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Atopic dermatitis: pathogenesis

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Abstract

Atopic Dermatis (AD) is a complex inflammatory cutaneous disorder characterized by immune mediated inflammation and epidermal barrier dysfunction. Arising from a complex interplay between environmental and genetic factors, the definitive etiology of AD is perplexing and controversial. Advances in molecular medicine are radically transforming our understanding of AD pathogenesis. Increasing knowledge on the pathogenesis of AD results in novel therapeutic targets and pathways. This article details the pathogenesis section of the Curriculum United for Better Eczema Care (CUBE-C), facilitating primary care and sub-specialist education on the scientific advances driving recent AD therapeutic innovations.

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Atopic dermatitis is a complex inflammatory cutaneous disorder characterized by immune-mediated inflammation and epidermal barrier dysfunction. Arising from a complex interplay between environmental and genetic factors, the definitive etiology of AD is perplexing and controversial. Advances in molecular medicine are radically transforming our understanding of AD pathogenesis. Increasing knowledge on the pathogenesis of AD results in novel therapeutic targets and pathways. This article details the pathogenesis section of the Curriculum United for Better Eczema Care (CUBE-C), facilitating primary care and sub-specialist education on the scientific advances driving recent AD therapeutic innovations.

Genetics

Numerous clinical investigations have highlighted a strong genetic susceptibility for AD. Concordance in monozygotic twin studies and case reports describing the transfer and subsequent development of AD following bone marrow transplantation highly suggested a genetic basis for AD prior to classification of the human genome.[1] Groundbreaking discoveries in molecular medicine worldwide have positively identified 46 genes linked to AD.[2] Implicated genes encode regulatory proteins involved in the terminal differentiation of keratinocytes, as well as innate and adaptive immune system factors.[2] The most frequently described mutations involve variations in the filaggrin (FLG) genes, influencing intermediate filament protein filaggrin expression. More common in certain regional populations than others, FLG gene mutations are found in 10%-50% of individuals with AD worldwide.[3] Variations in functional FLG gene copy numbers may modulate AD development and severity. Relative to AD patients with heterozygous FLG mutations, patients with homozygous FLG loss of function mutations present with greater frequency of early onset recalcitrant AD, associated atopic diseases (asthma and/or food allergies), and cutaneous superinfections.[4] Further supporting the role of skin barrier defects in the pathogenesis of AD, several additional barrier genes encoded by the epidermal differentiation complex (EDC) locus on chromosome 1q21, including claudins, loricrin (LOR), involucrin (IVL), SPINK5, and TMEM79/MATT, are also associated with AD.[5,6] Mutations in innate immune system genes identified in association with AD include NOD1, NOD2, TLR2, CD14, and DEFB1, encoding integral factors in the cutaneous immunologic response to nonspecific antigens. Adaptive immunity gene mutations implicated in AD pathogenesis, such as IL-4, IL-4RA, IL-13, thymic stromal lymphopoietin (TSLP), IL-31, and CCR5, encode Th2 cytokines and chemokines.[7]

"Inside-out" versus "outside-in"

Whether AD is primarily driven by immune abnormalities ("inside-out" theory) or epidermal barrier dysfunction ("outside-in" theory) has been highly controversial. The "outside-in" model postulates that inherent defects in barrier function and keratinocyte differentiation allow penetration of antigens with consequent immune sensitization and activation. In contrast, the "inside-out" model proposes that activation of Th2 cells and the resulting immunologic cascade result in the AD phenotype.[8-10] It is clear that AD pathogenesis is multifactorial and, despite lack of full etiologic understanding, results from a complex interaction between epidermal barrier dysfunction, environment, and immune dysregulation. Nevertheless, regardless of what the first culprit is, it is clear that the disease phenotype and its chronic nature predominantly related to immune abnormalities, further contribute to the epidermal abnormalities, and these are now targeted through specific treatments that are currently developed for AD.

Epithelial cutaneous barrier dysfunction:

Both affected and unaffected skin of AD patients demonstrates vast suppression of structural proteins and lipids of the superficial stratums of the epidermis that are essential to barrier function and water retention.[11] The insoluble cornified envelope in the stratum corneum encapsulates keratin proteins and is composed of disulfide and gamma-glutamyl-lysine bonded, cross-linked structural proteins (including loricrin, involucrin, and small proline-rich proteins) and a surrounding continuous, neutral lipid layer (including ceramides, cholesterol, and free fatty acids).[11] Additional protective barrier mechanisms (tight junctions) are positioned deeper in the stratum granulosum of the epidermis. In particular, claudins are tight junctions that form an insoluble barrier, and are downregulated in AD patients.[5,12]

During the final process of terminal differentiation, FLG helps to maintain skin cell integrity and barrier function through aggregating keratin filaments by preventing water loss and blocking the entrance of foreign substances. In addition, its amino acid breakdown products, pyrrolidone carboxylic acid and urocanic acid, promote skin hydration and provide ultraviolet protection. These acids also modulate immune function directly by lowering skin pH, and preventing the activation of serine proteases and the subsequent growth of bacteria.[3,11] Lack of FLG breakdown products is directly linked to transepidermal water loss, bacterial skin colonization with *Staphylococcus aureus*, and allergen penetration,[3] elucidating the association of FLG mutations with more severe atopic dermatitis and additional atopic conditions.

Skin barrier defects increase trans-epidermal water loss (TEWL) in AD skin. Therefore, climatic changes in environmental humidity and temperature may adversely affect AD patients. It is well recognized in the literature that radiant home heating, which is associated with decreasing environmental humidity, is a strong risk factor for AD flares. Furthermore, clinical investigations have collectively revealed that low temperature and low humidity temperate climates hinder skin barrier function and promote pro-inflammatory cytokine and mast cell reactivity within the skin.[10,13,14] Among a cohort of 177 Korean pediatric patients, a 5°C increase in outdoor temperature and a 5% increase in outdoor humidity was associated with a 12.8% and 3.3% decrease in AD symptoms respectively.[14] This suggests that meteorological variables, including cold and dry weather, may increase the frequency and risk of flares in AD patients.

The epidermal barrier defects in AD further allow allergens or microbial pathogens to penetrate AD skin, promoting allergic sensitization and infections. Mice with FLG mutations, exhibit increased penetration of allergens and irritants relative to unaffected controls.[15] This incites AD cutaneous inflammation through various mechanisms, including production of specific IgE and immunostimulatory cytokines, activation of basophils, and cytotoxic effects of bacterial toxins.

Microbiome and atopic dermatitis

Abnormalities in cutaneous microbial colonization may play an integral role in AD pathogenesis. Normal skin is colonized with billions of diverse commensal bacteria responsible for augmenting skin defenses against infectious agents, through the production of antimicrobial peptides. The main antimicrobial peptides in the skin, defensins and cathelicidins, both modulate immunity against microbial pathogens directly and through their immunostimulatory effects.[16] Deficiencies in these antimicrobial peptides (AMPs) in AD patients are extensively documented in the literature.[16,17] In addition to the lack of antimicrobial peptides in the skin, a loss of cutaneous microbial diversity of commensal skin bacteria during AD exacerbations relative to well controlled patients has been revealed.[18] Microbial diversity is subsequently reestablished following clinical improvement with topical anti-inflammatory management.[18] Taken together, these clinical findings suggest the skin microbiome may contribute to the severity of AD.

A lack of these commensal skin bacteria, including *S. epidermis* and other coagulase-negative staphylococci, may further lead to abnormal proliferation of *S. aureus*. The routine utilization of topical antibiotics in AD management may also decrease commensal bacteria, promoting *S. aureus* colonization.[19] In AD patients, colonization with *S. aureus* and the subsequent action of exotoxins may worsen symptoms through inducing the proliferation of immunomodulatory and inflammatory cytokines (IL-31 and IL-22) and T cells.[15,19] *S. aureus* also modulates barrier function, through the increased production of serine proteases known to damage the epidermal barrier.[20] In turn, IL-4, IL-13 and IL-22 were shown to promote *S. aureus* colonization.

Immune-mediated abnormalities

In AD skin, mechanical injury, allergens, and microbes trigger the skin's innate immune system inciting increased expression of inflammatory cytokines, especially TSLP, IL-25, and IL-33. TSLP especially is expressed in high quantities in AD lesions, and serves a critical role in activating the Th2 cascade. TSLP, IL-25, and IL-33 collectively trigger the innate lymphoid cell-2 (ILC-2) activation of Th2 cells, IL-5, and IL-13. ILCs are non-T and non-B effectors cells that trigger specific cytokines as above.[4] The ILCs also express skin-homing receptors, and are activated by IL-33, infiltrating human skin after allergen stimulation.[4]

Antigens are processed directly by Langerhans' cells (LC) and inflammatory dendritic epidermal cells (IDEC) and subsequently presented to Th2 cells. LC, myeloid dendritic cells (DCs), and IDECs in AD also produce chemokines, such as CCL17, CCL18, and CCL22, which further attract additional Th2 cells. Although IDECs were initially thought to be localized to the epidermis, their immune-activating effects have been demonstrated in the dermis.

They secrete proinflammatory chemokines, including CCL17, CCL18, and CCL22, which are associated with amplification of Th2 responses. These chemokines intensify Th2 and Th22 cytokines, including IL-4, IL-13, IL-31, and IL-22, which in turn have been shown to to downregulate terminal differentiation and tight junction proteins, such as FLG, LOR, PPL, and claudins.[4]

IL-4 and IL-13 are critical to the activation and perpetuation of Th2 T cells and downstream molecules. Exerting their effects on IL-4R alpha, expressed on B cells, T cells, macrophages, and other immune cells, these cytokines also modulate IgE level class switching in B cells and subsequent eosinophil expression.[21] In conjunction with Th2 polarization, which facilitates the binding of *S. aureus*, IL-4 and IL-13 predispose AD patients to *S. aureus* infection by inhibiting the production of AMPs in the cutaneous surface.[22]

IL-4 and IL-13 further modulate AD by inhibiting the expression of epidermal barrier proteins that are important in terminal differentiation and barrier function. Keratinocyte differentiated in the presence of IL-4 and IL-13 demonstrated considerably reduced expression of FLG gene, even in individuals with previously functional FLG genes.[23] Loricrin and involucrin expression are also decreased by IL-4 and IL-13 in both lesional and nonlesional skin of AD patients, further disrupting the cutaneous barrier.[24] Recent therapeutic advances directly targeting and inhibiting the signaling of IL-4 and IL-13 using dupilumab, a monoclonal antibody targeting IL-4R alpha, inhibiting IL-4 and IL-13 signaling, have demonstrated clear efficacy in clinical trials of moderate to severe AD patients.[25] These data were also extended to skin biopsies of AD lesions from patients with moderate to severe AD treated with dupilumab, which showed that the clinical disease improvement was coupled with molecular reversal of AD in skin tissues, providing a final proof for the pathogenic role of IL-4 and IL-13 in AD. Th2 cells also produce the itch associated cytokine, IL-31, which participates in the itch-scratch cycle along with several other important mediators, including histamine, TSLP, tryptase, and neuropeptides. Large increases in IL-31 have been demonstrated in acute lesions, and in direct relation to disease severity in some investigations.[25-28]

"Th22 cells" and associated cytokine, IL-22 are also implicated in inhibiting epidermal barrier function and have recently been linked to epidermal hyperplasia.[29]

AD is also characterized by peripheral eosinophilia, with variability in the number of eosinophils in the skin.[4] IL-5 is the cytokine largely responsible for eosinophil recruitment and is typically present in lesional skin. Interestingly, a monoclonal antagonist against IL-5 did not show improvement in AD clinical severity, although overall peripheral eosinophila was reduced, in a short 2-week study.[4] Thus, current research studies have shifted focus to IL-4,/IL-13 antagonism given the predominant role of these cytokines in AD skin.[4]

Although it is well recognized that the acute phase of AD is characterized by a strong modulation of Th2 and Th22 immune responses, clinical investigations have revealed other pathways, including Th17/IL-17 and IL-23, that further contribute to disease pathology.[4] Th17 cells, a vital mediator of psoriasis, produce IL-17 and, to a lesser extent IL-22, which both regulate AMP S100A7 (psoriasin) production in keratinocyte.[30] IL-17 also induces the production of other inflammatory mediators, contributing to an influx of neutrophils, T-cells, and DC chemokines.[30] IL-23, a key modulatory cytokine in the production and differentiation of Th17 cells, also induces Th22 differentiation, perhaps explaining its role in AD. The IL-23 receptor is expressed on immune cells, including LCs, DCs, and Th17 cells, and is upregulated in AD skin relative to normal skin.[31] In fact, the levels of IL-23 cytokine subunits in AD are similar to psoriasis. Given the success of IL-23 antagonism in psoriasis,[32] such a treatment approach may be useful in AD. This remains to be validated in future clinical trials.

Most recently, clinical investigations involving mice reveal that Th17 may propagate the production and development of IL-4.[33] Relative to the Th17 skewing of psoriasis, AD skin demonstrates decreased IL-17/IL-23 production,[31] perhaps providing a potential explanation for the increased infection rate in AD patients, given the known IL-17 regulation of AMP.[30] IL-4 and IL-13 reportedly decrease the production of IL-17 cytokines,[12] explaining the decreased Th17 response in AD patients.[34,35] Despite the groundbreaking advances in psoriasis therapeutics targeting the Th17 pathways, the role of Th17 cells in AD is not fully understood.

While acute AD pathogenesis is polarized towards Th2 and Th22 immune responses, chronic AD lesions additionally exhibit a substantial Th1 component.[4,35-37] The Th1 inflammatory cascade is characterized by the influx of numerous cytokines, including Interferon (IFN) gamma, and IL-12. The defining cytokine of the Th1 pathway, IFN gamma, promotes an intensified cutaneous inflammatory response and keratinocyte apoptosis.[38] IL-12 amplifies this inflammatory process, triggering the proliferation of additional IFN gamma, T cells, and NK cells.[39]

Conclusion

The pathogenesis of AD is complex and multifactorial, and results from a complex interaction between genetic and environmental factors, leading to an epithelial barrier-immune interplay. Our understanding of AD is currently being transformed by molecular medicine and therapeutic advances. Further advances are underway that will hopefully continue to shape AD understanding and management in the future.

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