

Atopic dermatitis

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The cutaneous inflammatory disease remains perhaps the greatest therapeutic challenge in dermatology in terms of prevalence, symptomatic severity and recalcitrance. Atopic dermatitis (AD), nearly 90 years since its first comprehensive description, remains a confused composite of proposed pathomechanisms. This report will examine some of the current hypotheses relating to pathogenesis and possible therapeutic targeting.

In spite of the considerable confusion in this realm, some information has been advanced in recent years that enhances our understanding of AD. Schultz-Larsen (10) has utilized careful casefinding techniques in a twin study on the island of Fyn and has not only confirmed the heritability but realized an unexpected informational dividend. In assessing cumulative incidence during the three, five-year periods from 1960-1975, he showed convincing data indicating that AD had increased from 3% in the first period to 10% during the first half of the last decade (10). Thus we have a rising incidence of a disease that has enormous impact in terms of infectious, allergic and socio-occupational consequences.

We have also, in recent years, been made aware of the tissue site of the basic abnormality in AD and the atopic diathesis. This information developed from marrow transplant cases where atopy was transferred to a nonatopic recipient or where the eczema of the Wiskott-Aldrich syndrome was eliminated (9). This information has been of great importance because it has allowed us to focus our search for basic abnormalities upon bone marrow-derived cells. It provides strong evidence that the cutaneous and neural abnormalities of AD are secondary to the infiltration of immuno-inflamma-

tory cells descended from bone marrow precursors. Presumably cytokines and other factors released by these cells serve to effect the cutaneous abnormalities including erythema and severe pruritus as well as edema, both in the dermis and in the epidermis where the characteristic spongiosis of dermatitis occurs.

The mechanisms of these changes remain obscure and, as is always true with obscure etiologies, multiple hypotheses ebb and flow. These hypotheses are roughly categorized as being either immunologic or pharmacophysiologic. The latter relates to well-known clinical and laboratory features of AD including paradoxical white dermographism, acetylcholine-stimulated bronchial hyperreactivity and delayed cutaneous blanching, increased erythema response to histamine, abnormal sweat responses and others (4).

These clinical aberrancies led to *in vitro* observations of reduced leukocyte cyclic AMP responses to adenylate cyclase-active agonists (8). The cyclic AMP abnormalities, in turn, stimulated our discovery of elevated cyclic AMP-phosphodiesterase (PDE) in bone marrow derived cells (3), along with evidence that the abnormal PDE might account for the increased B cell IgE synthesis and high basophil histamine release seen in atopic disease (2). The series of studies also developed evidence that increased PDE activity is present in cord blood leukocytes from newborns with hereditary predisposition to atopy (5). In adults too, elevated PDE activity appears to be intrinsic in atopic leukocytes; it does not fluctuate with disease activity, is present during remissions and is also seen in allergic rhinitis (7). Thus, the abnormal PDE activity may reflect the primary biochemical pathomechanism in atopy and may provide a useful marker of disease.

FUNCTIONAL DISTINCTIONS
IN CD-4 SUBSETS

T _H 1	T _H 2
1. IL-2 production	1. IL-4 (BSF-1) production
a. T cell growth	a. T cell growth
b. Stimulates expression of IgG ₂ a isotype	b. Regulates IgE synthesis IgM → IgE, IgG ₁ switch
2. IFN - γ production	c. Induces Fcε Receptor
a. Inhibits IgG ₃ , G ₁ , G ₂ b and IgE	d. Enhances Mast cell growth Synergy with IL-3 ? Autocrine growth
b. Induces Ia on monocytes	e. Ia expression on B cells
c. Antagonizes IL-4	2. IL-3 production
3. IL-3 production	3. ? IL-5 production
4. GM-CSF production	4. GM-CSF production
5. ? anti-viral activity	5. ? anti-parastic activity

Fig. 1.

From the immunological viewpoint, the question arises as to whether the increased PDE and other pharmacologic abnormalities are secondary to immune system aberrancies. Numerous immunological defects have been associated with AD in recent years. These include abnormal cell mediated immune responses, defective chemotaxis and overproduction of IgE.

Elevated serum IgE is one of the most prominent features of AD, present in approximately 80 % of patients. However, the presence of typical AD in agammaglobulinemic patients with neither IgE nor allergenic skin test reactivity keeps open the question of whether IgE has an essential pathogenic role.

Nevertheless, studies of IgE have provided important basic information relating to AD. Firstly, *in vitro* IgE synthesis systems give clues as to abnormal immune control mechanisms in AD. Secondly, IgE studies relate to the resurgent interest in foods, mites and bacterial allergens reacting with specific cytophilic IgE antibodies on mast cells, basophils, and possibly other effector cells, to trigger flares of AD. Finally, the recent evidence for low affinity Fcε receptors on Langerhans cells and macrophages provides new insights of possible pathways to cutaneous inflammation (1).

The ability to manipulate conditions modu-

lating and stimulating IgE synthesis by B lymphocytes in culture has revealed a complex, multi-step process requiring several distinct signals (7), possibly including lymphokines such as IL-4. IL-4 produced by the putative T_H2, CD4⁺ T-lymphocyte subset is a particularly intriguing cytokine in the study of allergology because of its activity in enhancing IgE synthesis and induction of B cell Fcε receptors (Fig. 1). Newly presented evidence for IL-4 induction of Fcε receptors on macrophages might indicate a similar effect on Langerhans cells and suggests a common mechanism controlling afferent and efferent arms of IgE mediated pathogenic pathways. Whether or not AD requires IgE, these studies of basic cellular control are yielding important information that may advance pathogenic and therapeutic understanding of this common disease.

Recent studies have suggested an important role for eosinophils in AD. Leiferman and colleagues (6) have shown abundant dermal deposition of eosinophil major basic protein in biopsy sections from AD. These studies suggest that eosinophils, triggered during acute reactions (possibly even via low affinity Fcε receptors) can establish a more chronic "late phase reaction" consistent with the clinical course of AD. It is not yet clear whether this eosinophil major basic protein deposition is specific for AD or may be seen also in other inflammatory situations such as allergic contact dermatitis. Also, the late phase reaction model does not account for the spongiosis which is a histologic hallmark of AD. Considering the various hypothetical mechanisms, including that involving Langerhans cell-triggering advanced by Bruynzeel-Koomen (1), it seems possible that the reaction in AD is actually a composite, combining elements of Type I, late phase and delayed type hypersensitivity.

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