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Current and emerging concepts in atopic dermatitis pathogenesis

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Abstract Atopic dermatitis is a common skin disorder with a complex, evolving pathogenesis. Research on the pathogenesis has shifted from focusing primarily on generalized immune system abnormalities in T helper 1/T helper 2 (T_H1/T_H2) activity to more targeted immune and skin barrier abnormalities contributing to the overall phenotype. Specific signaling pathways recently implicated in atopic dermatitis include production of interleukin (IL) 4 and IL-13, which promote immunoglobulin E production, T_H17 and T_H22 cells, and production of cytokines. Barrier defect abnormalities, such as a shared filaggrin mutation noted in ichthyosis vulgaris and atopic dermatitis, as well as reduced structural proteins and lipids (eg, ceramides), have been discovered as well. These alterations contribute to increased transepidermal water loss in addition to increased allergen exposure, resulting in debate over the "inside out" versus "outside in" theories—that is, the concept that immunity triggers barrier breakdown versus barrier abnormalities triggering immunologic alteration toward atopy. In fact, it is likely that all of these contribute to pathogenesis, with some individuals initially experiencing immunologic abnormalities more strongly than barrier defects and vice versa. Genetic analyses have continued to advance, leading to the discovery of potential candidate genes relating both to the impaired skin barrier and the altered immune system pathways. This review outlines the evolution of the field of current pathogenesis of atopic dermatitis, highlighting the most pertinent recent findings.

Introduction

Atopic dermatitis (AD) is a chronic, pruritic skin disorder that begins largely in childhood, continuing or occasionally beginning in adults worldwide with increasing prevalence over the past 30 years.[1] Cumulative incidence suggests about one-quarter to one-third of individuals will be affected in the United States. The 1-year prevalence of AD in the United States of approximately 10.7% of children in 2003-2004 and 13.0% of children in 2007-2008 has been reported, with the largest prevalence occurring in metropolitan areas and regions with lower humidity, lower temperatures, and lower UV indices.[2–6] Skin manifestations and site of involvement vary by age and range from weeping papulovesicles to lichenified plaques[7] initially affecting extensor surfaces, and later shifting to flexural surfaces and hands. Approximately 60% of childhood cases begin in the first year of life, with nearly 85% beginning by age 5 years.[8] There is a slight female-to-male predominance,[9] and approximately 70% of patients have a family history of atopic diseases, such as AD, asthma, or allergic rhinitis.[10]

The pathogenesis of AD is multifactorial, involving a complex interaction of genetic and environmental factors. Concordance rates among monozygotic twins was found to be 77%,

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compared with 15% for dizygotic twins, supporting a strong genetic contribution to disease development.[11] The original model of AD pathogenesis attributed disease to an imbalance in cell-mediated T helper (T_H) 1 versus T_H2 response.[12] Theories on AD pathogenesis continue to evolve, with a recent focus on newer immunologic pathways and barrier-based abnormalities. Some have suggested that AD may be driven by elevated immunoglobulin E (IgE), similar to asthma and allergic rhinitis, which are commonly present in AD patients[13–16]; however, recent research has uncovered significant contributions to AD pathogenesis by skin barrier impairment, additional inflammatory cell types, such as T_H9, T_H17, and T_H22, and broader cytokine profiles.[17–19] The evolution of these components of AD pathogenesis has led to questioning the origin of disease and whether it is triggered by external or internal factors (ie, the outside in versus inside out hypotheses).[20]

Impaired skin barrier

Focus on pathogenesis of AD has evolved from concentration on immune system dysfunction as the primary abnormality in disease development to incorporating the concept of epidermal barrier dysfunction.[21] Impaired skin barrier may be the primary abnormality or trigger of disease onset in many individuals, but it can also occur secondary to cutaneous inflammation.[22] Skin- and mucosal barrier–based abnormalities may also be the mechanisms by which cutaneous disease expands to food allergies, environmental allergies, and asthma (ie, the atopic march).[23]

The stratum corneum is composed of corneocytes, which secrete intercellular substances (eg, filaggrin) that breakdown to substances including amino acids (ie, the natural moisturizing factor) and lipids (eg, ceramides), serving to create a barrier layer protecting the epidermis against environmental insults.[24] Numerous alterations and deficiencies in the proteins and lipids of the stratum corneum of atopic individuals have been implicated in the disturbed skin barrier, highlighting the importance of the skin barrier in disease development.[21,25] Among these is a reduced content of hygroscopic and structural matrix materials that are believed to serve as important mediators in the pathogenesis of AD (eg, ceramides).[26] These epidermal alterations functionally appear as a key step in disease, because the stratum corneum in both affected and unaffected skin of patients with AD has altered barrier function, resulting in increased transepidermal water loss. AD patients manifest dry skin diffusely, even when the patient is not flaring.[27]

Another factor altering the skin barrier is the presence of a common, underlying loss of function mutation of filaggrin (FLG) found in both ichthyosis vulgaris and AD.[28–31] FLG is an epidermal protein that functions in combination with its breakdown products as a leading contributor to maintenance of hydration and homeostasis of the stratum corneum, particularly in response to a changing environment.[32] The FLG loss-of-function mutation is found in approximately 10% of the general population. Numerous reports have confirmed the predisposition of patients with ichthyosis vulgaris to the development of AD and asthma.[33] The discovery of this genetic predisposition for an impaired barrier provides a basis for the "outside in" hypothesis whereby the barrier triggers immunologic changes. Acquired reductions in filaggrin function have been reported even in the absence of a loss-of-function mutation, with reported triggers of environmental origin including low humidity and mechanical damage; triggers also include IL-4 and thymic stromal lymphopoietin (TSLP), and, to a lesser degree, IL-13, IL-17, IL-22, and IL-31.[34] IL-4 and IL-13 also stimulate B-cell production of IgE, which further promotes atopy. Keratinocyte products such as antimicrobial peptides can induce cytokines such as IL-4, IL-13, IL-25, IL-33 and TSLP.[35]

The discovery of the connection between AD and FLG mutations has led to further research into barrier defects. FLG is located within the epidermal differentiation complex (EDC), which is a complex of several genes important in the maturation of the stratum corneum. These include S100 calcium binding proteins (S100s), the small proline-rich proteins (SPRRs), the late expressed cornified envelope proteins, trichohyalin, repetin, involucrin, loricrin, and filaggrin[36–41] (Table 1).[42–44] The discovery of the FLG gene in the EDC as well as the EDC's importance in the creation of the epidermal barrier led to a screen of the EDC for mutations in which a repeat number variant in SPRR3 was discovered as another risk factor for eczema.[45]

Abnormalities in T-cell and immune function

$CD4^+$ helper T lymphocytes play an essential role in adaptive immunity. Once activated by cytokines from antigen-presenting cells, they differentiate into T_H1 and T_H2 lymphocytes. Th1 cells then secrete interferon (IFN) γ and IL-12 to promote destruction of intracellular pathogens while

Table 1 Components of the epidermal differentiation complex

Component	Association with disease
S100 calcium binding proteins (S100s)	Psoriasis (psoriasin-S100 A7)
Small proline-rich proteins (SPRRs)	Atopic dermatitis (SPRR3)
Late expressed cornified envelope proteins	
Trichohyalin	Atopic dermatitis (nonsense SNVs-TCHH [E207 X] and TCHHL1)[42]
Cornulin	Atopic dermatitis (missense variants)[42]
Hornulin	Atopic dermatitis (missense variants)[42]
Repetin	Atopic dermatitis (reduced expression)[43]
Involucrin	Atopic dermatitis[44]
Loricrin	Atopic dermatitis[44]
Filaggrin	Atopic dermatitis (nonsense variants in FLG1-Europe and FLG2-Ethiopia)[42]