Clinical correlations of recent developments in the pathogenesis of atopic dermatitis

Dermatite atópica: implicações clínicas de avanços recentes na patogênese

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Abstract: Atopic dermatitis is a chronic inflammatory skin disease with a steadily increasing prevalence affecting 10-20% of infants and 1-3% of adults globally. It is often the first clinical manifestation of atopic disease preceding asthma and allergic rhinitis. Probably half of the children with atopic dermatitis develop some other form of atopic disease later in life. The pathogenesis involves a complex interplay of factors including genetic predisposition due to altered immune or skin barrier function, interactions with the environment such as food and allergen exposures, and infectious triggers of inflammation. In this review, we summarize the recent advances in understanding the contribution of different factors in the pathophysiology of atopic dermatitis and how insights provide new therapeutic potential for its treatment.

Keywords: Asthma; Atopic Dermatitis, Eczema; Eosinophils; Genetics; Immunoglobulin E; Keratinocytes; Rhinitis, T-Lymphocytes

Resumo: A dermatite atópica é uma doença cutânea inflamatória crónica cuja prevalência tem aumentado de forma constante, afetando 10-20% dos lactentes e 1-3% dos adultos em todo o mundo. Ela é frequentemente a primeira manifestação clínica de doença atópica, precedendo a asma e a rinite alérgica. Provavelmente metade das crianças com dermatite atópica desenvolvem alguma outra forma de doença atópica em outras fases da vida. A patogenia envolve uma interação complexa entre fatores que incluem predisposição genética devido a uma função alterada da barreira cutânea ou imunológica, interações com o ambiente, tais como exposição a alimentos e alergenos, e desencadeadores infecciosos de inflamação. Nesta revisão, resumimos os avanços recentes na compreensão da contribuição de diferentes fatores à fisiopatologia da dermatite atópica e como os novos conhecimentos proporcionam novo potencial terapêutico.

Palavras-chave: Asma; Ceratinócitos; Dermatite atópica; Eczema; Eosinófilos; Genética; Imunoglobulina E; Linfócitos T; Rinite

INTRODUCTION

In the last 20 to 30 years the prevalence of atopic dermatitis (AD) has increased dramatically attracting the attention of public health, immunology, allergy and dermatology communities. The objective of the current review is to highlight cellular and molecular mechanisms involved in the pathogenesis of this disease, as well as to provide an overview of how this increased understanding can be translated...
Atopic dermatitis or atopic eczema is a chronic inflammatory skin disease with a high incidence in the first year of life, and while AD can persist into childhood, symptoms usually remit by puberty. Atopic dermatitis can also be present in adults and affects more than 10% of the total population, with 80 to 90% of those affected being children under 5 years of age. Atopic dermatitis is frequently perceived as a minor dermatological disorder. However, the high prevalence of this condition carries financial and social costs not only for the community, regarding medical and hospital costs, but also for the patient and the patient’s family. Studies carried out in Netherlands, England, Australia, United States and recently in Italy, support the idea that families with AD-affected children have significantly higher expenses, that correlate with the severity of the disease. In this regard, the last report published by Ellis et al., in the United States of America in 2002, estimates the annual cost to private insurance and Medicaid of AD illness ranges from $US 0.9 billion to $US 3.8 billion. This cost is comparable to the cost estimated for other diseases such as emphysema, psoriasis and epilepsy.

Atopic dermatitis, regarded as a chronic illness, can affect a child’s quality of life and has been extensively addressed in a recent review. In this regard, the chronic nature and severity of the lesions can not only negatively impact the child, but also primary family members. The stress associated with taking care of a child with AD can be aggravated by disturbed sleeping patterns, and consequences of its pruritic nature lead to physical and mental exhaustion, mood changes, lack of concentration at school or work, as well as increased parental and child morbidity.

As already mentioned, AD is a pruritic disease, whose diagnosis is based on physician examination, according to the criteria established by Hanifin-Rafka. The clinical pattern associated with AD differs depending on age (Figure 1 A, B, C). Mild cases are associated with erythema in localized areas of the skin. In infants, exudative lesions are more frequently observed in the cheeks, scalp and extensor surfaces of the arms and legs. Chronic skin inflammation can be further exacerbated by infection. Older children tend to have lesions in the flexural areas of the extremities. Acute lesions may appear as erythematous macules or papules. However, the intense scratching behavior as a consequence of its pruritic nature, induces a cycle of chronic/relapsing clinical course, inducing remodeling of the skin. Characteristic features of AD chronic skin lesions are dryness as a consequence of transepidermal water loss, lichenification or thickening and hypertrophy of the epidermis, disruption of the skin barrier and consequently increased permeability to allergens and
microbes, as well as an increase in the infiltrate of mononuclear cells and some eosinophils in the dermis.\textsuperscript{16}

Inflammation results from interactions of immune cells and keratinocytes. The complex picture of the AD lesion is aggravated by environmental and genetic factors that increase the difficulty of understanding the mechanisms behind this complex pathophysiology (Figure 2).

**ATOPI\textit{C DERMATITIS AND THE ALLERGIC MARCH**

Children with early onset AD are also more likely to be atopic individuals, defined by positive skin prick test (SPT) or elevated antigen-specific serum immunoglobulin E (IgE) against common environmental or food allergens.\textsuperscript{17} Moreover, the number of positive SPT and/or levels of specific IgE are associated with the severity of the AD disease.\textsuperscript{18} Fifty to 80\% of the children with AD will develop asthma or allergic rhinitis by 5 years of age. This temporal progression of atopic symptoms from atopic dermatitis to allergic sensitization of the skin, food allergy, hay fever (allergic rhinitis) and later airway hyperresponsiveness and airway inflammation or asthma, has been named the “allergic march”.\textsuperscript{19-21}

The pathogenesis of AD is still unclear. However, as different disorders seen in the same patient have specific IgE as a common feature, it seems that AD could be seen as a local manifestation of a systemic disease, where specific IgE has a central role. This type of AD is called the extrinsic or atopic form and accounts for 45 to 75\% of the individuals.\textsuperscript{22-25}

However, specific IgE by itself is not a useful discriminator for AD. Others risk factors such as maternal history of atopy, ethnicity,\textsuperscript{24} socioeconomic status,\textsuperscript{25} environmental and genetic factors, gender, and early day care attendance also contribute to the exacerbation of the eczema, and support the existence of a second variant, the intrinsic or nonatopic form, that can also account for up to two thirds of the eczematous patients.\textsuperscript{25}

**SKIN BARRIER DYSFUNCTION**

Atopic dermatitis is characterized by dry skin involving lesional and non-lesional skin, as well as increased transepidermal water loss (TEWL). The pathogenesis of AD resulting in dry skin and eczematous lesions is believed to be as a consequence of a defective permeability barrier leading to the absorption of environmental allergens into the skin. Defects in the
permeability barrier may be a result of an altered lipid composition, such as decreased ceramide, in the stratum corneum (SC). Ceramides are major water retaining molecules present in the extracellular space of the cornified envelope. During the process of cornification, the ceramide containing bilayer is covalently attached to various proteins on the extracellular surface of the cornified envelope. TEWL levels have been shown to correlate with the content of covalently bound ceramides. The mechanisms by which the ceramide content is altered include the decreased activity of epidermal acid sphingomyelinase (A-SMase) in lesional and non lesional skin which correlates with reduced SC ceramide content and defects in permeability barrier. Recent studies have demonstrated that stress, which is a known exacerbator for AD, can have direct effects on skin barrier properties. Reports have demonstrated that insomnia may impair the epidermal barrier in patients with AD. Exogenous proteases increase the production of this enzyme leading to impaired epidermal differentiation and reduces the formation of lamellar bodies (LB) ultimately resulting in reduced synthesis of epidermal lipids such as cholesterol, fatty acid and ceramides. The abnormalities in both permeability barrier homeostasis and SC integrity induced by psychologic stress may be mediated by increased endogenous glucocorticoids.

The pathogenesis of AD may involve both genetic and environmental factors. Several studies now demonstrate that genetic mutations alone are not sufficient to predispose to AD and the importance of impaired epidermal barrier in patients with AD has received increased attention. Both the acute eczematous lesions and uninvolved skin have impaired barrier function. This process is believed to occur in two phases, first by a genetic predisposition to synthesize elevated levels of stratum corneum chymotryptic enzyme (SCCE) which results in early degradation of corneodesmosomes thereby damaging the skin barrier. Secondly, environmental effects due to application of soap or long term topical corticosteroids may further increase the production of this enzyme leading to impaired epidermal function. Exogenous proteases from house dust mites and *Staphylococcus aureus* may also impair the epidermal barrier.

AD has been demonstrated to show genetic linkage to chromosome 1q21. The region on chromosome 1q21 contains the epidermal differentiation complex (EDC) where a number of genes associated with epidermal differentiation and barrier function reside. Recent reports have shown that two functional mutations in the epidermal differentiation complex gene filaggrin (FLG) are strongly associated with AD, the asthma often accompanying AD, and also the common skin disorder ichthyosis vulgaris. The FLG gene encodes for a protein profilaggrin, which becomes cleaved in the suprabasal keratinocytes to form the active protein filaggrin. Filaggrin is associated with keratin intermediate filaments and allows them to be packed into bundles. In the terminally differentiated keratinocytes, filaggrin becomes cross-linked to the cornified cell envelope resulting in an insoluble barrier in the stratum corneum. Thus, filaggrin is necessary for the formation and hydration of the skin barrier and protects the organism against environmental agents. Studies to date suggest FLG mutations predispose to extrinsic allergic rhinitis but not intrinsic AD implicating that the skin barrier defect is a key event in AD that can subsequently lead to the development of secondary allergic symptoms and respiratory atopy. It should be noted that in addition to genetic FLG mutations, presumably the amount of FLG can be regulated resulting in a functional loss of the barrier properties of skin.

**TRIGGERS FOR ATOPIC DERMATITIS**

**A. Food and aeroallergens**

Atopic dermatitis is commonly the first manifestation of atopic disease. As many as 75% of children with severe AD will eventually develop asthma and/or allergic rhinitis. The exact role however of allergen exposure in atopic dermatitis is controversial. Yet allergic triggers such as allergens in food and environment have been shown to be associated with the pathogenesis of AD.

The majority of IgE-mediated food reactions that affect the skin are urticarial. Therefore the ability of foods to exacerbate AD has been questioned. There are now a number of well-controlled studies demonstrating an association between food ingestion and the development of an eczematous rash in children with AD. Approximately 40% of children with moderate to severe AD have a food allergy and ingestion of the offending food will exacerbate AD. The most common food allergy associated with AD is hen egg. Dairy, wheat, soy and peanut allergy can also exacerbate AD. Diagnosis of food allergy is still problematic as the presence of a positive food skin prick test or positive serum IgE food assay does not always correlate with clinical sensitivity. These data have provided compelling arguments for food allergy involvement in AD. Hence, the clinician must carefully evaluate the impact of food avoidance on disease severity.

House dust mite is the most well studied aeroallergen. The application of dust mite allergen with a patch test will induce an eczematous lesion in sensitized patients with AD. Numerous controlled studies have not only shown an association between aeroallergen exposure and exacerbation of AD but
that appropriate avoidance measures can improve AD. Thus avoidance of food allergens and limiting exposure to aeroallergens may help in reducing the symptoms of AD.

B. Infectious Triggers

Atopic dermatitis patients have increased susceptibility to bacterial, viral and fungal skin infections. Approximately, 90% of AD patients demonstrate the presence of *Staphylococcus aureus* in the lesions. The *Staphylococcal* exotoxins can activate skin Langerhans cells and macrophages to produce keratinocyte inflammatory mediators including IL-1 and TNF-α. These mediators lead to increased expression of endothelial cell adhesion receptors and chemokines which can recruit T cells. The skin endothelial cell adhesion receptor, E-selectin binds to cutaneous lymphocyte associated antigen (CLA+) skin homing memory T cells. CLA+ T cells are biased to producing Th2 cytokines. *Staphylococcal* exotoxin specific IgE antibodies in AD patients can bind to basophils and mast cells to release histamine ultimately leading to pruritic skin.

The skin of AD patients is also susceptible to viral skin infections following inoculation with vaccinia virus. Studies examining the role of Th2 cytokines, IL-4 and IL-13 in vaccinia virus infection demonstrated increased vaccinia virus replication and decreased expression of the human cathelicidin LL-37 (antimicrobial peptide) in AD skin. The mechanisms underlying the above effects of increased vaccinia virus replication by Th2 cytokines may involve subversion of the innate immune responses to vaccinia virus via a Stat6-dependent pathway. Further studies indicated decreased expression of macrophage inflammatory protein 3α (MIP-3α) in AD skin by Th2 cytokines. Therefore it is suggested that neutralizing Th2 cytokines or increasing MIP-3α may reduce adverse reactions in AD after smallpox vaccination.

Atopic dermatitis patients, particularly those with head and neck dermatitis, are often affected by a fungal pathogen *Malassezia furfur*. The presence of IgE antibodies against *M. furfur* in these patients has been reported in patients with both extrinsic and intrinsic types of AD. Antifungal therapy has shown to be promising in a subgroup of AD patients.

To combat the bacterial infections, the body mounts innate immune responses via Toll like receptors (TLRs), antimicrobial peptides (AMPs) or production of proinflammatory cytokines. Antimicrobial peptides play an important role in determining the susceptibility to infection. A study involving cathelicidins and human β-defensin 2 demonstrated a synergistic antimicrobial effect to *Staphylococcus aureus*. A new antimicrobial peptide namely, human β-defensin 3 has been shown to kill a broad range of microbes including *Staphylococcus aureus*. Decreased expression of human β-defensin 3 has been demonstrated in the lesional skin of both extrinsic and intrinsic types of AD. Neutralizing the Th2 cytokine milieu in AD skin may lead to enhanced innate immune responses against bacterial and viral pathogens. AD skin has been reported to exhibit reduced expression of antimicrobial genes due to a lack of proinflammatory cytokines including TNF-α or IFN-γ important for induction of anti-microbial peptides. The severity of lesions is further enhanced by microbial products including superantigens, lipoteichoic acid and peptidoglycan.

IMMUNE MECHANISMS IN ATOPIC DERMATITIS

A. Effector cells

● T cells

Atopic dermatitis generally results from dysregulated Th2 biased immune responses to environmental and bacterial stimuli. Recent studies in acute and chronic lesions of AD patients have indicated the presence of Th2 cells secreting IL-4 in early lesions and unaffected skin, with skewing to a mixed Th1-Th2 profile or dominance of IFN-γ producing Th1 cells in late lesions. Studies have further indicated that acute T-cell infiltration in AD is associated with a predominance of IL-4 and IL-13 expression while chronic lesions reveal increased IL-5, GM-CSF, IL-12 and IFN-γ expression. In mouse models of transgenic and knockout mice, Th1 and Th2 cytokines are well known to affect allergic skin inflammation. Overexpression of the Th2 cytokine, IL-4 in the skin has been shown to result in the manifestation of AD-like symptoms in mice. On the contrary, allergen sensitized skin from mice deficient in IL-4 and IL-5 lack eosinophils and the skin from IFN-γ-deficient mice demonstrate decreased thickening of the dermis indicating the importance of Th1 and Th2 cytokines in AD. Other studies have indicated the importance of Th2-cytokines, IL-4 and IL-13 at the onset of AD and IL-5 at the later stages of AD. In addition to the Th1 and Th2 subset of T cells, defects in T regulatory cells have been implicated in the development of polyendocrinopathy X-linked syndrome involving hyper-IgE, food allergy, and eczema. In a murine model of AD, studies have suggested that invariant natural killer T cells (iNKT) cells, γδ T cells and B cells are dispensable in the development of allergic skin inflammation.

● Antigen-presenting cells

Two distinct antigen presenting dendritic cells (DCs) namely Langerhans cells (LCs) and inflammatory dendritic epidermal cells (IDCs) have been implicated in AD skin. LCs predominate at the initial phases of
AD and prime naïve T cells to the Th2 type.82
Triggering of the FcεRI receptor on the surface of LCs by allergens induces chemotactic signals and recruits precursor cells of IDECs and T cells in vitro. Engagement of FcεRI on IDECs further induces proinflammatory signals amplifying the immune response.83
Thus DCs expressing membrane IgE receptors play a critical role in the amplification of allergen specific T cell responses. It has been reported that low numbers of plasmacytoid DCs in the epidermal skin lesions of AD patients allows them to be highly prone to viral skin infections like herpes simplex-induced eczema herpeticum.85

● Keratinocytes
Keratinocytes of AD patients exhibit an increased propensity to produce cytokines and chemokines, a phenomenon that plays a major role in promoting and maintaining skin inflammation. The well known cytokine thymic stromal lymphopoietin (TSLP) produced by keratinocytes activates DCs which in turn primes T cells to support the maintenance of Th2 cells.84 Chemokines like RANTES are produced in significant amounts following stimulation with TNF-α and IFN-γ leading to increased recruitment of eosinophils.85,86 Epidermal keratinocytes of AD lesions also produce increased levels of GM-CSF.87,88

Keratinocytes also express functional receptors like CD14 and Toll-like receptor 4 (TLR4) and on stimulation with lipopolysaccharides (LPS) can trigger proinflammatory responses. In addition to secreting cytokines and chemokines, the keratinocytes synthesize antimicrobial peptides on exposure to microorganisms.89 Studies have implicated T cell mediated Fas-mediated keratinocyte apoptosis to play an important role in the development of eczematous lesions in AD.90

● Mast cells
Mast cells contribute significantly to the pathogenesis of AD. Cross-linkage of specific IgE receptors on dermal mast cells provokes the release and synthesis of a vast array of mediators.91,92 Following their recruitment and activation into the skin, eosinophils are also thought to contribute relevantly to tissue damage. Thus, a complex network of cytokines and chemokines contributes to establishing a local milieu that favors the permanence of inflammation in AD skin.

The importance of mast cells in controlling the expression of IFN-γ and circulating IgE levels in a model of allergen-induced skin inflammation was studied in mast cell deficient mice (W/W(v)).93 In this model W/W(v) mice were sensitized epicutaneously with OVA (ovalbumin) and the results indicated comparable infiltration of mononuclear cells, T cells and eosinophils between wild type controls and mast cell deficient mice. However, a significant upregulation of IFN-γ in OVA sensitized skin and elevated total serum IgE levels were observed in mast cell deficient mice in comparison to wild-type controls. These results suggest that mast cells may regulate multiple aspects of the immune response following epicutaneous sensitization.

In addition to the role of mast cells in allergic reactions, they are also involved in neuro-inflammatory diseases which are worsened by stress.94 AD among other inflammatory diseases has been reported to be aggravated by psychological stress by trigerring pruritis. Mast cells are a key component of the stress response in addition to nerve growth factor, corticotrophin releasing hormone and substance P.

It is well documented that TSLP expression is correlated to the pathogenesis of AD. TSLP can stimulate mast cells and dendritic cells to initiate the innate allergic immune responses.95 In the latter phases, TSLP activated DCs mediate the T cell dependent adaptive phase of the allergic immune response.

● Eosinophils
Activated eosinophils in the peripheral blood and skin lesions play an important role in the pathogenesis of AD.96,97 Although, human eosinophils express several chemokine receptors including CCR2, CCR3 and CXCR4, most studies have indicated the importance of CCR3 in the development of human AD and mouse models of AD. The ligands associated with CCR3 linked to the development of human AD include CCL5, CCL11, CCL13 and CCL26. Further studies have suggested RANTES also plays a role in activation and chemotaxis of eosinophils.

Leptin, a pleiotropic adipocyte-derived cytokine used in hypothalamic regulation of body weight and modulation of immune response, has been proposed to have a role in eosinophil survival and activation.98,99 Leptin was shown to up-regulate cell surface expression of adhesion molecules ICAM-1 and CD18 and suppress ICAM-3 and L-selectin on eosinophils. It also stimulated the release of IL-1β, IL-6, IL-8 and MCP-1 via differential intracellular signaling mechanisms.99

B. Effector cytokines and chemokines
Several studies have reported the initiation of atopic skin lesions to be mediated by IL-4 producing Th2 cells whereas chronic lesions may have a mixed Th2 and Th1 coexistence or may be predominated by Th1 cells alone.95,96 The involvement of IL-4 and IL-13 in the initial phases and IL-5 in the later phases has also been noted.74 Despite the clear association of Th2 cytokines with AD, in several mouse models of AD, allergic skin inflammation develops in the absence of Th2 cells. Chronic AD is associated with
Th1 like cytokines IL-12 and IL-18 and remodeling cytokines including IL-11 and TGF-β1. IL-10 may also have a role in regulating allergic skin inflammation. Reduced skin specific infiltration of eosinophils and expression of IL-4, IL-5 and eotaxin mRNA were observed in IL-10-/− mice sensitized epicutaneously to OVA. In vitro stimulation of splenocytes from sensitized IL-10-/− mice demonstrated significant enhancement in the levels of IFN-γ concomitant with reduced levels of IL-4, compared to wild type mice. Thus, IL-10 may modulate AD.

IL-31, a Th2 effector cytokine plays an essential role in allergic skin inflammation, AD and allergic asthma. The activity of IL-31 is mediated through a heterodimeric receptor made up of IL-31RA and oncostatin M receptor (OSMR) expressed on epidermal keratinocytes and bronchial epithelial cells. Ligand stimulation of receptor expressing cells results in increased expression of chemokines and cytokines that potentiate allergic inflammation.

Numerous chemokines including CCL1, CCL2, CCL3, CCL4, CCL5, CCL11, CCL13, CCL18, CCL20, CCL22, CCL26 and CCL27 have been implicated in the pathogenesis of AD. CCL27 is a skin specific chemokine made by keratinocytes following induction by TNF-α and IL-1β. The CCL27-CCR10 interaction plays an important role in controlling recruitment of memory T cells to the skin though CCR4 has also been reported to play a role in this process, and skin homing CCLA+ memory T cells have been shown to express CCR10 and CCR4. The CCR4 ligand, CCL17 is expressed by cutaneous venules and may play a role in recruiting CCR4+ cells. However, CCL18 is the most highly expressed ligand specific to AD with levels in the lesional skin reported to be 100 fold higher than CCL17. The regulation of CCL18 by allergen exposure and microbial products suggest a crucial role for this chemokine in the initiation and amplification of atopic skin inflammation. Further, CCL1-CCL8 mediated recruitment has been shown to play a role in DC-T cell interactions at the sites of atopic skin inflammation. Further work will delineate whether targeting these molecules might provide therapeutic benefit.

C. Lipid-derived mediators

Lipid-derived mediators include the eicosanoids derived from arachidonic acid and platelet-activating factor derived from glycerophosphocholines. Arachidonic acid released from membrane phospholipids can be metabolized by cyclooxygenase to form prostaglandins (PGs), and by 5-lipoxygenase to form leukotrienes (LTs). The PGs, comprising PGE2, PGD2, 6-ketoPGF1α, PGF2α, and thromboxane A2 (TXA2), exhibit diverse pharmacological activities, including those related to inflammation, reproduction, nociception, gastrointestinal protection, platelet aggregation, and renal blood flow and vascular homeostasis. Recent studies suggest that cutaneous pruritus, one of the hallmarks of atopic dermatitis, is regulated by PGs, especially PGD2. Using NC/Nga mice, agonists of PGD2 inhibit, and cyclooxygenase inhibitors have been reported to augment, skin pruritus. Though PGs negatively regulate pruritus, studies demonstrating that cyclooxygenase inhibitors block IL-10 production in keratinocytes as well as other cell types suggest a complex role for these lipid mediators.

Leukotrienes consisting of LTB4, and the cysteinyl leukotrienes LTC4, LTD4 and LTE4 also have significant proinflammatory effects. Cysteinyl leukotrienes in particular through their ability to induce bronchoconstriction and increased vascular permeability, have been implicated in asthma. Cysteinyl leukotriene receptor antagonists such as monteleukast are effective for asthma, though do not appear to be useful for acute flares. Monteleukast has also been found to be mildly effective in atopic dermatitis.

Platelet-activating factor (1-alkyl-2-acetyl-glycrophosphocholine; PAF) is a lipid mediator usually produced concomitantly with eicosanoids. Several lines of evidence suggest involvement of PAF in inflammatory skin diseases, especially atopic dermatitis. First, PAF has been measured in urticarial-like eruptions, including cold urtica and bullous pemphigoid. Of significance, the PAF receptor appears to be able to bind to ligands other than PAF. These ligands include oxidatively modified other cell types. Of significance, the PAF receptor appears to be able to bind to ligands other than PAF. These ligands include oxidatively modified glycerophosphocholines as well as bacterial products including lipoteichoic acid. The ability of the PAF receptor to respond to bacterial products could provide one mechanism by which bacterial infection can...
serve as a trigger for worsening of atopic dermatitis (Figure 2). PAF receptor antagonists are not routinely available, but rupatadine, a novel compound with both H1 antihistamine and PAF receptor antagonistic effects, has been shown to have efficacy in allergic disorders including allergic rhinitis. 135

VI. Genetic susceptibility
Atopic dermatitis is recognized as a multifactorial heterogeneous genetic disease known to occur as a result of genetic interactions with environmental factors. Around 80% of eczema developing in children is atopic, characterized by allergen specific IgE and high total IgE in their sera. Twin studies of AD demonstrated concordance rates of 0.72-0.86 in monozygotic, and 0.21-0.23 in dizygotic twin pairs. 134 Total serum IgE levels show a heritability of 50%. 135-137 These studies indicate the importance of genetic components in AD.

Association of AD with other atopic conditions such as asthma and allergic rhinitis implicate a genetic correlation between these conditions as evidenced by cross phenotype familial clustering. 138 Functional polymorphisms of the genes and their association with disease may provide novel mechanisms for the pathogenesis of the disease. Various approaches underlying the identification of genes are discussed below.

A. Genome wide screens
In studies of large families, genetic polymorphisms are mapped to discrete chromosomal regions and genetic regions associated with disease are identified. The linkage regions may contain several disease associated genes. Genome screens have identified at least 4 regions of genetic linkage to AD on chromosomes 1q, 3q, 3p and 17q. 32,139-141 Other mapped loci using composite phenotypes of AD and asthma combined have shown genetic linkage to chromosome 20p. 32 Composite phenotypes for AD with increased total serum IgE (16q) 52 and allergen specific IgE (3p, 4p, 18q) 140 have also been reported. Overlap of some of these loci with psoriasis (1q, 3q, 17q, 20p) 142 or asthma (13q, 17q, 20p) 141 has been demonstrated.

B. Candidate gene studies
Candidate gene studies determine correlations between phenotype and genotype at 1 or more polymorphic loci within a gene of interest. Candidate genes for AD include FLC, CTLA4, TLR2, TLR9, IRF2, CD14, GM-CSF, IL-13, IL-4, SPINK5, CARD4, FcɛRIβ, IL-18, TIM1, PHF11, MCC, RANTES, Eotaxin, TGFβ1, SCCE, CARD15, GSTT1. 138 A brief description for some of the genes is outlined below.

a. FcɛRIβ
FcɛRIβ is encoded by a single gene, MS4A2 on chromosome 11q12-13, a region demonstrating linkage to atopy. 143,144 Polymorphisms in this gene have shown linkage with different atopy phenotypes. 145-147 Moreover, an excessive transmission of maternal FcɛRIβ has been demonstrated in AD patients. 148

b. RANTES and Eotaxin
RANTES encoded by CCL5 and Eotaxin 1 encoded by CCL11 are located on chromosome 17 next to an AD linked region. Polymorphisms in the CCL5 promoter region have been shown to correlate with increased levels of RANTES in AD patients. 149,150 Similarly polymorphisms in CCL11 promoter region are associated with enhanced total serum IgE in AD patients. 150

c. Cytokine gene cluster
The cluster located on chromosome 5q31-33 comprises linked genes including IL3, IL4, IL5, IL9, IL12, IL13, GM-CSF, CD14 antigen, T cell immunoglobulin mucin domain (TIM-1) and SPINK5. 143 Mutations in the gene encoding SPINK5 are reported to cause Netherton’s disease, a rare recessive disorder characterized by generalized congenital erythroderma. 151,152 Further studies also demonstrated variants of SPINK5 to modify the risk of development of AD, asthma and increased serum IgE levels. 155-156 Several of the cytokine cluster genes have been associated with AD and total IgE levels.

d. Epidermal differentiation complex
AD shows genetic linkage to chromosome 1q21 which contains the epidermal differentiation complex (EDC). This complex is comprised of genes and gene families expressed in the terminally differentiating epithelium. 32 Gene families in the EDC include the S100 calcium binding proteins, small proline rich proteins and late expressed cornified envelope proteins. The single copy genes in EDC include trichohyalin, reten, loricrin, filaggrin and involucrin. Recent studies have demonstrated that two functional mutations in the gene encoding filaggrin (FLG) are strong risk factors for AD and asthma in European populations. 55 Other studies demonstrated that these mutations result in an extrinsic AD in patients suggesting that the skin barrier defect precedes the development of allergic sensitization in AD. 157 Since FLG mutations have not been commonly described in other non European populations, studies have analyzed mutations in other ancestral groups to determine the contribution of FLG mutations to AD pathogenesis worldwide. 158 In this regard, two novel FLG mutations reported in Japanese IV patients have recently been associated with AD. 159 It
is also reported that half of Irish AD cases carry FLG null mutations.\textsuperscript{160} The role of other EDC genes in the pathogenesis of AD needs to be explored further.

**TRANSLATING LESSONS FROM LAB TO CLINIC**

The treatment of AD entails education of the patient and family. Given the heterogeneity of this disorder, an individualized treatment regimen is essential. The family and patient need to understand that AD is a chronic disease with exacerbations due often to exogenous environmental factors and psychological factors. Molecular and immunological studies that have begun to illuminate the underlying pathogenic mechanisms of AD have impacted therapy. Figure 2 and Table 1 outline therapeutic clinical correlations of AD pathogenesis. These new “therapies” can be divided into those impacting the barrier abnormalities, and those affecting the immune dysregulation, though the two are certainly intertwined.

**A. Barrier Restorative Creams**

The recent discovery of filaggrin mutations associated with a significant number of AD cases have confirmed the importance of barrier dysfunction in this enigmatic disorder. To treat the dry skin associated with AD, most clinicians recommend daily baths, followed by an occlusive lubricant to retain the water absorbed by the stratum corneum. Use of emollient creams during the day is also helpful in fighting the increased TEWL seen in many AD patients.

Several topical barrier creams have become available for use in the management of AD. These physiologic moisturizers can be divided into three categories; the ceramide-dominant agents Cera-Ve, TriCeram\textsuperscript{TM} and EpiCeram; Mimyx, which contains the fatty acid palmitamide; and Atopiclair\textsuperscript{TM} cream containing the antiinflammatory molecule glycyr rhetic acid, telmesteine, shea butter, caprylol glycine, and hyaluronic acid in a hydrolipidic base. Atopiclair\textsuperscript{TM} has been shown to promote some modest improvement in patients with mild- to moderate AD. The physiological based ceramide-containing cream TriCeram\textsuperscript{TM} has been shown to result in significant improvement in childhood AD, both in clinical score as well as improved barrier function.\textsuperscript{161} Other reports also demonstrate efficacy of other ceramide-dominant agents.

**B. Reduction of allergic triggers**

If investigations reveal the presence of allergies in the AD patient, avoidance of the allergic triggers is

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**CHART 1: Therapeutic clinical correlations of atopic dermatitis pathogenesis**

<table>
<thead>
<tr>
<th>Clinical Disease Component</th>
<th>Pathogenesis</th>
<th>Treatment Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry skin</td>
<td>Barrier disruption and increased TEWL associated with genetic or functional FLG mutations or other causes</td>
<td>Daily baths, with mild/absent soap, lubrication of skin. Barrier restorative creams. Avoiding irritants and psychological stress</td>
</tr>
<tr>
<td>Seborrheic dermatitis-like lesions</td>
<td>Allergies/hypersensitivity to yeasts such as <em>M. Furfur</em></td>
<td>Antifungals, selenium either in shampoo or cream vehicle</td>
</tr>
<tr>
<td>Food/airborn allergies</td>
<td>IgE directed against foods</td>
<td>Identification of specific allergens and avoidance; use of dietician to assist in education. Chronic H-1 antihistamines. Consideration of specific immunotherapy or immunosuppressive therapy (e.g., azathioprine, cyclosporine, mycophenolic acid) for short period of time.</td>
</tr>
<tr>
<td>Infected skin lesions</td>
<td>Infection with <em>S. aureus</em> or Group A.<em>streptococcus</em></td>
<td>Treat active infections; avoid potential fomites such as sponges in bath, toys, etc. Topical antibiotic treatment of carriage of nares, umbilicus, anus, fingernails. Baths with antiseptic including dilute bleach.</td>
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by far the optimal treatment strategy. If this is problematic, other potential therapies/strategies are potentially available and are listed below.

- **Anti-IgE therapy**
  Omalizumab (Xolair, Novartis, East Hanover,NJ) is a recombinant monoclonal antibody to IgE. It is currently approved for the treatment of asthma in patients greater than 12 years of age with poorly controlled atopic asthma and IgE levels < 700 IU/ml. Patients with AD often have significant elevation of serum IgE. There are a few case reports of improvement in AD with omalizumab. However given the cost and lack of controlled trials it currently can not be recommended for treatment.

- **Specific Immunotherapy (SIT)**
  SIT is allergen specific desensitization given by subcutaneous injection (SCIT) or orally (SLIT). Two controlled SCIT studies for dust mite allergic patients with AD have been published. Long-term treatment with high dose SCIT produced statistically significant improvement in AD in both groups. One controlled SLIT study has shown skin improvement in dust mite allergic children with AD. SLIT is currently not approved for use in the United States.

**C. Antimicrobial agents in the reduction of Infectious triggers**

- **a. Yeasts**
  Based on the reports that demonstrate abnormal cutaneous reactions and IgE antibodies to Malassezia yeasts in some patients with AD, especially those with significant head and neck involvement that can somewhat resemble the distribution of seborrheic dermatitis, several reports have demonstrated effectiveness of topical antifungals as part of the treatment regimen. In particular, a recent study demonstrated the effectiveness of ciclopiroxolamine in a subgroup of AD patients with IgE antibodies directed against malaalsezia yeast. It should be noted that that many anti-fungals, including ciclopiroxolamine exert anti-inflammatory, as well as antimicrobial effects. Thus, it is not clear whether the reported improvement was due to the eradication of yeasts which serve as a potential immune stimulus or a direct anti-inflammatory effect.

- **b. Bacteria**
  Bacterial superinfection is a known trigger for worsening AD. Bacteria, especially *Staphylococcus aureus*, can be cultured from the majority of AD patients. Thus, clinicians experienced in AD treatment are vigilant in regards to both looking for and treating secondary infections in AD patients. The usual treatment for secondary bacterial infection of AD consists of oral antibiotics, as well as topical antibiotics. Unfortunately, the chronic use of antibiotics can be associated with bacterial resistance, and increased numbers of methicillin-resistant *staphylococcal* strains are emerging. A new antibiotic, retapamulin, which is a member of the pleuromutilin class of antibiotics, has been shown to be as effective topically in infected AD patients as oral antibiotic cephalixin. At this time, there are no reports of bacterial resistance to retapamulin.

**D. Calcineurin Inhibitors**
  Topical corticosteroids have been the mainstay of AD treatment. The regimen used most commonly by the authors is a mid-potency topical corticosteroid ointment for thickened areas of dermatitis on body, with weaker non-fluorinated corticosteroids for larger areas, face, or maintenance. Though effective, their use is limited by side effects which can include inhibition of barrier function, thinning of skin and resultant striae, as well as acneform eruptions. Systemic absorption of glucocorticosteroids can cause adrenal suppression in young children due to their higher body surface area-to-weight ratios. Although these adverse effects are usually avoidable by prudent use of corticosteroids, these side effects have made it desirable to have effective non-steroidal antiinflammatory agents for topical use in AD.

Calcineurin inhibitors (pimecrolimus, tacrolimus) are effective topical agents that have been demonstrated to be effective in AD. Through their ability to interrupt calcineurin pathways, they have potent effects on T cells. Recent studies indicate they also have immunomodulatory effects on other cell types important in AD including dendritic cells and mast cells. Given the large size of these molecules, there is very little penetration in normal skin, unlike active AD lesions characterized by defective barrier properties. Consistent with this, some of the first reports demonstrated low levels of tacrolimus in blood at the beginning of therapy, which then were much lower as the patient improved. Other side effects include transient burning and stinging, seen more often with tacrolimus over pimecrolimus. These effects can be lessened by refrigerating the medicine, and concomitant use of a topical steroid.

The rather selective effects of these agents results in a better safety profile. There are recent concerns about possible risk of malignancy associated with long-term use of these agents. In March, 2005, the US Food and Drug Administration (FDA) issued a public health advisory regarding the potential cancer risk from the use of tacrolimus and pimecrolimus topical preparations. This advisory was historical as it was not based upon data indicating an increase in cancers associated with the topical use.
of calcineurin inhibitors, but theoretical concerns as long term use of systemic calcineurin inhibitors (eg, for organ transplant patients) is known to result in increased skin cancers. Thus, the FDA recommended that these agents should be reserved for patients who have failed other therapies. These concerns have resulted in a “black box warning” of possible cancer risk for the use of these agents.

Though the FDA “black box warning” is present for these agents, a nested case-control study examining AD patients following exposure to topical calcineurin inhibitors found no increased risk of lymphoma, unlike systemic exposure to these agents. A scientific consensus conference convened by the American Academy of Dermatology concluded there is no causal proof that topical calcineurin inhibitors cause lymphomas or non-melanoma skin cancers. However, the prudent use of these agents is recommended, especially minimal use as second-line agents for recalcitrant AD.

CONCLUSION
Atopic dermatitis is a significant health problem in Western society. While AD is not life threatening, it poses a chronic problem that impacts affected individuals and their families both emotionally and financially. The pathogenesis of AD is still not well understood, but clearly involves the culmination of altered barrier function of the skin, increased exposure of innate immune cells to allergens, and the sensitization of T cells that are primed to secrete Th2 cytokines, which subsequently potentiate the local inflammatory response (Figure 2). Microbial products, and the immune response to pathogens can further exacerbate allergic inflammation (Figure 2). Animal models have defined some of the cell types and mediators involved in the development of AD. These cells and mediators have been verified both biologically and genetically to be important in patient populations. As more aspects of allergic inflammation have been revealed, therapies have become directed to interfering with local immune function and focus less on generalized immunosuppression. Ongoing studies in patients and animal models will uncover additional details of disease that should have a significant impact on diagnosis, treatment and prevention of atopic dermatitis.

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