

Atopic dermatitis: pathogenetic mechanisms

A. Wollenberg, S. Kraft,* T. Oppel and T. Bieber*

Department of Dermatology, Ludwig-Maximilians-University of Munich, and *Department of Dermatology, Friedrich-Wilhelms-University of Bonn, Germany

Summary

Atopic dermatitis (AD) is a chronic inflammatory skin disease with increasing incidence and socio-economical relevance. The diagnosis is made on clinical grounds and different diagnostic criteria sets have been established. The majority of all AD cases is associated with a sensitization to environmental allergens and increased serum IgE (so-called extrinsic AD), but about 10–30% of all cases suffer from the so-called intrinsic AD, which obviously lacks any link to the classical atopic diathesis. The genetic background of AD has been investigated by target gene approach by different groups with mostly contradictory results for each of the genes under study. An imbalance in the spectrum of Th1/Th2 responses, a disturbed prostaglandin metabolism, intrinsic defects in keratinocyte function, delayed eosinophil apoptosis, IgE-mediated facilitated antigen presentation by epidermal dendritic cells, a two phase model of the inflammatory response and staphylococcal superantigen effects are among the currently studied pathogenetical aspects of extrinsic AD, which are reviewed in this paper.

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease that has shown as increasing incidence over the past 20–30 years. Thus, AD has become an increasing socio-economical problem. Progress in the fields of allergy and immunology research has lead to dramatic improvement of our ability to dissect the complex mechanisms underlying this condition. However, the pathophysiological puzzle of AD is far from being elucidated completely and its complexity has increased since it became clear that at least two distinct forms of AD can be delineated: (i) the so-called extrinsic AD (accounting for 70–90% of cases) i.e. AD associated with sensitization to environmental allergens and increased serum IgE; and (ii) the so-called intrinsic AD (accounting for the remaining 10–30% of cases) i.e. having no relationship to the classical atopic diathesis.¹ Because data about the pathophysiology of the intrinsic

form are still scarce,² we will concentrate on the classical extrinsic form of AD and expose some concepts which may illustrate current knowledge of this fascinating skin disorder.

Atopic dermatitis: a genetically complex disease

Family history of atopy and numerous Scandinavian sibling studies³ have confirmed that AD must have a distinct genetic background (reviewed in Coleman *et al.*).⁴ Recent progress in molecular biology and reverse genetics has allowed the disclosure of a series of candidate genes, most of which have been associated either with the atopic diathesis as such or at least to increased IgE. This is further supported by the observation of the transfer of 'atopic status' by allogeneic bone marrow transplantation to a previously nonatopic individual.⁵ Whether linkage analysis or association analysis, both strategies have lead to the proposal of some interesting genes as important candidates. While the 'beta adrenergic blockade theory of the atopic abnormality' of Szentivanyi⁶ has recently found little

Correspondence: T. Bieber, Department of Dermatology, Friedrich-Wilhelms-University, Sigmund-Freud-Strasse 25, D-53105 Bonn, Germany.
Tel.: +49 228287 4388. Fax: +49 228287 4881.
E-mail: thomas.bieber@meb.uni-bonn.de

genetic support,⁷ other genes more related to immunological abnormalities have been suggested. Besides MHC class II (HLA-DR),⁸ the significance of a gene locus on chromosome 5q encoding the interleukin (IL)-4 gene cluster, remains a matter of debate.^{9,10} Similarly, the finding of a gene on 11q13, a region encoding the beta chain of the high affinity IgE receptor FcεRIβ, remains rather controversial^{11–13} as does the involvement of a gene for mast cell chymase that has been explored mainly in Japan.^{14–16} More recently, however, much interest has been focused on the polymorphism of the gene encoding the α-chain of the IL-4 receptor at 16p11.2–12.^{17–19} This is of particular importance as this kind of polymorphism may be linked to abnormalities in the IL-4-mediated signal transduction and, as a consequence, in the regulation of IgE synthesis. The last candidate gene proposed to be relevant for AD is that of the chemokine RANTES for which abnormalities in the promotor region have been suggested to be of functional importance.²⁰

The atopic diathesis: an imbalance in the spectrum of Th1/Th2 responses

Based on the dichotomical concept of Th1 and Th2 cells established in the mouse model, it has been proposed that this subdivision may be applied to human T-cells. Following antigen presentation by dendritic cells of either the so-called DC1 or DC2 type,^{21,22} Th precursor cells (Thp) are triggered to differentiate into Th1 or Th2 cells, characterized by the secretion of IL-2 and interferon (IFN)-γ, or IL-4 and IL-5, respectively. Th0 cells probably represent either a transitory state or an intermediate cell type in the spectrum between Th1 and Th2 cells. From a clinical point of view, the Th1 pattern is associated with delayed type hypersensitivity reactions such as the tuberculin reaction, while a Th2 pattern is associated with increased secretion of IgE and IgE-mediated reactions such as allergic rhinitis.²³ In this regard, AD has a particular status: clinically it is a cell-mediated hypersensitivity reaction but kinetics studies in the model of atopy patch test have shown that the initial phase is characterized by a Th2 pattern and the subsequent phase clearly has a Th1 profile.

Immunopharmacological aspects: the phosphodiesterase and cAMP concept

It has been reported that patients with AD have increased phosphodiesterase IV activity, particularly in their monocytes. This would explain a decreased level of cAMP and consequently a higher formation of the

proinflammatory prostaglandin-E2 in patients.^{24,25} While prostaglandin-E2 is known to inhibit Th1 responses and to increase the IL-4 production of Th2 cells,²⁵ it has also been postulated that this mediator may be responsible for the maturation of dendritic cells into the DC2 type which is assumed to trigger Th2 cells. Whether these mechanisms are also of relevance to the inflammatory response that occurs in the skin, and thus may provide a valuable rationale for the therapeutic effect of topical type IV phosphodiesterase inhibitors,²⁶ remains to be confirmed.

First evidence for an intrinsic defect in keratinocytes of patients with AD

Clinically, AD is characterized by an impaired function of the epidermal barrier as manifested by an increased transepidermal water loss. It has long been a matter of debate whether this represents the result of the underlying atopic disease or rather is a *primum movens* of this disease, implying some kind of intrinsic defect in keratinocyte biology in these patients.^{27–29} Recently, the first evidence has been provided supporting the latter hypothesis. An enhanced production of granulocyte-macrophage colony stimulating factor by keratinocytes from AD patients has been shown in response to IL-1 and IFN-γ³⁰ and the culture supernatants could support phenotypic and functional maturation of peripheral blood precursors into dendritic cells.³⁰ Whether this putative intrinsic defect is also responsible for the other disturbances reported in the epidermal biology in AD patients remains to be verified.

Role of eosinophils

Eosinophilic infiltration of AD lesions, as well as increased eosinophil counts in the peripheral blood are seen frequently in AD patients. In addition to basophils and mast cells, eosinophils act as FcεRI-expressing effector cells of the IgE-mediated allergic inflammation.³¹ Consequently, serum levels of the eosinophil cationic protein have been used successfully to monitor the disease activity in AD.³² Delayed apoptosis and FAS resistance of eosinophils have been described in certain atopic diseases³³ including both the extrinsic and intrinsic type of AD³⁴ and may represent a molecular basis for the observed eosinophilia. Interference with the eosinophil recruiting and activation processes, e.g. with chemokine receptor antagonists such as met-RANTES,³⁵ might provide the basis for novel therapeutic concepts of AD.

Evidence for an IgE-mediated delayed type hypersensitivity reaction driven by FcεRI expressing antigen presenting cells

Because AD resembles a classical allergic contact dermatitis from the clinical and immuno-histological point of view, it has long been postulated that cell-mediated immune reactions must play a critical role in the pathomechanisms of these diseases. However, this was hardly compatible with the atopic context with increased IgE and IgE-mediated allergic reactions in these patients. First evidence for the missing link was provided 1986 by Bruijnzeel-Koomen *et al.* as they described the presence of IgE molecules on epidermal antigen presenting Langerhans cells,³⁶ introducing a new pathophysiological concept in which skin antigen presenting cells bearing IgE may be able to trigger a cell-mediated delayed type hypersensitivity reaction. In this regard, monocytes and dendritic cells such as Langerhans cells or the recently described inflammatory dendritic epidermal cells³⁷ perform IgE-mediated antigen focusing, i.e. they increase their presenting capacity up to 100–1000 fold *in vitro*.^{38,39} Antigen focusing has been shown to be effective in different cell systems.^{39–41} Three different IgE-binding structures have been shown to be expressed on epidermal antigen presenting dendritic cells: (i) the low affinity IgE-receptor CD23/FcεRII,⁴² (ii) the high affinity IgE-receptor FcεRI^{43–45} and (iii) the IgE-binding protein Galectin3/εBP.⁴⁶ Due to its affinity, FcεRI is obviously the most interesting and relevant structure.⁴⁷ Epidermal dendritic cell phenotyping, a recently standardized diagnostic procedure for the identification of AD lesions,⁴⁸ is based in part on the significant upregulation of FcεRI³⁷ on lesional epidermal dendritic cells of AD.

T cell infiltrates in AD skin

As mentioned above, the model of atopy patch test⁴⁹ has revealed two distinct phases (initial Th2 and subsequent Th1) in the inflammatory reaction elicited by the application of aeroallergens on the skin of AD patients.⁵⁰ This implies that some cells locally induce the switch by secreting IL-12. Two non-mutually exclusive populations could be responsible for this phenomenon: (i) eosinophils which have been shown to be present during the first 24–48 h of the reaction and then disappear morphologically⁵¹ and (ii) the inflammatory dendritic epidermal cells and other cutaneous dendritic cells armed with FcεRI. Although this switch has been shown in the model of atopy patch

test, and allergen-specific skin-infiltrating T cells of a Th2 as well as Th1 type have also been identified in chronic skin lesions of AD,⁵² it remains to be verified whether this two-phase model holds true for the naturally occurring AD lesions.

Role of Staphylococcal superantigens

It is well accepted that the skin of AD patients is heavily colonized by *Staphylococcus aureus* and that these bacteria are responsible for some flare-ups or exacerbation of AD. As *S. aureus* expresses a variety of so-called superantigens,^{53,54} and superantigen-specific IgE has been shown to be produced in some AD-patients,⁵⁵ it has been speculated that such structures could not only activate T cells with distinct Vβ-chains locally but could also contribute to the enhancement of IgE synthesis specifically or unspecifically.⁵³ Thus, oral antibiotics or topical antiseptic strategies are often of clinical benefit and not only help to control the outcome of the acute skin lesions but could also influence the more central immune mechanisms involved in the regulation of IgE synthesis.

Conclusion

The continuous and successful research activities undertaken by numerous investigators from around the world have greatly enhanced our knowledge of many aspects of this ever fascinating disease. However, our present knowledge still resembles a large, partly assembled puzzle with many single pieces, some clusters, and a large fringe being assembled, indicating that some of the pieces are still to be found and connected.

References

- 1 Wüthrich B. Neurodermitis atopica. *Wien Med Wochenschr* 1989; **139**: 156–65.
- 2 Werfel T, Kapp A. What do we know about the etiopathology of the intrinsic type of atopic dermatitis? *Curr Probl Dermatol* 1999; **28**: 18–28.
- 3 Schultz-Larsen F, Holm NV, Henigsen K. Atopic dermatitis. A genetic-epidemiologic study in a population-based twin sample. *J Am Acad Dermatol* 1986; **15**: 487–94.
- 4 Coleman R, Trembath RC, Harper JI. Genetic studies of atopy and atopic dermatitis. *Br J Dermatol* 1997; **136**: 1–5.
- 5 Agosti JM, Sprenger JD, Lum LG *et al.* Transfer of allergen-specific IgE-mediated hypersensitivity with allogeneic bone marrow transplantation. *N Engl J Med* 1988; **319**: 1623–8.
- 6 Szentivanyi A. The beta adrenergic theory of the atopic abnormality in asthma. *J Allergy* 1968; **42**: 203–232.

- 7 Deichmann KA, Schmidt A, Heinzmann A *et al.* Association studies on beta2-adrenoceptor polymorphisms and enhanced IgE responsiveness in an atopic population. *Clin Exp Allergy* 1999; **29**: 794–9.
- 8 Marsh DG, Meyers DA, Bias WB. The epidemiology and genetics of atopic allergy. *N Engl J Med* 1981; **305**: 1551–9.
- 9 Doull IJ, Lawrence S, Watson M *et al.* Allelic association of gene markers on chromosomes 5q and 11q with atopy and bronchial hyperresponsiveness. *Am J Respir Crit Care Med* 1996; **153**: 1280–4.
- 10 Blumenthal MN, Wang Z, Weber JL, Rich SS. Absence of linkage between 5q markers and serum IgE levels in four large atopic families. *Clin Exp Allergy* 1996; **26**: 892–6.
- 11 Cookson WO, Sharp PA, Faux JA, Hopkin JM. Linkage between immunoglobulin E responses underlying asthma and rhinitis and chromosome 11q. *Lancet* 1989; **I**: 1292–5.
- 12 Hizawa N, Yamaguchi E, Ohe M *et al.* Lack of linkage between atopy and locus 11q13. *Clin Exp Allergy* 1992; **22**: 1065–9.
- 13 Coleman R, Trembath RC, Harper JJ. Chromosome 11q13 and atopy underlying atopic eczema. *Lancet* 1993; **341**: 1121–2.
- 14 Mao XQ, Shirakawa T, Yoshikawa T *et al.* Association between genetic variants of mast-cell chymase and eczema. *Lancet* 1996; **348**: 581–3.
- 15 Tanaka K, Sugiura H, Uehara M *et al.* Association between mast cell chymase genotype and atopic eczema: comparison between patients with atopic eczema alone and those with atopic eczema and atopic respiratory disease. *Clin Exp Allergy* 1999; **29**: 800–3.
- 16 Kawashima T, Noguchi E, Arinami T *et al.* No evidence for an association between a variant of the mast cell chymase gene and atopic dermatitis based on case-control and haplotype-relative-risk analyses. *Hum Hered* 1998; **48**: 271–4.
- 17 Hershey GK, Friedrich MF, Esswein LA *et al.* The association of atopy with a gain-of-function mutation in the alpha subunit of the interleukin-4 receptor [see comments]. *N Engl J Med* 1997; **337**: 1720–5.
- 18 Deichmann KA, Heinzmann A, Forster J *et al.* Linkage and allelic association of atopy and markers flanking the IL4-receptor gene. *Clin Exp Allergy* 1998; **28**: 151–5.
- 19 Kruse S, Japha T, Tedner M *et al.* The polymorphisms S503P and Q576R in the interleukin-4 receptor alpha gene are associated with atopy and influence the signal transduction. *Immunology* 1999; **96**: 365–71.
- 20 Nickel RG, Casolaro V, Wahn U *et al.* Atopic dermatitis is associated with a functional mutation in the promoter of the C-C chemokine RANTES. *J Immunol* 2000; **164**: 1612–6.
- 21 Rissoan MC, Soumelis V, Kadowaki N *et al.* Reciprocal control of T helper cell and dendritic cell differentiation. *Science* 1999; **283**: 1183–6.
- 22 Kapsenberg ML, Hilken CM, Wierenga EA, Kalinski P. The paradigm of type 1 and type 2 antigen-presenting cells. Implications for atopic allergy. *Clin Exp Allergy* 1999; **29** (Suppl. 2): 33–6.
- 23 Mosmann TR, Sad S. The expanding universe of T-cell subsets: Th1, Th2 and more. *Immunol Today* 1996; **17**: 138–46.
- 24 Hanifin J. Atopic dermatitis and other endogenous eczemas. *Semin Dermatol* 1983; **2**: 1–44.
- 25 Hanifin JM, Chan SC. Monocyte phosphodiesterase abnormalities and dysregulation of lymphocyte function in atopic dermatitis. *J Invest Dermatol* 1995; **105**: S84–S8.
- 26 Hanifin JM, Chan SC, Cheng JB *et al.* Type 4 phosphodiesterase inhibitors have clinical and in vitro anti-inflammatory effects in atopic dermatitis. *J Invest Dermatol* 1996; **107**: 51–6.
- 27 Werner Y, Lindberg M. Transepidermal water loss in dry and clinically normal skin in patients with atopic dermatitis. *Acta Derm Venereol* 1985; **65**: 102–5.
- 28 Uehara M. Dry skin and inflammation. In: Ruzicka T, Ring J, Przybilla B, eds. *Handbook of Atopic Dermatitis* Berlin: Springer, 1991: 84–9.
- 29 Loden M. Biophysical properties of dry atopic and normal skin with special reference to effects of skin care products. *Acta Derm Venereol* 1995; **192**: 1–48.
- 30 Pastore S, Fanales Belasio E, Albanesi C *et al.* Granulocyte macrophage colony-stimulating factor is overproduced by keratinocytes in atopic dermatitis. Implications for sustained dendritic cell activation in the skin. *J Clin Invest* 1997; **99**: 3009–17.
- 31 Gounni AS, Lamkhioed B, Ochiai K *et al.* High-affinity IgE receptor on eosinophils is involved in defence against parasites. *Nature* 1994; **367**: 183–6.
- 32 Czech W, Krutmann J, Schopf E, Kapp A. Serum eosinophil cationic protein (ECP) is a sensitive measure for disease activity in atopic dermatitis. *Br J Dermatol* 1992; **126**: 351–5.
- 33 Simon HU, Yousefi S, Schranz C *et al.* Direct demonstration of delayed eosinophil apoptosis as a mechanism causing tissue eosinophilia. *J Immunol* 1997; **158**: 3902–8.
- 34 Wedi B, Raap U, Lewrick H, Kapp A. Delayed eosinophil programmed cell death in vitro: a common feature of inhalant allergy and extrinsic and intrinsic atopic dermatitis. *J Allergy Clin Immunol* 1997; **100**: 536–43.
- 35 Elsner J, Petering H, Kimmig D *et al.* The CC chemokine receptor antagonist met-RANTES inhibits eosinophil effector functions. *Int Arch Allergy Immunol* 1999; **118**: 462–5.
- 36 Bruijnzeel-Koomen C, van Wichen 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.
- 37 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**: 446–53.

- 38 Mudde GCRF, van Reijssen FC, Bruijnzeel KC. IgE-positive Langerhans cells and Th2 allergen-specific T cells in atopic dermatitis. *J Invest Dermatol* 1992; **99**: 1035.
- 39 Maurer D, Fiebiger E, Ebner C *et al*. Peripheral blood dendritic cells express FcεRI as a complex composed of FcεRIα and FcεRIγ-Chains and can use this Receptor for IgE-mediated Allergen presentation. *J Immunol* 1996; **157**: 607–16.
- 40 Pirron U, Schlunck T, Prinz JC, Rieber EP. IgE-dependent antigen focusing by human B lymphocytes is mediated by the low-affinity receptor for IgE. *Eur J Immunol* 1990; **20**: 1547–51.
- 41 van der Heijden FL, van Neerven RJJ, van Katwijk M *et al*. Serum-IgE-facilitated allergen presentation in atopic disease. *J Immunol* 1993; **150**: 3643–50.
- 42 Bieber T, Rieger A, Neuchrist C *et al*. Induction of FcεR2/CD23 on human epidermal Langerhans cells by human recombinant Interleukin-4 and gamma interferon. *J Exp Med* 1989; **170**: 309–14.
- 43 Bieber T, de la Salle H, Wollenberg A *et al*. Human epidermal Langerhans cells express the high affinity receptor for immunoglobulin E (Fc εpsilon RI). *J Exp Med* 1992; **175**: 1285–90.
- 44 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**: 1353–65.
- 45 Grabbe J, Haas N, Hamann K *et al*. Demonstration of the high-affinity IgE receptor on human Langerhans cells in normal and diseased skin. *Br J Dermatol* 1993; **129**: 120–3.
- 46 Wollenberg A, de la Salle H, Hanau D *et al*. Human keratinocytes release the endogenous β-galactoside-binding soluble lectin eBP which binds to Langerhans cells where it modulates their binding capacity for IgE glycoforms. *J Exp Med* 1993; **178**: 777–85.
- 47 Klubal R, Osterhoff B, Wang B *et al*. The high-affinity receptor for IgE is the predominant IgE-binding structure in lesional skin of atopic dermatitis patients. *J Invest Dermatol* 1997; **108**: 336–42.
- 48 Wollenberg A, Wen S, Bieber T. Phenotyping of epidermal dendritic cells – clinical applications of a flow cytometric micromethod. *Cytometry* 1999; **37**: 147–55.
- 49 Darsow U, Vieluf D, Ring J. Atopy patch test with different vehicles and allergen concentrations: an approach to standardization. *J Allergy Clin Immunol* 1995; **95**: 677–84.
- 50 Grewe M, Walther S, Gyufko K *et al*. Analysis of the cytokine pattern expressed in situ in inhalant allergen patch test reactions of atopic dermatitis patients. *J Invest Dermatol* 1995; **105**: 407–10.
- 51 Grewe M, Czech W, Morita A *et al*. Human eosinophils produce biologically active IL-12: implications for control of T cell responses. *J Immunol* 1998; **161**: 415–20.
- 52 Werfel T, Morita A, Grewe M *et al*. Allergen specificity of skin-infiltrating T cells is not restricted to a type-2 cytokine pattern in chronic skin lesions of atopic dermatitis. *J Invest Dermatol* 1996; **107**: 871–6.
- 53 Leung DY, Hauk P, Strickland I *et al*. The role of superantigens in human diseases: therapeutic implications for the treatment of skin diseases. *Br J Dermatol* 1998; **139** (Suppl. 53): 17–29.
- 54 Abeck D, Mempel M. *Staphylococcus aureus* colonization in atopic dermatitis and its therapeutic implications. *Br J Dermatol* 1998; **139** (Suppl. 53): 13–6.
- 55 Bunikowski R, Mielke M, Skarabis H *et al*. Prevalence and role of serum IgE antibodies to the *Staphylococcus aureus*-derived superantigens SEA and SEB in children with atopic dermatitis. *J Allergy Clin Immunol* 1999; **103**: 119–24.