The pathogenesis of atopic eczema

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Atopic eczema is associated with a genetic predisposition to dysregulation of the immune system. T lymphocytes differentiate towards the Th2 type with promotion of immunoglobulin E antibodies. Allergic responses to environmental allergens develop and microbes, including staphylococci and pityrosporum yeasts, may contribute to the inflammatory process.

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The atopic state is a genetically determined disorder involving dysregulation of the immune system. The immune response to common environmental antigens is characterized by the generation of antibodies of the immunoglobulin (Ig) E class rather than the IgG class. This is accompanied by immediate-type clinical allergies and with the clinical syndromes of atopic eczema, asthma, and rhinitis.

AETIOLOGY

The fundamental cause and mechanisms giving rise to atopic eczema are not understood. There is clearly an interaction of genetic factors conferring susceptibility, environmental factors, which may include environmental allergens and various microbes, as well as 'constitutional' factors, including psychological state and sex hormone effects.

GENETIC MECHANISMS

The atopic state appears to be inherited in an autosomal dominant fashion. So far, despite much searching, no definitely causal genetic association has been identified. A number of genetic loci have been found to link either to the atopic state or to production of high levels of IgE – for example 11q13. Candidate regions on chromosomes 5q31 (interleukin (IL)-4 gene cluster), 11q13 (high-affinity IgE receptor FCεR1) (Cookson et al, 1992; Soderhall et al, 2001), 14q11.2 (mast cell chymase) (Mao et al, 1996), and 16p12 (IL-4 receptor alpha-chain, IL4RA gene) (Oiso et al, 2000) have all been claimed to show linkage to atopic eczema in some studies, but not in others. There are particular influences of the presence of atopy on the maternal side that augment the expression of atopy in the offspring.

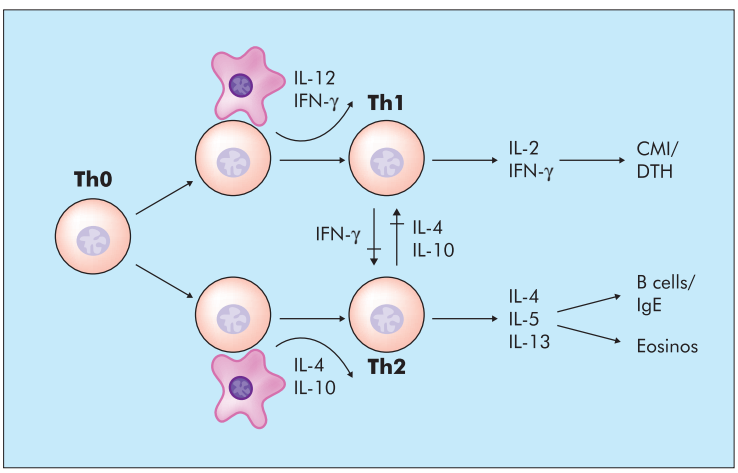
IMMUNE DYSREGULATION

The defining characteristic of the atopic immune system is the capacity to generate IgE antibodies in response to allergens. The regulatory mechanisms that underlie this appear to involve the interaction between dendritic antigen-presenting cells (DCs) and CD4+ helper T lymphocytes (*Figure 1*).

The outcome of the interaction is that naive precursor Th_0 cells are induced to differentiate into Th_2 cells, characterized by the production of IL-4, IL-5 and IL-13. Th_2 cells 'help' or control the type of Ig that B lymphocytes make, inducing synthesis of IgE.

Much work has gone into examining the mechanisms by which DCs regulate the differentiation of Th cells. The critical stimulus 'signal 1' is given during the presentation of antigenic peptide held in the groove of major histocompatibility complex (MHC) class II molecules. Secondary signals come via interactions of 'co-stimulatory' surface molecules such as CD80

Figure 1. Differentiation of T helper (Th) lymphocytes. Precursor Th_0 cells interact with dendritic antigen-presenting cells during recognition of antigenic peptides. Depending on which cytokines are present the differentiation of the Th cell may be driven towards a Th_1 type (by interleukin (IL)-12 and interferon-γ; IFN-γ) or Th_2 type by the presence of IL-4 and possibly IL-10. Th_1 cells produce IL-2 and IFN-γ and are effector cells of cell-mediated immunity (CMI). Th_2 cells produce IL-4, IL-5 and IL-13 and induce IgE production by B cells, activation of mast cells and eosinophils (Eosinos). DTH = delayed-type hypersensitivity.



and 86 on the DCs with their counter receptors CD28 and CTLA4 on the T cells. There is evidence that signalling through CD28 gives a positive activation signal, whereas signalling through CTLA4 may either give an inhibitory signal or activate T regulatory cells which have inhibitory (suppressor) activities. In addition, cytokines released from the DCs give 'signal 3' which is important in determining the final differentiation into Th_1 or Th_2 cells. IL-12 drives a Th_1 response while IL-4 drives a Th_2 response.

There is little direct evidence that DC function is altered in atopic individuals. However, it has been observed that monocytes from atopic donors produce greater quantities of prostaglandin E_2 (PGE_2) than cells from non-atopic individuals. PGE_2 can suppress production of interferon-gamma – a cytokine which is not only produced by Th_1 lymphocytes, but which also favours the differentiation of naive Th_0 cells towards the Th_1 phenotype. DCs have yet to be shown to behave similarly.

There is evidence that activation signalling in T cells may be different in atopic individuals. Thus, constitutional overactivity of cyclic AMP phosphodiesterase is associated with blunted or attenuated cAMP-mediated signalling. This has been shown to tie up with differentiation of atopic T cells towards a Th_2 phenotype (Hanifin and Chan, 1995). Also, the fetal immune system is normally weighted towards generating Th_2 responses. This is reflected by production of low basal levels of interferon-gamma. In the postnatal period the immune system appears to 'mature' and production of interferon-gamma increases. However, in infants destined to develop infantile atopic eczema, the basal production of interferon-gamma is particularly low (Warner et al, 1994).

The reasons why the atopic immune system responds with ready generation of Th_2 lymphocytes are not clear, but a hypothesis attracting much attention is the so-called hygiene hypothesis. This proposes that exposure in early life to microbes of various types, but especially those possessing lipopolysaccharide endotoxins, such as *Escherichia coli* and other enteropathogens, is critical in pushing immune responses towards a Th_1 type. The lipopolysaccharide activates production of IL-12 by DCs, which promotes production of interferon-gamma and hence can deviate T cell activation induced by any other antigen, present at the same time, towards a Th_1 response.

Apart from alterations in immune regulatory mechanisms, the allergens themselves seem to evoke different responses in atopic individuals. Thus, both atopic and non-atopic people make IgG antibodies against *Candida albicans*, whereas house dust mite antigen Der p1 evokes IgE antibodies in atopics but IgG antibodies in non-atopics. It has been suggested that this property is related to the natural function of many allergens as proteases.

THE ROLE OF ALLERGY

A variety of types of allergy can be demonstrated by formal challenges in atopic individuals. The clinical/causal relevance of such allergies can be difficult to assess with confidence. Skin challenges with allergens administered by 'prick test' elicit weal and flare responses, seen 10–15 minutes after the challenge. This so-called immediate hypersensitivity reflects the presence of specific IgE antibodies on the surface of mast cells. Antigen-mediated cross-linking of the IgE activates mast cells to degranulate, releasing histamine as the major mediator. Weal and flare reactions correspond very closely with the radioallergosorbent test which detects allergen-specific IgE in serum.

The immediate-type hypersensitivity reaction generally reflects clinical allergy in mucosal surfaces in the form of hay fever and asthma. Most patients with atopic eczema also exhibit immediate weal and flare response to prick-test challenges with atopic allergens, and these individuals also usually have mucosal allergies in the form of hay fever and/or asthma.

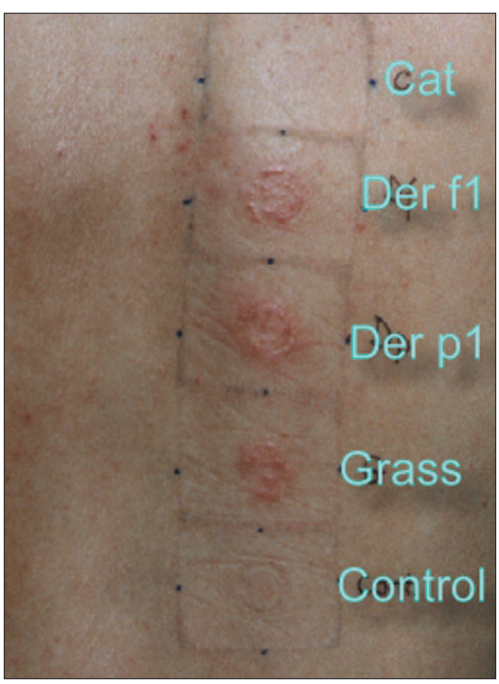
Intradermal challenge with allergens, usually in greater amounts than are administered by prick challenge, can evoke three types of allergic response (Munro et al, 1991). First is the weal and flare reaction as seen with prick tests. In many atopic subjects, a second reaction – the so-called late-phase response – develops from 6 hours onwards reaching a peak between 8 and 12 hours. This reaction has been thought to reflect generation of cysteinyl leukotrienes by eosinophil leucocytes. It is regarded as reflecting allergic processes in asthma, but it is unclear whether it has any involvement in atopic eczema. Over 24–48 hours, the third type of allergic response – the delayed-type reaction – develops. This is seen mainly in atopic individuals who have eczema. When allergens are administered by topical patch test challenge to skin on which the stratum corneum barrier has been partially disrupted by tape stripping, the same pattern of allergic responses can be seen (*Figure 2*) (Langeveld Wildschut et al, 1996; Ring et al, 1997). The delayed-type reaction reproduces the clinical and histological appearances of atopic eczema and this only occurs in atopic individuals with eczema.

When allergen patch test challenges are biopsied at different times to follow the inflammatory changes, there is rapid infiltration by eosinophils and lymphocytes. The eosinophils reach a peak by 6 hours and persist in large numbers until at least 48 hours. The lymphocytes that infiltrate in the first 24 hours are thought to be of the Th_2 phenotype because Th_2 cytokines – IL-4 and IL-5 – can be detected by immunocytochemistry and reverse transcriptase polymerase chain reaction. Over the next 24–48 hours, Th_1 lymphocytes are thought to arrive (Thepen et al, 1996).

Interestingly, in patients treated with cyclosporin to the point that the eczema is in clinical remission, the responses to patch test and intradermal challenge with allergens remain unchanged in magnitude (Munro et al, 1988). Hence, it can be argued that the initial allergic response to allergens is not the same as the eczematous process. It may be that the 'allergic response' involves activation of Th_2 cells, whereas the generation of the complete picture of eczema requires additional involvement of Th_1 cells. Suppression of Th_1 cell activation by cyclosporin seems to be sufficient to prevent the generation of eczema.

It has been observed that in people with atopic eczema, the epidermal Langerhans' cells which

Figure 2. Patch test responses to different allergens applied 48 hours previously in a patient with atopic dermatitis. Skin was stripped 10 times with adhesive tape before application of allergens on standard patch tests. Der f1 = Dermatophagoides farinae*; Der p1 =* Dermatophagoides pteronyssinus.



'present' antigens to T lymphocytes have IgE on their surface (Bruijnzeel Koomen et al, 1986). The IgE is bound mainly to the high-affinity receptor for IgE, FcεR1. Some IgE is also bound by the low-affinity receptor (CD23). The IgE is specific for a variety of allergens and has been shown to enhance the antigen-presenting function of Langerhans' cells. Thus Langerhans' cells bearing surface IgE can activate specific CD4+ T cells with 1000-fold less antigen than when the IgE is removed from the surface (Mudde et al, 1990). It is proposed that this 'antigen-focusing' plays an important role in the generation of allergen-induced skin reactions. Indeed, one group suggested that allergen-induced patch test reactions could only be elicited if the Langerhans' cells carried IgE specific for the allergen in question.

In order to answer the question of what is the causal relevance of allergy, it is necessary to examine the effects on the eczema of avoidance of contact with allergens. In a double-blind, placebo-controlled study, patients with atopic eczema received treatments to eliminate contact with house dust allergens. Full encasement of the bedding (mattress, pillows, and top covers), accompanied by a high powered vacuum cleaner and treatment of carpets with a spray with acaricidal and allergen-denaturing properties, did result in great reductions in the amounts of dust mite allergen (Der p1) in the patients' environment (Tan et al, 1996). This was accompanied by highly significant clinical improvements in the eczema. Most patients showed some benefit but the biggest improvements were seen in patients with the most severe atopic eczema. This demonstrates that allergy to environmental allergens, such as house dust mites, is of clinical or causal importance in many patients. But it is also clearly not the whole story.

THE ROLE OF SKIN MICROBES

There is evidence that skin surface microbes can play an active role in the generation of eczema in a number of ways. First, continuing with the allergy theme, there is evidence that a proportion of patients with atopic eczema actually become allergic to the ubiquitous yeast fungus *Pityrosporum orbiculare* (*Malassezia furfur*). Everyone is colonized by this organism and makes an immune response comprising IgM and IgG antibodies as well as sensitized T lymphocytes.

However, clinical allergy, reflected by positive epicutaneous patch tests is not found in non-atopic individuals but is found in a subgroup of patients with atopic eczema (Tengvall et al, 2000). The causal relevance of this allergy is

indicated by the clinical improvements that can follow from treatment with antipityrosporum treatments such as azole antifungals.

Staphylococcus aureus can play a role in exacerbating atopic eczema in at least two ways. First, and very commonly, staphylococci infect the skin, aggravating itch symptoms and inducing more scratching. There is clearly a subgroup of patients who show clinical features of active infection with crusting, exudation, pustule formation and fissuring, who improve greatly with full courses of systemic antibiotics. A second mechanism by which staphylococci can exacerbate atopic eczema is through the production of toxins which act as superantigens (Leung and Soter, 2001). Superantigens are able to bind to the surface of CD4+ T cells without needing to be 'recognized' by specific T cell receptors. Instead, superantigens bind to all T cells that express particular β chain variable regions (Vβ) in their T cell receptors – so a polyclonal activation of T cells takes place independent of their antigen specificity (*Figure 3*).

Exotoxins are detectable in two-thirds of all cultures containing *S. aureus*, which have been generated from skin swabs in atopic eczema. Improvement of eczema following eradication of *S. aureus* that may be producing superantigens, with appropriate antibiotic therapy, shows the clinical relevance of this mechanism.

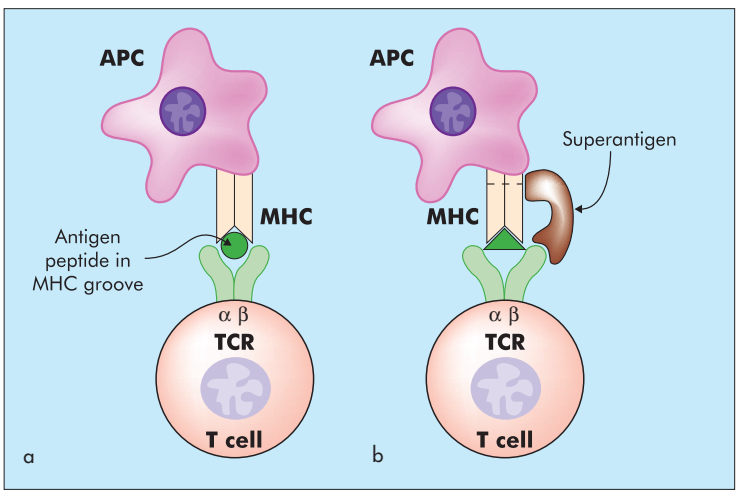


Figure 3. Activation of T cell by staphylococcal superantigen. a. Normal presentation of antigenic peptide lying in the MHC-II groove on antigen presenting cell (APC). The T cell receptor (TCR) engages with the peptide and MHC-II molecules. b. Superantigen engaging with TCR Vβ chain and the MHC-II of APC without the involvement of the TCR in recognizing an antigenic peptide.

KEY POINTS

- Atopy is associated with immune dysregulation.
- Th2 lymphocytes determine production of immunoglobulin E, activation of mast cells and eosinophils.
- Atopy patch test responses are a lymphocyte mediated, delayed response observed only in atopic eczema.
- Allergic responses to environmental allergens is a major causal factor in many patients with atopic eczema.
- Skin microbes can be important pathogenetic factors in atopic eczema.

CONCLUSION

The atopic state appears to be a genetically determined alteration of immune controls so that certain protein antigens activate immune responses characterized by generation of Th_2 lymphocytes and IgE antibodies. The interaction of the antigens with the skin results in allergic inflammatory reactions. However, there are still many questions to be answered in order to explain all the phenomena and natural history of this disease. **HM**

Conflict of interest: none.

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