AD skin, also reducing the proinflammatory ***pathogen-associated molecular patterns*** orchestrating AD chronification by means of innate immune sensing.[72]

T LYMPHOCYTES AND DCS AS MAJOR CELLULAR PLAYERS IN PATIENTS WITH AD

One of the most striking features of AD is the presence of T cells in the affected skin (Fig 1). Although their numbers are already moderately increased in the dermis in nonlesional sites, in lesional AD skin a marked influx of T cells is found in both the dermis and epidermis, leading to keratinocyte apoptosis and spongiosis in the epidermis between the stratum corneum and stratum basale (Fig 1).[73,74] In the atopy patch test model T cells in the skin display an initial T_H2 polarization, with increasing populations of T_H1 cells in patients with chronic AD.[75-79] The high proportion of T_H2-polarized T cells appears to be a key factor in patients with allergic inflammation,[80] and pharmacologic inhibition of T_H2 cytokine receptors by dupilumab is rapidly improving AD, irrespective of the effect on IgE.[27] T_H2 cells are also the target cells of specific immunotherapy,[81,82] which has shown modest efficacy in patients with AD in some clinical studies.[83]

Recently, the paradigm of an exclusive T_H2 polarization has been questioned because T_H17 and T_H22 polarizations have been described as well.[84,85] Next to CD4 T cells, CD8 T cells are found also in AD skin. These cells are potent releasers of ***IFN-γ***, IL-13, and IL-22 and are speculated to be relevant for the early responses in patients with AD.[49,86,87] There is no doubt that allergen-specific T cells infiltrate the skin in sensitized patients, but autoreactive T cells and T cells detecting microbial antigens were identified in a recent study as possibly driving cells in cutaneous inflammation in subpopulations of patients with AD as well, some of them also having specific IgE to those antigens.[88-90]

DCs comprise morphologically and functionally defined subsets of cells specialized in antigen uptake and presentation. There is a dynamic DC subset distribution in the different phases of inflammation.[91] Resident epidermal DCs are ***Birbeck granule***–containing ***Langerhans cells*** present in the lesional and nonlesional skin of patients with AD. In contrast to non-AD skin, they express high-affinity IgE receptors ***(FcεRI)*** and are critical for initiation of immune responses to protein antigens penetrating the epidermis.[92] IgE on FcεRI facilitates allergen uptake to a great extent through DCs.[93] Exaggerated ***indoleamine 2,3-dioxygenase*** 1 expression and activity in Langerhans cells in patients with AD might serve as a potential predictive biomarker for high risk of ***eczema herpeticum***.[94]

Another DC subset, inflammatory dendritic epidermal cells, infiltrates the early AD lesions within 48 hours after induction of AD lesions with an atopy patch test.[95] Inflammatory dendritic epidermal cells do not contain Birbeck granules; express ***CD11b***, ***CD11c***, and high levels of FcεRI in AD lesions[96]; and are a treatment target for topical and systemic therapy of AD.[97] Plasmacytoid DCs are present in normal human skin and specialize in production of ***type I interferons*** on stimulation with viral DNA or RNA. Plasmacytoid DC numbers are increased in patients with cutaneous lupus erythematosus but almost completely depleted in patients with AD because of T_H2

cytokine–induced plasmacytoid DC apoptosis, which contributes to the eczema herpeticum susceptibility seen in patients with AD.[98]

EOSINOPHILS, MAST CELLS, BASOPHILS, *INNATE LYMPHOID CELLS*, B LYMPHOCYTES, AND THEIR ROLE IN AD

The skin lacks eosinophils under physiologic conditions but is infiltrated by eosinophils in patients with a broad spectrum of cutaneous disorders, including AD.[99] Tissue eosinophilia is often associated with increased blood eosinophil levels and correlates with disease severity.[100] Eosinophils are often activated, leading to extracellular granule protein deposition in the skin.[101,102] Thus far, the role of eosinophils in the pathogenesis of AD remains uncertain. It seems possible that eosinophils contribute to host defense against invading microbes through the defective skin barrier by generating extracellular eosinophil traps, regulating the immune response, and/or remodeling.[103-105]

In contrast to eosinophils, normal human skin contains mast cells. In patients with AD, mast cell numbers are increased in skin lesions. However, whether mast cells play a role in the pathogenesis of AD remains unclear. Skin mast cells also produce IL-17,[106] IL-22,[106] and IL-31,[107] suggesting that mast cells contribute to the pathogenesis of AD through cytokine production. AD seems also to be associated with basophil recruitment and activation.[108] Recently, it has been demonstrated that basophils form extracellular traps in patients with AD[109] that can exhibit antibacterial activity.[110]

As discussed above, in the context of the innate immune mechanism in patients with AD, ILC2s are currently discussed to play a role in the disease. They express skin-homing receptors and infiltrate the skin after allergen challenge, where they produce the type 2 cytokines IL-5 and IL-13.[65] Focus has recently been placed on ILC2s, suggesting a role for these cells in subjects with FLG mutations.[4,65] In addition to T cells and innate lymphoid cells, systemic B-cell abnormalities have been reported in patients with AD.[111,112]

ROLE OF SPECIFIC IGE IN PATIENTS WITH AD

The course of AD is characterized by exacerbations and remissions. It is influenced by individual exogenous trigger factors, such as inhalant allergens, food allergens, or autoallergens; microbial factors; or climatic conditions.[89,113-116] Because the vast majority are sensitized through specific IgE antibodies to inhalant or food allergens, the determination of IgE antibodies to inhalant allergens is common in clinical practice. However, their effect on the clinical course of AD is often not clear. In a 10-year follow-up study, such IgE measurements did not predict later manifestation of AD.[117] In general, specific IgE is only the witness of a sensitization, but it does not mean that it is clinically relevant. With regard to the patient's history, a higher specificity compared with skin prick and *in vitro* IgE testing has been demonstrated for the atopy patch test with aeroallergens in patients with AD.[118] However, the gold standard of proving a diagnostically relevant sensitization is a challenge test with allergens, eg, with birch pollen–related food[119] or with grass pollen[120] allergens, as has been published in adults with AD.

Worsening of AD on allergen challenge supports the hypothesis that specific IgE might play a critical role in cutaneous inflammation in the activation of mast cells and DCs through high-affinity Fc receptors. IgE-mediated histamine release from cutaneous mast cells can aggravate AD through the itch-scratch cycle, but mast cell degranulation is not always detectable in AD lesional sites or after atopy patch testing.[121] Still, increased cutaneous inflammation, mediated through histamine receptors on T lymphocytes, antigen-presenting cells, and keratinocytes, is probable.[122] Induction of eczematous lesions in the skin in the atopy patch test is strongly related to IgE-bearing DCs.[96,123] This might be explained by IgE-facilitated allergen presentation by DCs and activation of DCs through high-affinity Fc receptors in the skin.[93,124]

Some data indicate a less clear relationship between allergen-specific IgE and AD. Comparing extrinsic and intrinsic AD demonstrated a similar disease pathomechanism independent of IgE.[38] Blocking IgE with omalizumab does not often improve AD, but this might be difficult to interpret because of the high levels of IgE in patients with eczema. Blocking receptors for IL-4 and IL-13 with dupilumab has been described to lead to improvement of AD well before IgE levels change. Moreover, dupilumab is equally effective in patients with intrinsic and extrinsic AD.[27] Overall, there is a strong relationship between IgE and AD, but the functional pathomechanism of IgE in patients with AD still needs further examination.

IMMUNE MECHANISMS AND THEIR INTERACTION WITH FLG AND OTHER SKIN BARRIER PROTEINS

FLG is a molecule that might in part explain the disease in a subgroup of patients with AD.[125] It has been shown that up to 50% of patients with AD carry FLG loss-of-function mutations. FLG is a structural protein that builds up the outer epidermal barrier through aggregation of intermediate filaments. This is considered a key step in establishing the structure and function of the stratum corneum. Moreover, FLG influences cell differentiation, and processed FLG contributes to natural moisturizing factors, which are important for skin hydration. Recently, it was found that FLG inhibits antigen formation by house dust mite (HDM)–derived phospholipase, indicating that FLG can directly affect allergens.[126] There is evidence that a lack of FLG breakdown products favors transepidermal water loss, allergen penetration, and skin colonization with *S aureus*. This explains why FLG loss-of-function mutations are associated with higher total IgE levels, more sensitizations, and a more severe course of AD, as well as allergic asthma.[127]

During the last 2 decades, interaction of the immune system with the skin barrier has been addressed in numerous studies. Several cytokines, such as IL-4, IL-31, and IL-33, have been described to negatively affect the FLG expression in keratinocytes (Fig 1).[71,128,129] Later, it was shown that other skin barrier proteins, such as FLG2, hornerin, or loricrine, are also critically regulated by T_H2 mediators that can be overexpressed in the skin of patients with AD. These findings suggest that lesional skin is always associated with a disturbed skin barrier in patients with AD.[130,131] In addition to the stratum corneum barrier, the tight junction barrier is located in the granular layer of the epidermis and contributes to the barrier dysfunction and immune dysregulation observed in patients with AD.[132]

Neonatal skin barrier dysfunction is predictive of food allergy and supports the concept of transcutaneous allergen sensitization.[133] Findings of worsening of the skin, mainly on air-exposed

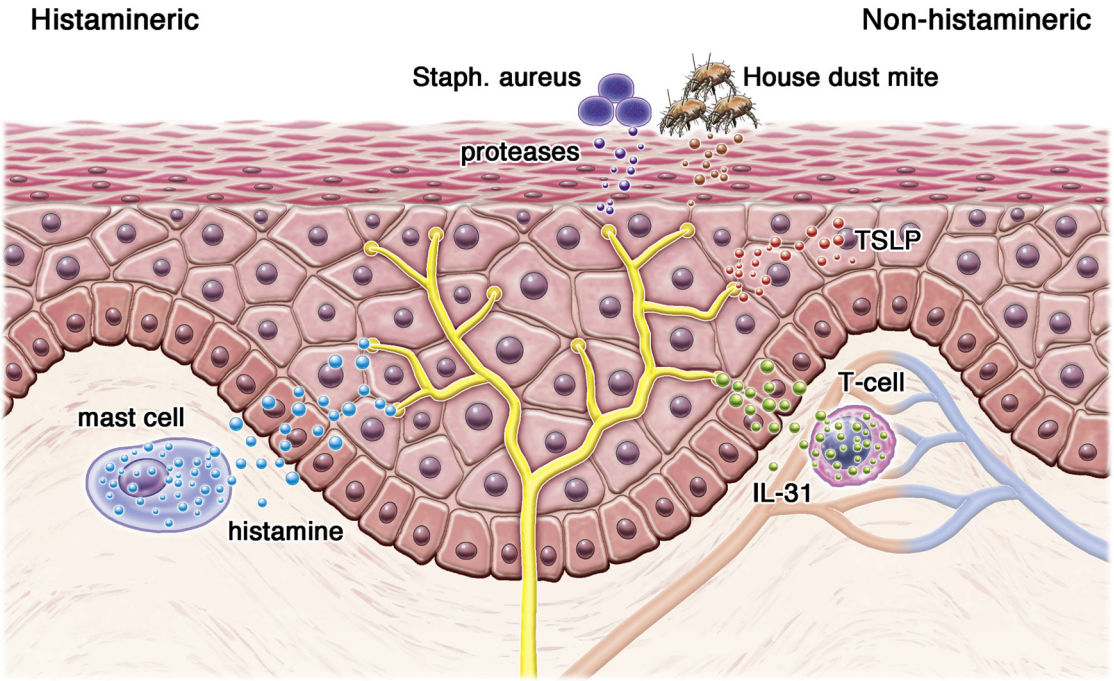

FIG 2. Pruritus is a sensory phenomenon mediated by histamine-dependent and independent mechanisms. Key mediators of pruritus, such as TSLP, IL-31, or histamine, are targets of current therapeutic approaches in patients with AD.

skin sites, on aeroallergen challenge in sensitized patients with AD[120] suggest that because of dysfunction of the epidermal barrier, allergen exposure is followed by direct penetration of the allergen into the skin in patients with AD.

PRURITUS IN PATIENTS WITH AD AND THE IMMUNOLOGY BEHIND IT

Chronic pruritus defined by persisting itch lasting longer than 6 weeks is considered the dominant clinical feature of AD, representing a major burden for affected patients.[134] Thus the understanding of the underlying mechanisms of chronic pruritus in patients with AD is of great importance not only to understand the disease course but also to develop new therapeutic strategies to provide relief for this dominant clinical symptom. Pruritus is a sensory phenomenon mediated by both histamine-dependent and histamine-independent mechanisms (Fig 2).[134] Chronic pruritus in patients with AD seems independent of histamine effects mediated through histamine 1 receptors; the role of histamine 4 receptors on pruritus in dermatitis is currently being discussed.[122] The signal for pruritus is transmitted by cutaneous nerve fibers (CNFs) located within the dermis and epidermis in close proximity to resident cells, such as fibroblasts, keratinocytes, mast cells, and Langerhans cells.[134] These CNFs form varicose-like neural webs at their terminal end, allowing nonsynaptic transmission of neurotransmitters and neuropeptides. Patients with AD can have nerve fiber alterations in their skin.[135] Several mediators induce nonhistaminergic pruritus through receptors, such as transient receptor potential (TRP) A1, proteinase-activated receptors 2 and 4, and others.[136] Mediators for pruritus can derive from endogenous or exogenous sources. *S aureus* and HDM, 2 triggers for AD exacerbation, are able to induce pruritus through proteases.[137] TSLP and IL-31 are recently published endogenous mediators for the induction of chronic pruritus in patients with AD.[134] Epithelial cells are the major source of TSLP in the skin, and TSLP expression of keratinocytes in AD skin is highly upregulated.[138] Overexpression of TSLP in mice provokes robust pruritus.[139] TSLP induces itch directly through activation of cutaneous sensory neurons by means of TRPA1 activation.[140] IL-31 is primarily produced by T_H2 cells and signals through the IL-31 receptor, which is expressed on keratinocytes and CNFs (Fig 1).[134]

Recent data suggest that IL-31–mediated pruritus requires coexpression of TRPV1 and TRPA1 on CNFs.[141] IL-31 is highly expressed in pruritic AD lesions, and IL-31 serum levels correlate with AD severity and itch sensation in patients with cutaneous T-cell lymphoma.[17,142] Because IL-31 induces delayed onset of pruritus, it can actually be caused through an indirect mechanism.[143]

EFFECT OF ALLERGENS AND ENVIRONMENTAL FACTORS ON PATIENTS WITH AD

Environmental factors can influence the cause of AD. Climatic[144] and anthropogenic factors, such as indoor[145-147] and outdoor[148,149] air pollutants and psychosocial stress,[150-152] exert their greatest influence during prenatal and early postnatal life, causing enhanced predisposition for AD development (for an overview, see Table I).[144-148,150-154] In addition, other factors, such as reduced environmental UV exposure[155] or high water hardness,[156,157] are controversially discussed as possible drivers of the manifestation of AD.

Exposure of sensitized patients to food allergens or aeroallergens can cause flare-ups and exacerbation of AD in patient subgroups. The most relevant food allergens include milk, egg white, soy, and peanut. Food allergen intake can lead to

TABLE I. Studies on environmental factors affecting AD development

Exposure type (associated factor)	Study design	Population/cohort	Readout parameter	Reference
Climatic factors (humidity, air temperature, UV index)	Retrospective, questionnaire-based survey	Children 0-17 y old (n = 91,642)	Physician-diagnosed eczema or any other type of skin allergy in previous 12 mo	Silverberg et al, 2013[144]
Indoor air pollutants (VOCs)	Prospective study on clinical cohort	Children with AD (n = 30)	SCORAD score	Kim et al, 2015[145]
Indoor air pollutants (tobacco smoke)	Case-control association analysis	n = 83 cases n = 142 control subjects	Physician-diagnosed adult-onset AD	Lee et al, 2011[147]
Indoor air pollutants (tobacco smoke, $PM_{2.5}$)	Prospective cohort study	n = 469 pregnant mothers and their babies	Infantile eczema during first year of life	Jedrychowski et al, 2011[153]
Indoor air pollutants (total VOCs)	Prospective birth cohort study	n = 257 infants	AD at age 36 mo	Kwon et al, 2015[146]
Outdoor air pollutants (CO)	Prospective birth cohort study	n = 24,200 infant-mother pairs	Physician-diagnosed AD at age 6 mo	Huang et al, 2015[148]
Outdoor air pollutants (ozone)	Cross-sectional survey	n = 21,311 schoolchildren aged 6-7 y	AD prevalence and symptoms (ISAAC III questionnaire)	Morales-Suárez-Varela et al, 2008[154]
Psychosocial stress (job strain)	Prospective birth cohort study	n = 32,104 pregnant mothers and their children	AD prevalence at age 7 y (maternal self-report)	Larsenet al, 2014[150]
Social stress	Experimental study; social stress evaluated by using the TSST	n = 30 adult patients with AD and control subjects	CLA^+ lymphocytes and IL-5 in the circulation	Schmid-Ott et al, 2001[152]
Social stress	Experimental study; social stress evaluated by using the TSST	n = 22 adult patients with AD and control subjects	NGF^+ nerve fibers and neurogenic inflammation markers in lesional l skin	Peters et al, 2014[151]

CLA, Cutaneous lymphocyte antigen; *ISAAC*, International Study of Asthma and Allergies in Childhood; *$PM_{2.5}$*, fine particulate matter; *TSST*, Trier social stress test; *VOC*, volatile organic chemicals.

TABLE II. Novel immunologic approaches in the therapy of AD

Target	Biological agent	Level of evidence	Key outcome/reference
T_H2 immunity			
IL-4Rα chain	Dupilumab (further substances: AMG-317, pitrakinra)	Phase III	EASI 50: 47/55[27,174]
IL-5	Mepolizumab	Phase II	EASI 50: 0/18[175]
IL-13	Tralokinumab, lebrikizumab	Phase II	Unpublished
IgE	Omalizumab (further substances: MEDI4212, QGE031)	Stopped after proof of concept	Heterogeneous reports ranging from EASI or SCORAD 50 0/20[176] to 21/21[177]
CD20	Rituximab	Case series	EASI 50: 6/6,[178] long-term: 0/2[179]
IL-31	BMS-981164	Phase I ongoing	
IL-31R	CIM331	Phase II ongoing	
TSLP	AMG-157	Phase I completed	Unpublished
CRTH2	QAW039	Phase II completed	Unpublished
Histamine 4 receptor	ZPL389	Phase IIa completed	Recent congress report by Werfel et al (EAACI 2016): Significant improvement of EASI and SCORAD over placebo
Non-T_H2 immunity			
IL-1R1	Anakinra	Phase I completed	Unpublished
IL-6	Tocilizumab	Case series	EASI 50: 3/3[70]
IL-22	ILV-094	Phase II ongoing	
IL-23p40	Ustekinumab	Case series; phase II completed	Heterogeneous reports: successful[24,180] vs noneffective[181]; no significant clinical response over placebo[47]
TNF-α	Etanercept	Case series	EASI 50: 0/2[182]
IFN-γ		Phase III	EASI 50: 18/40[183]
PDE-4	Apremilast	Case series	
NK-1R	Aprepitant	Phase II ongoing	

CRTH2, Chemoattractant receptor–homologous molecule expressed on T_H2 lymphocytes; *EASI*, Eczema Area and Severity Index; *IL-4Rα*, IL-4 receptor α; *IL-31R*, IL-31 receptor; *NK-1R*, neurokinin 1 receptor; *PDE-4*, phosphodiesterase-4.

exacerbation or persistence of AD, mostly in children with AD. Moreover, even sensitization through barrier-disrupted skin is discussed.[158] Two recent clinical studies suggested that early-life exposure of the skin to peanut in household dust might increase the risk for sensitizations and peanut allergy in children carrying FLG loss-of-function mutations or those with AD.[159,160]

The aeroallergens most relevant to AD are HDM and pollen. A new marker allergen for AD in patients with HDM allergy could be Der p 11, a paramyosin present in mite bodies.[161] HDM allergens activate an array of pathogen-associated molecular patterns and ***danger-associated molecular patterns***. Lately, the S100 proteins have moved into focus because lesional skin of patients with AD displays markedly increased levels of these proteins.[36,162] In a recent *in vitro* study ***Dermatophagoides farinae*** extracts directly induced S100A8 and S100A9 in human primary keratinocytes, leading to upregulation of IL-33 through the S100A8/A9 receptor for advanced glycation end-products (RAGE), thereby amplifying T_H2-driven cutaneous inflammation.[163]

The clinical phenomenon of eczema flare-ups during the pollen season in pollen-sensitized patients with AD has spawned the concept of pollen-induced contact dermatitis. However, the inflammatory infiltrate used in pollen patch tests is typical for type I hypersensitivity reactions and mimics the inflammatory infiltrate in lesional AD skin.[164,165] Notably, in a recent experimental, placebo-controlled study timothy grass pollen exposure induced eczema flare-ups in adults with AD sensitized to grass pollen allergen, providing direct evidence for a role of pollen in triggering AD.[120]

Apart from being a carrier of allergens, pollen grains harbor various substances that signal danger to the tissue.[166] Ragweed pollen extracts, for example, activate the ***NLRP3 inflammasome***,[167] and NLRP3 was recently implicated in T_H2 differentiation.[168] To what extent innate immune activation is relevant for eczematous reactions to pollen remains to be established.

EFFECT OF IMMUNE DEVIATION ON DIAGNOSIS AND THERAPY IN PATIENTS WITH AD

Increasing knowledge on the pathogenesis of AD results in novel diagnostic and therapeutic strategies. Current diagnostic gold standards are clinical phenotype and histology, but they neither are valid for all phenotypes of AD nor do they predict therapeutic benefit at the individual patient level. Thus new molecular classifiers are needed. Several attempts to define classifiers of varying size and predictive value were made.[169,170] Recently, an accurate classifier to distinguish AD from psoriasis consisting of only 2 genes was proposed.[25] This might stand as an example for customized and easy-to-use molecular classifiers answering specific questions, eventually including natural clinical course and risk for comorbidities. A prerequisite for successful use of such classifiers is a precise clinical phenotyping of this heterogeneous disease.

The heterogeneity of AD is also reflected by the therapeutic outcome of distinct specific immune-targeting therapies. Allergen immunotherapy has only a modest efficacy on AD.[83,171] Nevertheless, in recent years, the main therapeutic concepts, besides repairing the epidermal barrier or influencing the microbiome, target acute-phase inflammation or T_H2 immunity (Table II).[24,27,47,70,172-183] A breakthrough came with dupilumab, an antibody targeting the IL-4 receptor α chain, which is the overall most efficient therapy on the basis of available data from clinical studies.[27,174] However, a subgroup of patients with AD did not benefit from dupilumab treatment. It can be proposed that AD in such nonresponders is driven primarily by epidermal barrier impairment, autoallergy, or non-T_H2 immunity. Thus those patients could benefit from therapies targeting acute-phase inflammation, such as the anti–IL-6 receptor tocilizumab, even if such therapies seem to come with higher side effects than T_H2-targeting therapies.[70] Hence objective biomarkers predicting the optimal therapeutic concept at the individual patient level are needed. Taken together, the numerous therapeutic strategies of AD reflect its heterogeneity and complex pathogenesis. A precise stratification of individual patients will be key to future success.

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