

New concepts in the pathogenesis of atopic dermatitis

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Atopic dermatitis is a chronic, relapsing, inflammatory skin disease that is characterized by pruritic, eczematoid skin lesions. The disease results from interactions between susceptibility genes, the host environment, skin barrier defects, susceptibility to infection and immunological factors. An increased prevalence of atopic dermatitis has generated increased interest and research into each of these areas, and new treatment strategies are being developed based upon an increased understanding of these issues.

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Abbreviations

AD	atopic dermatitis
CCR	CC chemokine receptor
GM-CSF	granulocyte-macrophage colony-stimulating factor
IFN	interferon
IL	interleukin
IL-4R	IL-4 receptor
MCP-1	monocyte chemotactic protein 1
MDC	macrophage-derived chemokine
RANTES	regulated on activation, normal T-cell expressed and secreted
STAT	signal transducer and activator of transcription
TARC	thymus and activation-regulated chemokine
TGF	transforming growth factor
Th	T helper
TNF	tumor necrosis factor
TSLP	thymic stromal lymphopoietin

Introduction

Atopic dermatitis (AD) is a chronic, relapsing, inflammatory skin disease that is characterized by pruritic, eczematoid skin lesions. AD commonly presents in early infancy and childhood, although it can present later in life and persist into adulthood. At least two types of AD have been identified: an extrinsic type, which is associated with allergen-specific IgE-mediated sensitization accounting for 70–80% of patients; and an intrinsic type without IgE-mediated sensitization, also called ‘pure AD’ which accounts for 20–30% of patients [1]. The preva-

lence of AD has been steadily increasing, especially in industrialized nations where the current lifetime prevalence in children is estimated to be 10–20% [2]. This disease results from interactions between susceptibility genes, the host’s environment, skin barrier defects, bacterial and viral skin infections, and immunological factors. An increased prevalence of AD has generated considerable interest and research into each of these areas, and new treatment strategies are being developed based upon an increased understanding of these issues.

Here, we will review some of the recent advances in our understanding of the pathogenesis of this disease.

Investigating the genetics of atopic dermatitis

AD is a genetically complex, familially transmitted disease. Parental AD confers a higher risk to offspring than parental asthma or allergic rhinitis, suggesting the existence of genes specific to AD [3•]. Several researchers have investigated various genetic aspects of AD, ranging from polymorphisms present in genes that are important in the barrier function of skin to those present in implicated cytokines, chemokines and their receptors [4,5,6•,7].

Genetic linkage analyses have identified several chromosomal regions with linkage to AD [4]. These include: regions on chromosomes 5q31–33, which contain a clustered family of type 2 T-helper cell (Th2) cytokine genes (i.e. IL-3, -4, -5 and 13); regions on chromosomes 1q21 and 17q25, which are closely coincident with regions known to contain psoriasis susceptibility genes, suggesting that common candidate genes are involved in the control of skin inflammation; a region on chromosome 3q21 that encodes the co-stimulatory molecules CD80 and CD86; and regions 3p24–22, 18q21, 3q14, 13q14, 15q14–15 and 17q21, which are currently uncharacterized [4].

Candidate genes that have been studied for their role in AD (Table 1) include the β chain of the high-affinity IgE receptor (Fc ϵ RI), mast cell tryptase, the CC chemokine RANTES (for regulated on activation, normal T-cell expressed and secreted), SPINK5 (the serine proteinase inhibitor implicated in Netherton’s disease), IL-4, IL-4 receptor (IL-4R), IL-13R and STAT-6 (for signal transducer and activator of transcription) [4,5,6•]. Of these genes, the polymorphisms in STAT-6, the proximal promoter of RANTES, IL-4, IL-4R α and TGF- β are significantly associated with AD [4,5,6•,7,8]. Polymorphisms in the β chain of Fc ϵ RI could result in increased surface

Table 1**Candidate genes and their possible role in atopic dermatitis.**

Gene	Potential role in atopic dermatitis
FcεRIβ	Increased mast-cell degranulation; increased surface expression of FcεRI
SPINK5 (Netherton's disease gene)	Serine protease inhibitor with potential importance in protection against serine protease allergens
RANTES	Increased eosinophil and lymphocyte recruitment; increased IgE production
IL-4, IL-4R, IL-13R	Regulation of IgE synthesis; B-cell class switching
STAT-6	Proximal promoter of RANTES, IL-4 and IL-4Rα; important in IL-13 activity

expression of the receptor as well as the amplification of intracellular signaling, resulting in increased mast-cell degranulation and activity [4]. Increased levels of RANTES, together with high levels of IL-4/IL-4R activity, might result in increased production of IgE. IL-4 and RANTES are also known to increase lymphocyte and eosinophil adhesion to endothelial surfaces [3^{••},4]. Although STAT-6 knockout mice retain the ability to develop AD-like skin lesions, increased activity of this transcription factor may contribute to the T helper 2 (Th2) shift seen in AD and other atopic diseases by increasing production of IL-4 and IL-13 [8]. Low levels of TGF-β could lead to increased skin inflammation [7].

Pathophysiology of atopic dermatitis

Disruption of the barrier function of the skin is an important and well-recognized etiologic factor in the pathogenesis of AD. A decreased production of ceramides by keratinocytes in both normal and affected skin of patients with AD results in increased permeability to environmental irritants and allergens, and transepidermal water loss. Hata and colleagues [9] recently demonstrated

a new technique by which the rate and depth of penetration of hydrophilic dyes could be measured, and the degree of penetration correlated strongly with the severity of skin disease and IgE levels.

A variety of immune effector cells have been investigated for their potential role in the pathogenesis of AD. Skin lesions evolve as the result of complex interactions between IgE-bearing antigen presenting cells (APCs), T-cell activation, mast-cell degranulation, keratinocytes, eosinophils, and a combination of immediate and cellular immune responses, although T-cell mediated processes play an essential role in pathogenesis [3^{••}]. Table 2 summarizes some of the cytokines and chemokines involved in the pathogenesis of AD.

Several factors contribute to the Th2 immune process seen in patients with acute AD lesions. Peripheral blood mononuclear cells from patients with AD have a decreased capacity to produce IFN-γ, which is possibly related to an IL-18 deficiency [10]. Preferential apoptosis of IFN-γ-producing Th1 memory and effector T cells contributes to an imbalance between the Th1/Th2 immune response, as shown by a decreased number of CC chemokine receptor 6 (CCR6)-expressing T cells in AD patients [11,12^{*}]. The number of CCR4-expressing memory CD4⁺ T lymphocytes is increased in the lesional skin of patients with AD [13]. The ability of keratinocytes to produce high levels of pro-inflammatory cytokines may help to explain the link between scratching and the triggering of Th2-mediated skin inflammation in AD. Keratinocytes in patients with AD have high levels of thymic stromal lymphopoietin (TSLP) and macrophage-derived chemokine (MDC). TSLP activates CD11c⁺ dendritic cells resulting in increased thymus and activation-regulated chemokine (TARC) and MDC production, and the priming of naïve Th cells to produce IL-4, IL-5, IL-13 and TNF-α [14]. Keratinocytes from

Table 2**Cytokines/chemokines involved in the pathogenesis of atopic dermatitis.**

Cytokine/chemokine	Role in atopic dermatitis
CCL22/MDC	T-cell recruitment and priming; increases T-cell production of IL-4, IL-5, IL-13 and TNF α
CCL17/TARC	T-cell recruitment and priming; increases T-cell production of IL-4, IL-5, IL-13 and TNF α
TSLP	Activates dendritic cells resulting in increased production of TARC and MDC
IL-4	B-cell class switching and IgE production
IL-5	Increases eosinophil survival in chronic AD
IL-13	B-cell class switching and IgE production
CCL27/CTACK	Lymphocyte recruitment and migration
IL-11	Type I collagen production in chronic AD
IL-17	Skin remodeling in acute AD
TGF-β	Skin remodeling, anti-inflammatory action
RANTES	Eosinophil and T-cell migration/activation; increases lymphocyte adhesion to endothelial cell surfaces
IFN-γ	Increased production of MCP-1 and RANTES by keratinocytes in chronic AD
TNF-α	Increased production of MCP-1 and RANTES by keratinocytes in chronic AD

CTACK, cutaneous T-cell-attracting chemokine.

patients with AD also produce high levels of RANTES, TARC and MDC upon stimulation with IFN- γ [15,16]. Levels of cutaneous T-cell-attracting chemokine (CTACK), MDC and TARC correlate strongly with AD disease severity [17].

In chronic AD, the microenvironment consists of both Th1 and Th2 cytokines [3**]. Eosinophil survival is prolonged as a result of high levels of IL-5 and GM-CSF in the skin. RANTES is secreted at high levels as well, promoting eosinophil and CCR3-bearing T-cell migration to the skin. Keratinocytes participate in the ongoing inflammatory process by producing high levels of RANTES and monocyte chemoattractant protein 1 (MCP-1) after stimulation with TNF- α and IFN- γ , leading to further T cell, dendritic cell and eosinophil recruitment. TGF- β , IL-17 and IL-11 appear to be important in the remodeling of skin lesions in patients with AD, and these cytokines are preferentially expressed at various stages of affected skin [18**]. IL-11 is significantly increased in chronic lesions and is correlated with type I collagen deposition, whereas IL-17 is associated with more acute lesions. Type I appears to be the major collagen subtype involved in the repair process.

Immunological triggers of atopic dermatitis

Several triggers are known to contribute to the pathogenesis of AD. Food allergens, aeroallergens, bacteria and even emotional stress have been implicated as immunological triggers of AD. Foods, such as peanuts, milk, wheat, eggs and soy have been described as triggers for up to 40% of children with moderate to severe AD [19,20]. This is supported by evidence that T cells specific to food allergens can be cloned from AD patients [21]. Further evidence suggests that aeroallergens can increase pruritus and atopic lesions after bronchial inhalation challenge in sensitized individuals [22]. The degree of IgE sensitization to aeroallergens is associated with the severity of the AD [23]. In patients with chronic AD, although the initial sensitization may be linked with triggers such as foods or aeroallergens, autoallergens may play a role in perpetuating skin inflammation, and treatment with systemic immunosuppressants suppresses the production of IgE in response to autoallergens [24]. Emotional stressors have been noted to contribute to rising eosinophil and natural killer (NK)-cell numbers [25,26]; AD patients also respond to emotional stressors with increased pruritus and scratching, which can exacerbate the state of the AD.

The role of infection in pathogenesis of atopic dermatitis

Many patients with AD have increased numbers of *Staphylococcus aureus* cultured from their skin lesions, and antibiotic therapy can be a useful means of controlling the AD [27]. *S. aureus* exacerbates chronic inflammation by secreting superantigens and α -toxin, which stimulate T cells, macrophages and eosinophils [28,29*]. Superanti-

gens can also cause T cells to become glucocorticoid resistant, leading to AD that is refractory to conventional topical glucocorticoid treatment but sensitive to calcineurin inhibitors [30,31]. α -Toxin is another bacterially-derived molecule thought to play a role in chronic inflammation, and it can induce the release of TNF- α , arachidonic acid and platelet-activating factor by forming a transmembrane pore that behaves similar to a calcium ionophore [32].

The immunological factors that contribute to increased numbers of *S. aureus* have recently been investigated. AD skin has increased expression of *S. aureus* adhesins, such as fibronectin, which are induced by IL-4 [33]. When bound to AD skin, *S. aureus* replicates more freely than in normal skin, as AD skin is deficient in the production of keratinocyte-derived antimicrobial peptides, such as LL-37 and the β -defensins [34*]. These molecules are essential in host defense against viruses, bacteria and fungi. Their reduced levels in AD skin may be the result of increased levels of Th2 cytokines suppressing the expression of antimicrobial peptides. This concept is supported by the observation that topical tacrolimus, a potent anti-inflammatory agent, reduces *S. aureus* colonization and skin inflammation [35].

Recurrent skin infections may be common in AD patients because of defects in Th1 cytokine generation and cytolytic-T-cell function. AD patients have perforin hyperreleasability, which results in the depletion of essential components of cytolytic mechanisms within cytolytic T cells [36]. In addition, monocytes from AD patients do not generate sufficient amounts of IL-18 and IFN- γ , which have been shown to inhibit vaccinia-induced pock formation in mice [10]. Recently, the susceptibility and reactions of AD patients to smallpox vaccine and other viral infections have been a topic of considerable interest and active investigation into this problem [37**]. Furthermore, some fungi such as *Malassezia furfur* (*Pityrosporum orbiculare*) have recently been investigated as another trigger for patients with AD. Treatment with antifungals in susceptible persons reduces the overall AD severity [38].

Implications for treatment of atopic dermatitis

Traditional treatment with topical corticosteroids still remains a mainstay of treatment, but newer, non-steroidal medications are now available. When maintenance therapy has been achieved, twice weekly applications of medications, such as topical fluticasone propionate, have been shown to control AD [39]. However, treatment with higher potency corticosteroids should be restricted to short periods of time to reduce the chance of significant side-effects. Calcineurin inhibitors, such as tacrolimus (FK506) and pimecrolimus, which both bind to the 12 kDa macrolipin, have shown the greatest promise

in long-term maintenance therapy for AD [40,41]. These medications inhibit the production of Th1 and Th2 cytokines, and inhibit mediator release from basophils and mast cells [42]. Both medications have been shown in long-term studies in adults and children to be safe even for large surface area applications [43*].

Topical calcineurin inhibitors can have advantages over topical corticosteroids in some circumstances, such as in patients who do not respond well to topical corticosteroids, those who are steroid phobic, and those who have areas of AD on their face and neck, where low-potency steroids still have a risk of skin thinning. Nevertheless, both classes of medications have their role in the control of AD skin inflammation [3**].

Imbalances in microbial colonization of the gastrointestinal tract may also play a role in modulating the immune response in AD. Patients with AD have lower counts of *Bifidobacterium*, a commensal bacterium that induces Th1 responses [44,45*]. By contrast, a higher frequency of *S. aureus* has been reported in the fecal microflora of AD patients in comparison to normals. A double-blind placebo-controlled crossover study found that oral administration of *Lactobacillus* was beneficial in the management of AD [46*]. Thus, probiotics, such as *Lactobacillus*, may hold some promise for the treatment of AD through its immunomodulatory effects on the balance of Th1/Th2 cells.

Conclusions

Significant gains have been made in our understanding of AD in the past year. The current understanding of AD pathogenesis, including the role of active cytokines and chemokines, as well as regulatory genes, sheds light on the immunological basis of AD. *S. aureus* and superantigens play an important role in skin inflammation. New insights into the use of prophylactic topical glucocorticoids and topical calcineurin inhibitors promise to alleviate the clinical symptoms and skin inflammation of AD. Understanding the complex interactions of AD from the genetic level, through cell-cell interactions, to the role of infection will lead to further improvements in clinical therapy and insights into the immunological pathogenesis of AD.

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