Cellular and molecular immunologic mechanisms in patients with atopic dermatitis

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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).

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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