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## Atopic dermatitis: a paradigmatic allergic skin disease

### Thomas Bieber

Department of Dermatology,  
Friedrich-Wilhelms-University,  
Sigmund-Freud-Straße 25, D-53105 Bonn,  
Germany

Tel: +49 228 287 4388

Fax: +49 228 287 4881

E-mail: thomas.bieber@meb.uni-bonn.de

## Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease clinically and histologically highly similar to allergic contact dermatitis. Recently, it has been proposed to subdivide AD into two distinct forms: the

extrinsic form (occurring in the context of sensitization toward environmental allergens), and the intrinsic form (occurring in the absence of any typical atopic background).<sup>1</sup> While the pathophysiology of the intrinsic form remains almost elusive, tremendous progress has been made in the understanding of the extrinsic form. Thus, since IgE plays a major role in other atopic diseases such as asthma and rhinitis, it is assumed that, in this extrinsic form, immunoglobulin E (IgE) also mediated the specificity of the inflammatory conditions in the skin.

## Presence of IgE-bearing dendritic cells in the skin of patients with AD

The emergence of extrinsic AD (i.e. a cell-mediated inflammation) in atopic patients (i.e. individuals prone to have increased IgE production and to develop IgE-mediated hypersensitivity reactions) remained puzzling until the mid-1980s, when the presence of IgE molecules on the surface of Langerhans cells (LC) from patients presenting AD was first reported.<sup>2,3</sup> A new pathophysiological concept was proposed in which LC and inflammatory dendritic epidermal cells (IDEC)<sup>4</sup> armed with allergen-specific IgE would trigger an eczematous inflammation.

## Molecular structure, regulation and function of FcεRI on human dendritic cells

The identity of the relevant IgE-binding structure of cutaneous dendritic cells (DC) was unclear for some years, until other workers and myself demonstrated the presence of the high-affinity receptor for IgE (FcεRI) on these cells as well as on other antigen presenting cells (APC), including monocytes, and circulating DC.<sup>5-7</sup> It also became clear that FcεRI on APC lacks the classical β-chain and thus, in contrast to effector cells of anaphylaxis (i.e. mast cells and basophils that express an α,β,γ2 conformation), APC display an α,γ2 conformation that implies profound functional consequences. Moreover, its expression and the function may be highly variable, depending on the microenvironment.<sup>8</sup> However, the highest expression is specifically observed in AD skin.<sup>9</sup> One may speculate that FcεRI ligation on APC putatively triggers the synthesis and release of mediators that may initiate a local inflammatory reaction, as has been demonstrated for mast cells.

FcεRI/IgE-mediated allergen uptake and subsequent antigen presentation has been attributed a key event in the pathogenesis of atopic dermatitis.<sup>10</sup> Using this kind of antigen uptake, APC may, in the presence of antigen-specific IgE, increase their presenting capacity up to 100-fold.<sup>11</sup> This mechanism, also known as 'antigen focusing' or 'facilitated antigen presentation', has been shown effective by different research groups in different cell systems. The observation that the

presence of FcεRI-expressing LC/IDEC, bearing IgE molecules, is a prerequisite to provoking eczematous lesions, observed after application of aeroallergens to the skin of atopic patients, strongly supports this concept. Thereby, IgE receptors are the connecting link between the specificity gaining IgE molecules and the APC. However, FcεRI seems to play the major role in these phenomena. It should be noted that FcεRI expressed on circulating monocytes may have other functions, mainly in regulating their survival and differentiation outcome.<sup>12</sup>

Following the presentation of allergens to T cells, allergen-specific B cells may be activated to produce high amounts of allergen-specific IgE. This IgE may then in turn bind to the FcεRI on the APC, closing a vicious circle of facilitated antigen presentation. The intermittent or continuous supply of aeroallergens or autoantigens to the process of facilitated antigen presentation may define the pathophysiological basis of the recurrent or self-perpetuating course of AD frequently seen in untreated patients. The successful application of aeroallergens such as cat dander in the recently standardized atopy patch test<sup>13</sup> shows that it is possible to elicit eczematous skin lesions by solely external application of aeroallergens to the skin. Based on the facilitated antigen presentation model of AD, the need for an identification of the individual provocation factors in each patient calls for diagnostic procedures based on the allergen-specific IgE. Cat dander, house dust mite allergens and a variety of food allergens may be successfully avoided following a thoroughly undertaken prick test and *in vitro* IgE diagnostic evaluation.

## Conclusion

Consequently, AD may represent a paradigm of IgE/FcεRI-mediated, delayed-type hypersensitivity reaction. A similar role could be attributed to other FcεRI-expressing DC in the lung, where such cells may also be considered as putative targets for new therapeutic strategies.

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## Why is the prevalence of allergic diseases increasing? A critical assessment of some classical risk factors

Denis Charpin<sup>CA</sup> and Marion Gouitaa  
Department of Chest Diseases & Allergy,  
Hospital North, Marseille, France

<sup>CA</sup> Corresponding author

Tel: +33 4 91 96 86 31

Fax: +33 4 91 09 09 94

E-mail: dcharpin@ap-hm.fr

## Introduction

Many epidemiological surveys, among which repeated cross-sectional surveys have most validity, have demonstrated a twofold increase in the prevalence of allergic and asthma during the past two decades.<sup>1,2</sup>

The next presentations will deal with newly-identified or suspected risk factors such as repeated childhood infections, the role of the gut flora and the potential protective effect of contact with farm animals.

In this paper, we review some risk factors whose responsibility is often given for granted but which do not actually appear to play a major role in the increase of allergic diseases, namely allergen exposure, air pollution and passive smoking.

## Allergen exposure

Among allergens, house-dust mites have been advocated to be responsible for the increasing trend in the prevalence of allergic diseases.<sup>3</sup> We will present the pros and cons of this hypothesis.

- Because of the worldwide energy crisis in the 1970s, there has been a large decrease in the ventilation rate of private houses in Western countries, which could have led to multiplication of house-dust mites. Actually, there is a single study supporting this latter statement.<sup>4</sup> Another hypoth-