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). 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. A new pathophysiological concept was proposed in which LC and inflammatory dendritic epidermal cells (IDEC) armed with allergen-specific IgE would trigger an eczematous inflammatory reaction.

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 high-affinity receptor for IgE (FcεRI) on human dendritic cells in vivo and in vitro. FcεRI on epidermal Langerhans cells (LC) presents an atopic predisposition for IgE-mediated reactions, such as allergen contact dermatitis and atopic dermatitis. The binding of IgE to FcεRI on LC upregulates the expression of inflammatory mediators, such as inducible nitric oxide synthase (iNOS), and enhances the ability of LC to present allergens to T cells. This leads to the activation of allergen-specific T cells and the induction of a Th2 cytokine profile, which is characteristic of atopic dermatitis. The binding of IgE to FcεRI also enhances the presentation of allergens to T cells, which results in the induction of a Th2 cytokine profile and the activation of allergen-specific T cells. The activation of allergen-specific T cells leads to the release of cytokines, such as interleukin-4 (IL-4) and IL-13, which further enhance the Th2 response and promote the development of atopic dermatitis.

Atopic dermatitis: a paradigmatic allergic skin disease

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

Tel: +49 228 228 4388
Fax: +49 228 228 4881
E-mail: thomas.bieber@med.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
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.1,2

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-mediated, delayed-type hypersensitivity reaction. A similar role could be attributed to other 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.1,2

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 test13 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.

References
1. Wüthrich B. Neurodermitis atopica. Wien Med Wochenschr 1989; 139: 156–165.
2. Brujinzeel-Koomen C, van Wichten DE, Toonstra J, et al. The presence of IgE molecules on epidermal Langerhans cells in patients with atopic dermatitis. Arch Dermatol Res 1986; 278: 199–205.
3. Bieber T, Dannenberg B, Prinz JC, Rieber EP, Stolz W, Ring J, Braun-Falco O. Occurrence of IgE bearing Langerhans cells in atopic eczema: a study of the time course and with regard to the IgE serum level. J Invest Dermatol 1989; 92: 215–219.
4. Wollenberg A, Kraft S, Hanau D, Bieber T. Immunomorphological and ultrastructural characterization of Langerhans cells and a novel, inflammatory dendritic epidermal cell (IDEC) population in lesional skin of atopic eczema. J Invest Dermatol 1996; 106: 446–453.
5. Bieber T, de la Salle H, Wollenberg A, et al. Human epidermal Langerhans cells express the high affinity receptor for immunoglobulin E (Fc epsilon RI). J Exp Med 1992; 175: 1285–1290.
6. Wang B, Rieger A, Kilgus O, et al. Epidermal Langerhans cells from normal human skin bind monomeric IgE via FcεRI. J Exp Med 1992: 175: 1353–1365.
7. Maurer D, Fiebig E, Reininger B, et al. Expression of functional high affinity immunoglobulin E receptors (Fc epsilon RI) on monocytes of atopic individuals. J Exp Med 1994; 179: 745–750.
8. Jürgens M, Wollenberg A, de la Salle H, Hanau D, Bieber T. Activation of human dendritic Langerhans cells by engagement of the high affinity receptor for IgE FcεRI. J Immunol 1995; 155: 5184–5189.
9. Wollenberg A, Wen S, Bieber T. Langerhans cell phenotyping: a new tool for differential diagnosis of inflammatory skin diseases. Lancet 1995; 346: 1620–1627.
10. Bieber T. FcεRI-expressing antigen-presenting cells: new players in the atopic game. Immunol Today 1997; 18: 311–313.
11. Maurer D, Ebner C, Reininger R, Fiebig E, Kraft D, Kinet JP, Stingl G. The high affinity IgE receptor (FcεRI) mediates IgE-dependent allergen presentation. J Immunol 1995; 154: 6285–6290.
12. Katoh N, Kraft S, Wessendorf JH, Bieber T. The high-affinity IgE receptor (Fc epsilon RI) blocks apoptosis in normal human monocytes. J Clin Invest 2000; 105: 183–190.
13. Darsow U, Viehol D, Ring J. Atopy patch test with different vehicles and allergen concentrations: an approach to standardization. J Allergy Clin Immunol 1995; 95: 677–684.

Why is the prevalence of allergic diseases increasing? A critical assessment of some classical risk factors
Denis CharpinCA and Marion Gouita CA
Department of Chest Diseases & Allergy, Hospital North, Marseille, France
CA Corresponding author
Tel: +33 4 91 96 86 31
Fax: +33 4 91 09 09 94
Email: 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.1,2 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.3 We will present the pros and cons of this hypothesis.4 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.4 Another hypoth-