Advances in Atopic Dermatitis

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Atopic dermatitis (AD) is a highly pruritic, chronic, and relapsing inflammatory skin disorder affecting 10-20% of children worldwide. During the past year there have been significant advances in our understanding of the cellular and immunologic mechanisms underlying AD as well as the immunologic triggers involved in its pathogenesis. The introduction of a new class of topical anti-inflammatory medications, topical calcineurin inhibitors, has significantly increased our treatment options and led to the rethinking of potential management approaches in AD. (Chang Gung Med J 2005;28:1-8)

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Atopic dermatitis (AD) is a highly pruritic, chronic, and relapsing inflammatory skin disease that commonly presents during early infancy and childhood.(1) Two types of AD have been identified: an extrinsic form associated with IgE responses, which affects 70-80% of patients; and an intrinsic form with normal IgE levels, which affects 20-30% of patients.(2) Recent interest in AD has been sparked by reports of its increasing prevalence and the significant adverse effects of AD on patient's quality of life.(3,4) This review examines some of the recent advances in our understanding of AD and new management strategies that are introduced.

Immune Mechanisms

Immunologic and cellular mechanisms play an important role in the pathogenesis of AD (Fig. 1).(5)

![Fig. 1 Immunologic pathways in atopic dermatitis. LC: Langerhans cells; MC: mast cells; CLA: cutaneous lymphoid antigen; IL: interleukin. The figure is from reference 5 with permission from Mosby/Elsevier Science, St Louis.](image-url)
**T cells and Keratinocytes**

In animal models of AD, T cells are critical to the induction of eczematoid skin lesions. Activated T cells have been found to induce keratinocyte apoptosis, contributing to the spongiotic process found in AD. The process is mediated by T-cell-derived IFN-γ which upregulates Fas on keratinocytes. The lethal hit is delivered to keratinocytes by Fas-ligand expressed by skin-infiltrating T cells. Keratinocytes from patients with AD, as compared to psoriasis, produce significantly higher levels of RANTES after stimulation with TNF-α and IFN-γ. The keratinocytes from AD patients, but not from nonatopic subjects, are also an important source of thymic stromal lymphopoietin, which activates dendritic cells to prime native T helper (TH) cells to produce IL-4, IL-13 and TNF-α. These observations might explain the link between scratching and the triggering of TH2-mediated skin inflammation in AD.

**Antigen Present Cells (APC)**

AD skin contains an increased number of IgE-bearing Langerhans cells and inflammatory dendritic epidermal cells expressing the high-affinity receptor for IgE. The clinical importance of IgE-bearing Langerhans cells is supported by the observation that the presence of FcεRI and IgE-bearing Langerhans cells is required to provoke eczematous skin lesions by application of aeroallergens on the skin of patients with atopic disease. After treatment with topical tacrolimus or Chinese herbs, downregulation of dendritic cell function has been found. A potential link between APC and immediate hypersensitivity reactions also has been found. In this regard, total serum IgE levels are increased after epicutaneous sensitization in mast cell-deficient mice relative to wild-type mice. Furthermore, histamine can downregulate IL-12 production by human monocyte-derived dendritic cells and may thereby enhance the development of TH2 cells.

**Cytokines**

Figure 1 shows the different cytokine patterns expressed in skin lesions of AD. Analyses of biopsy samples from uninvolved skin of patients with AD, as compared with healthy non-atopic skin, have an increased number of TH2 cells expressing of IL-4 and IL-13 mRNA, but not IL-5, IL-12 or IFN-α mRNA. When compared with healthy skin or unaffected skin of patients with AD, acute and chronic skin lesions have significantly more cells expressing of IL-4, IL-5, and IL-13 mRNA. However, acute AD does not contain significant numbers of IFN-α or IL-12 mRNA-expressing cells. In contrast, chronic AD skin lesions have significantly fewer IL-4 and IL-13 mRNA-expressing cells, but increased number of cells expressing IL-5, GM-CSF, IL-12, and IFN-α mRNA as compared to acute AD.

The CC chemokines, monocyte chemotactic protein 4, and eotaxin have been found to be increased in AD skin lesions and likely contribute to the chemotaxis of CC chemokine receptor 3-expressing eosinophils and TH2 lymphocytes into the skin. Increased cutaneous T-cell attracting chemokine (CCL-27) also play a role. Recent studies suggest that selective recruitment of CC chemokine receptor 4-expressing (CCR4) TH2 cells into AD skin might also be mediated by the chemokines macrophage derived chemokine (MDC) and thymus and activation-regulated chemokine (TARC), which are increased in AD. Plasma levels of TARC and MDC correlate significantly with disease activity of AD. IL-16, a chemoattractant for CD4+ T cells, is more highly expressed in acute than chronic AD skin lesions and is primarily found in CD1a+ Langerhans cells. Increased expression of IL-11 and TGF-α contributes to dermal fibrosis in lichenified skin lesion of AD.

**Immunologic Triggers**

**Foods**

Approximately 40% of infants and young children with moderate to severe AD have food allergy. Infants and young children with food allergies generally have positive immediate skin tests or serum IgE directed to various foods, especially egg, milk, wheat, soy, and peanut. Importantly, food allergen-specific T cells have been cloned from AD skin lesions, providing direct evidence that foods can contribute to skin T cell responses. In mouse models of AD, oral sensitization with foods also results in eczematous skin lesions on repeat oral food challenges.

**Aeroallergens**

Epicutaneous application of aeroallergens (e.g., house dust mites, weeds, animal danders, and molds)
by atopy patch test on uninvolved atopic skin elicits eczematoid reactions in patients with AD sensitized to relevant aeroallergens.\(^{(29)}\) This is likely to be a T cell-mediated response, because dust mites were recently found to have no direct proinflammatory effect on human keratinocytes.\(^{(30)}\) Several studies have reported that a combination of effective house dust mite reduction measures is associated with significantly greater improvement in AD.\(^{(31)}\) However, more recent studies have revealed that reduction of dust mite levels at home with mattress, duvet, and pillow encasings is not effective in reducing the symptoms of AD.\(^{(32)}\) These different results suggest that reduction of allergens in other environments (such as work and school) may be necessary as well to gain control of allergic symptoms.

**Autoantigens**

Recent studies have found that most sera from patients with severe AD contain IgE antibodies directed against human proteins.\(^{(33)}\) Although these autoallergens characterized to date are mainly intracellular proteins,\(^{(34)}\) they have been detected in IgE immune complexes of AD sera, suggesting that release of these autoallergens from damaged tissues could trigger responses mediated by IgE or T cells. This concept is supported by the observation that IgE autoallergen titers decrease with successful treatment of AD with cyclosporine,\(^{(35)}\) suggesting that although IgE immune responses are initiated by environmental allergens, allergic inflammation can be maintained by human endogenous antigens, particularly in severe AD.

**Microbes**

The skin of patients with AD exhibits a striking susceptibility to colonization and infection with microbes such as *Staphylococcus aureus*, *Pityrosporum ovale*, or *Candida albicans*. Increased numbers of *S. aureus* are found in over 90% of AD skin lesions,\(^{(36)}\) and antibiotic therapy can be a useful adjunct in the management of poorly controlled AD.\(^{(37)}\) Scratching probably enhances *S. aureus* binding by disturbing the skin barrier and exposing extracellular matrix adhesions for *S. aureus*, such as fibronectin and collagens. In studies of *S. aureus* binding to skin lesions undergoing TH1 versus TH2 inflammatory responses, bacterial binding was significantly greater at skin sites with TH2-mediated inflammation because of expression of fibronectin induced by IL-4.\(^{(38,39)}\)

One strategy by which *S. aureus* exacerbates or maintains skin inflammation in AD is by secreting a group of toxins known to act as superantigens, which stimulate marked activation of T cells and macrophages.\(^{(40,41)}\) An analysis of the peripheral blood skin-homing CLA+ T cells from AD patients colonized with superantigen-producing *S. aureus* and T cells in their skin lesions, it was found that had undergone a T-cell receptor V (expansion consistent with superantigenic stimulation,\(^{(42,43)}\) AD skin is also deficient in the production of keratinocyte derived antimicrobial peptides (α-defensins and cathelicids) needed for host defense against bacteria, fungi, and viruses.\(^{(44,45)}\) Thus, once *S. aureus* binds to AD skin, inadequate local host defense allows the microbe to colonize and predispose patients to infection. Interestingly, TH2 cytokines inhibit the expression of human α-defensin 2,\(^{(45)}\) and human α-defensin 3,\(^{(46)}\) thus providing a reason why antimicrobial peptide expression is low in AD skin.

**New Treatment**

**Topical Calcineurin Inhibitors**

Tacrolimus: Topical applied FK-506 (tacrolimus), a calcineurin inhibitor that acts by binding with high affinity to the 12-kd macrophilin, has been successfully used in the treatment of AD.\(^{(47)}\) Tacrolimus inhibits the activation of several key cells involved in AD, including T cells, dendritic cells, mast cells, and keratinocytes.\(^{(42,43)}\) Multicenter, blinded, vehicle-controlled phase three trials with tacrolimus ointment (0.03% and 0.1%), in both adults and children with AD have shown tacrolimus to be both effective and safe.\(^{(48)}\) In more recent reports the efficacy and safety of tacrolimus treatment has been proven for head/neck AD\(^{(49)}\) and atopic eyelid disease.\(^{(50)}\) Local burning sensation has been the only common adverse event, but this usually resolves within 3-5 days of initiation of therapy with clearing of the skin disease. Long-term studies with tacrolimus ointment applied on up to 100% body surface area have been performed in adults and children with demonstrated sustained efficacy and no significant side effects; for example, no increased skin infections have been observed. Tacrolimus ointment does not cause cutaneous atrophy and is as effic-
Pimecrolimus: Ascomycin compounds, such as pimecrolimus, which has the same mechanism of action as tacrolimus, have been developed in topical and oral forms. Like tacrolimus, they also inhibit Th1 and Th2 cytokine production, and they have been shown to inhibit mediator release from mast cells and basophils.\(^\text{53}\) Multicenter, blinded, vehicle-controlled phase three trials with pimecrolimus ointment (1%), in both adults and children with AD have shown pimecrolimus to be both effective and safe for both adults and children with AD.\(^\text{54}\) Recently the safety and efficacy of 1% pimecrolimus has also been demonstrated in infants.\(^\text{55}\) When used as maintenance therapy, topical 1% pimecrolimus cream reduces the number of flares related to AD and reduces requirements for corticosteroid therapy.\(^\text{56}\)

**Other Potential Treatments**

Leucocytes from patients with AD have increased cAMP-PDE enzyme activity. Monocytes from AD patients produce elevated levels of PGE2 and IL-10, which both inhibit production of INF-\(\gamma\) by T cells. Topical application of high-potency PDE inhibitors has demonstrated clinical benefit in AD.\(^\text{57}\) High-dose intravenous immunoglobulin reduces skin inflammation in patients with refractory AD, however these effects are usually short-lived.\(^\text{58}\) Results of several studies have also demonstrated that patients with AD benefit from treatment with traditional Chinese herbal therapy.\(^\text{59}\) The possibility of hepatic toxic effects, cardiac side-effects, or idiosyncratic reactions remains a concern. The specific ingredients of the herbs also remain to be elucidated and some preparations have been found to be contaminated with corticosteroids.\(^\text{60}\) The putative benefit of probiotics has been discussed as a complementary treatment and the total scoring of AD (SCORAD) index has been found to be decreased in the group of extrinsic AD patients.\(^\text{61}\)

**Future Directions**

AD is often the first presentation of an individual destined to a lifetime of allergy and asthma. Since the skin is a highly sensitizing organ that contributes greatly to the systemic allergic response, effective treatments need to be developed to reduce skin inflammation in this disease. Advances are likely to need better characterization of the various clinical phenotypes of AD, including identification of the genes leading to AD, a better understanding of the immunoregulatory abnormalities underlying AD, and new paradigms for preventing relapses of this skin disorder. Such advances will probably be tied to the development of pharmacogenetics and targeting of effective treatments to the various phenotypes of AD.

**REFERENCES**


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異位性皮膚炎新發展

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異位性皮膚炎是一種慢性發炎的復發性皮膚疾病，在世界上約有百分之十到二十的孩童受到影响。在最近一年中我們對異位性皮膚炎病理機轉中的免疫機制及誘發因子有更進一步的了解，而新的抗發炎藥物也提供我們新的選擇，並讓我們重新思考對異位性皮膚炎的治療及處理。(長庚醫誌2005;28:1-8)

關鍵字：異位性皮膚炎。