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Immunobiochemical Aspects of Atopic Dermatitis

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A long-term goal is to understand the pathomechanisms of atopic dermatitis. A major advance in the understanding of atopy was provided by observations from bone marrow transplantations which documented the transfer of the atopic diathesis by marrow cells (1). Conversely, the eczema of patients with Wiskott-Aldrich syndrome resolves after bone marrow transplantation (2). Thus, the immune and inflammatory cells that populate and infiltrate the skin in atopic dermatitis, or the nasal membranes in allergic rhinitis, or the bronchial mucosa in asthma, appear to be "vectors" that predispose the tissues to the hyperreactivity typical of the atopic diathesis.

A wide variety of factors have been reported to trigger flares of atopic dermatitis (3) (Table I). Of these, only stress and foods have been documented to cause flaring of dermatitis under controlled, experimental conditions (4, 5). Graham & Wolf reportd increasd skin temperature and decreased reactive hyperemia during experimental emotional stress interviews (4), a phenomenon frequently observed in the clinical setting. The mechanism for these reactions is not fully understood, but it seems likely that the initial event is the release of mediators from skin mast cells. Neuropeptides such as Substance P stimulate histamine release from skin mast cells and may link the central nervous system to cutaneous inflammatory cells (6, 7). Sampson has shown that double-blind food challenges cause itching and erythema accompanied by increased plasma histamine (5, 8) and later infiltration of eosinophils (9). Current concepts suggest that, following mast cell mediator release, infiltrates of basophils, eosinophils, neutrophils, and mononuclear leukocytes may interact to establish a continuing, subacute immune response (10). This may be a hybrid, with components of delayed hypersensitivity (11) and "late phase reactions" which could account for the chronic, indurated, inflammatory condition typical of AD.

In addition to evidence for abnormal inflammatory activity in atopic dermatitis, there are several lines of evidence indicating defects of chemotaxis and cellular immunity. However, our past studies of these abnormalities suggested they were secondary to the dermatitis and normalized rapidly during clinical remissions (12, 13). Abnormalities of IgE are perhaps the most consistent immunological defect in atopic dermatitis. Serum IgE levels are elevated in approximately 80% of patients and correlate roughly with disease severity (14). Cultured mononuclear leukocytes, from patients with elevated serum IgE, produce excessive quantities of IgE during seven to ten day incubations and IgE production appears to be influenced by T cell factors but, as with inflammatory events, the mechanisms of this dysfunction remain to be clarified (15).

In addition to the in vitro IgE overproduction, another very consistent functional leukocyte abnormality in atopic dermatitis is the hyperreleasability of histamine by blood basophils (16–18). We have been interested in the cellular regulatory defects that allow for hyper-IgE production by B lymphocytes as well as the pathomechanism that allows for excessive basophil histamine release. A number of clinical clues, as well as certain in vitro findings, suggest this may relate to abnormal cyclic nucleotide metabolism in atopic dermatitis (19). The blunted cAMP response to catecholamines was initially interpreted as a beta-adrenergic receptor defect but we found no such abnormality in atopic leukocytes (20) and, along with other laboratories, we showed that this cyclic AMP defect was evident whether cells were stimulated with beta-agonists, prostaglandin (PG) or histamine (21).

These findings led us to the demonstration that reduced cAMP levels in stimulated mononuclear leukocytes (MNL) resulted from excessive hydrolysis by cAMP-phosphodiesterase (PDE) rather than inadequate cAMP production (22). This increased PDE activity was present consistently in MNL from pa-

Table I. *Confirmed and putative activators of atopic dermatitis*

Irritants	Immune complexes
Stress	Mites
Foods	Molds
Staphylococci	Yeasts
Viruses	Human dander

tients with active and inactive atopic dermatitis and also from patients with no dermatitis but only allergic respiratory disease. Non-atopic patients with widespread allergic contact dermatitis had normal levels of PDE activity (22).

Functional ramifications of increased leukocyte PDE activity were studied in two systems. The increased basophil histamine-releasability associated with atopic dermatitis showed a striking correlation to increased PDE activity and the abnormal histamine release was consistently reduced to normal levels by in vitro exposure of cells to the PDE inhibitor, RO 20-1724 (17). Likewise, the elevated IgE synthesis by cultured MNL from atopic dermatitis patients correlated with high PDE activity; exposure of the cells to Ro20-1724 for 1 hour, prior to the 10 day cultures, caused a consistent reduction in IgE synthesis (23).

Thus, excessive PDE hydrolysis of cAMP may have a functional role in IgE hyper-production and in basophil/mast cell hyper-releasability of mediators in atopic dermatitis. We have also been interested in abnormalities of other cell systems. We have focused especially on the blood monocyte, which has a particularly high level of PDE activity in atopic dermatitis (24), and is of major interest to our development of specific anti-PDE antibodies. Interestingly, our chromatofocusing studies have shown evidence of distinct PDE enzymes in atopic lymphocytes and monocytes, raising the possibility that different post-translational changes may be acting in the two cell types, or perhaps, in each of the many cell lines originating from bone marrow (25). Understanding these changes may potentially lead to development of a new therapeutic approach for atopy.

It is obvious from our studies that abnormally high PDE activity is present in atopic disease, in cells that are central to immune function. The resulting, inadequate cAMP levels would be expected to cause a permissive, functional hyper-reactivity which is certainly typical of the atopic diathesis. In therapeutic terms, these studies provide a focus for pharmacologic intervention and indeed, studies have shown the effectiveness of a topically applied PDE inhibitor (unpublished placebo-controlled trial). Additionally, our in vitro studies have shown that chronic, oral theophylline administration is ineffective for atopic dermatitis because of tachyphylaxis (26) and, perhaps, because of inadequate delivery of oral drug to the skin, since intravenous theophylline is rapidly effective at relieving the pruritus of atopic dermatitis (27).

A very important question relating to our research is whether increased PDE activity reflects a basic biochemical genetic defect or whether underlying immunological events, possibly of allergic origin, cause elaboration of factors or differences in immune cellular differentiation which in turn generate a secondary rise in PDE activity. These questions are very basic but potentially have enormous medical and socio-occupational value, considering the substantial proportion of the population carrying the atopic diathesis.

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