

Allergy and the skin

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Accepted for publication April 23 2008

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Conflicts of interest: The authors have declared
that they have no conflict of interest.

IgE-mediated skin disorders

Allergic skin pathology include disorders which are immunoglobulin E (IgE)-mediated, such as urticaria/angioedema, cell-mediated, such as contact dermatitis, or mediated by both these mechanisms, such as atopic dermatitis. While contact dermatitis is typically local, consisting in a skin inflammation in the site where contact with the hapten takes place, urticaria/angioedema (UA) and atopic dermatitis (AD) are systemic in their expression, as contact with the specific allergen in the gastrointestinal tract (as occurs for foods in both UA and AD) or the respiratory tract (as occurs for house dust mites in AD) is able to elicit an allergic reaction in the skin.

Urticaria/angioedema

The typical skin lesion of urticaria is the wheal, featured by a central swelling surrounded by erythema, associated with itching and generally receding after a few hours [1]. In

Summary

Allergic skin disorders include urticaria, angioedema, contact dermatitis and atopic dermatitis, but the model fitting most closely the systemic concept of allergy is atopic dermatitis (AD), the pathogenesis of which is linked to a complex interaction between skin barrier dysfunction and environmental factors such as allergens and microbes. In particular, an important advance was the demonstration that the mutation of the skin barrier protein filaggrin is related strictly to allergen sensitization and to the development of asthma in subjects with AD. The altered skin barrier function, caused by several factors, results in the passage of allergens through the skin and to systemic responses. A pivotal role in such a response is exerted by Langerhans cells which, via their immunoglobulin E (IgE) receptor, capture the allergens and present them to T cells. When T helper type 2 (Th2) cells are activated, the production of a proinflammatory cytokines and chemokines pattern sustains the persistence of inflammation. Known AD-related cytokines are interleukin (IL)-5, IL-13 and tumour necrosis factor (TNF)- α , with emerging importance for IL-17, which seems to drive airway inflammation following cutaneous exposure to antigens, and IL-31, which is expressed primarily in skin-homing Th2 cells. Skin-homing is another crucial event in AD, mediated by the cutaneous lymphocyte-associated antigens (CLA) receptor, which characterizes T cell subpopulations with different roles in AD and asthma.

Keywords: atopic dermatitis, filaggrin, IgE-mediated skin disorders, urticaria

angioedema the swelling is more pronounced, involves dermis and subcutis, is associated with pain more than itching, and has a slower resolution, requiring up to 72 h [1]. UA may be induced by a large number of causes, including physicochemical stimuli, infections, autoimmunity, vasculitis and others [2], and may have an acute (duration < 6 weeks) or chronic (> 6 weeks) presentation [1]. Allergy is a relatively frequent cause of acute UA, but accounts only for 5–10% of chronic UA [3]. The exposure to the specific allergen causes the release of mast cell mediators, with a prominent role for histamine [4]. In the case of local contact, as occurs for example with latex, urticaria may present at the site of contact (local urticaria), but most commonly the presentation is as generalized urticaria, which is elicited by the ingestion of the culprit food. It is of interest that in the oral allergy syndrome contact between the food and the oral mucosa is able to trigger only local symptoms, but if the food is ingested despite the local disturbance systemic symptoms are commonly observed, with the highest frequency for urticaria [5]. Recent data also suggest reconsideration of the role

of IgE antibodies in types of urticaria classified generally as non-allergic: this is true for cold-induced urticaria, which was already suspected as an IgE-mediated form because it could be reproduced by passive transport [6], and it has now been shown that anti-IgE treatment is able to prevent the clinical manifestations caused by exposure to cold [7]. Urticaria diagnosed as idiopathic may also be caused by IgE: three patients have been described recently with chronic urticaria resistant to any drug treatment who had total clearance following treatment with the anti-IgE omalizumab [8]. Similarly, three cases of refractory idiopathic angioedema were resolved by the same treatment [9], and this should lead to a reappraisal of the frequency of IgE-mediated urticaria/angioedema.

Atopic dermatitis

The skin disorder best fitting the concept of systemic disease is atopic dermatitis (AD). Current knowledge of the pathophysiology of AD attributes a major role to skin barrier dysfunction and to hyperreactivity, as well as exposure to immunological stimuli such as allergens and microbes [10]. This interaction, in which dendritic cells seem to play a pivotal role [11], leads to a T cell response in the skin initially of T helper type 2 (Th2) but later of Th1, and to a systemic Th2 response inducing the isotype switching to IgE synthesis and the involvement of eosinophils [12,13]. When Th2 cells are activated, the production of a proinflammatory cytokines and chemokines pattern sustains the persistence of inflammation. Known AD-related cytokines are interleukin (IL)-5, IL-13 and tumour necrosis factor (TNF)- α , with emerging importance for IL-17, which seems to drive airway inflammation following cutaneous exposure to antigens [14], and IL-31, which is expressed primarily in skin-homing Th2 cells [15]. Skin-homing is another crucial event in AD, mediated by the cutaneous lymphocyte-associated antigens (CLA) receptor, which characterizes T cell subpopulations with different roles in AD and asthma.

The importance of the systemic response is made evident by the natural history of the atopic disease, characterized by early presentation with AD and subsequent respiratory manifestations with asthma and rhinitis, summarized by the term 'atopic march' [16].

Concerning the role of skin barrier dysfunction, many recent data have focused interest upon filaggrin, which consists of filament-associated proteins which are bound to keratin fibres in epidermal cells. It has been found that loss-of-function null mutations of the filaggrin gene predispose to AD [17] and that the filaggrin gene is related to sensitization to allergens, to more severe phenotypes of eczema and to eczema-associated asthma [18]. Filaggrin is not present in the bronchial mucosa [19] but its null mutations – which are not observed if eczema is absent – were found to be associated with asthma severity [20]. On the other hand, it was reported that in patients with AD without filaggrin

mutations the cytokines IL-4 and IL-13 (typical of the Th2 profile) are able to inhibit filaggrin expression [21], thus indicating that, if filaggrin deficiency favours atopic manifestations, an atopic pattern of response may also alter the filaggrin-mediated skin barrier. Such data suggest a pivotal role of filaggrin in favouring allergen absorption through the skin with subsequent systemic sensitization and development of respiratory symptoms. In this view, experimental studies have demonstrated that epicutaneous sensitization to protein antigens was associated with the development of airway hyperresponsiveness following inhalation of the same antigens [22]. With regard to skin exposure to dust mite allergens, their application by the atopy patch test (APT) induces a T cell response adherent to the aforementioned model with an early Th2 but a late Th1 dominance in the inflamed skin. It is of interest that the APT is able to detect sensitization to mites in patients with AD in remission but with respiratory symptoms such as asthma or rhinitis: a European multicentre study reported that a substantial number of patients with AD in clinical remission had an exclusive positivity to APT. This has received current confirmation from a study in which patients with rhinosinusitis and asthma were divided according to current or past AD and compared regarding the results of APT and SPT to mite extract, using patients with rhinosinusitis and asthma without either current or past AD as a control group [23]. A positive APT was observed in 78% of subjects, with no significant difference between current or past AD, but in 12% of the control subjects. This suggests that a positive APT is a marker of sensitization through the skin in subjects with a positive history for AD.

There are also serological markers of disease activity of AD: in one study Kakinumi *et al.* found that the levels of macrophage-derived chemokine CCL22 were related closely to the activity of AD as assessed by the generally used scoring index SCORing AD (SCORAD) [24], and in another study a notable correlation between AD activity and the serum levels of eotaxin-3/CCL26 was reported [25], both chemokines suggested as being involved in the pathogenesis of AD.

With regard to microbial infections in AD, it is evident that a defective defence against microbes induces an altered immunological response. The infectious agent most involved in AD is *Staphylococcus aureus*, which colonizes about 90% of AD patients but only 5–30% of non-atopic subjects [26]. By superantigens IgE, *S. aureus* in the skin is able to activate responses correlated with disease severity [27] and to induce glucocorticoid resistance, and an effective antibiotic treatment improves AD severity [28]. Also viruses, including vaccinia, molluscum contagiosum and herpes simplex, cause infections – the best-known being eczema herpeticum, which is related to high total IgE levels – and worsening of AD [29]. Recent data indicate that AD patients with eczema herpeticum have a significantly lower production of antimicrobial peptides, particularly the cathelicidin family, from keratinocytes [30]. These cells are known to express Toll-like

receptors (TLRs), which are characterized by their specificity for microbial ligands [31] and play an important role in immunological processes triggered by microbes. For instance, a mutation in the TLR-2 gene R753Q was correlated with a more severe AD, higher IgE levels and greater susceptibility to *S. aureus* colonization [32].

In conclusion, AD has a complex pathophysiology which recognizes as *primum movens* a dysfunction in skin barrier related to a defective filaggrin expression; this favours the passage of microbes and allergens through the skin which drive an immune response implicating a number of actors and resulting in systemic manifestations. Increasing understanding of the fine mechanisms regulating this process is likely to achieve significant advances in the diagnosis and management of AD.

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