

Recent Highlights in the Pathophysiology of Atopic Eczema

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Key Words

Atopic eczema · Chemokines · Dendritic cells · Cytokines · Genetics

Abstract

Atopic eczema (AE) belongs to the group of atopic diseases that have become increasingly prevalent over the last decades. The pathophysiology of AE has long remained enigmatic, but much scientific effort has been invested in elucidating the genetic background and the immunological mechanisms underlying AE, leading to a better understanding of this complex disease and to new therapeutic strategies. This review provides an update on the scientific progress that has been achieved in clarifying the pathophysiological mechanisms of AE.

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Introduction

Atopic eczema (AE) is a chronic inflammatory pruritic skin disease which usually emerges for the first time during early infancy and may persist throughout adulthood. In some cases, initial lesions of AE may also arise later in adults. Over the last decade, AE has shown a rising prevalence and, together with allergic rhinitis and allergic asthma, AE belongs to the group of atopic diseases which are characterized by an increased Th2 immune response with a complex hereditary background [1]. In re-

cent decades, many efforts have been made to elucidate the immunological mechanisms underlying AE investigate its genetic background. Scientific achievements in these fields have led to a better understanding of the underlying pathophysiology and gave rise to a more precise definition of AE as reflected by a very recently revised nomenclature for AE by the Nomenclature Review Committee of the World Allergy Organization. In this context, the term 'atopic eczema' is only used for skin reactions based on IgE sensitization as proven by allergen-specific IgE assays and/or skin tests [1].

Pathophysiology

Much progress has been achieved in recent years in understanding the pathophysiology of this chronic skin disorder. Genetic predisposition, immunological abnormalities and environmental factors represent important pieces in the pathophysiological puzzle of AE. The natural course of AE flares shows an acute and a chronic phase, with different leading immunological processes resulting in diverse histological pictures. In acute eczematous skin lesions, spongiosis of the epidermis prevails, with large numbers of antigen-presenting cells (APC) binding IgE molecules on their surface. In addition, infiltration of mostly CD4+ T cells in the dermal compartment is present as well. In chronic skin lesions showing strong lichenification with an acanthotic epidermis and elongation of rete ridges, increased numbers of IgE-bearing APC are

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present next to eosinophils that most likely contribute to the chronic inflammation by the production and release of proinflammatory cytokines and degranulation of toxic cationic proteins provoking tissue damage [1, 3].

Genetics

The complex genetic basis of this hereditary skin disease is reflected by the observed increased risk of newborns of developing AE whenever both parents are affected. This increased risk is superior to the risk of developing AE if the parents suffer from another atopic disease such as allergic asthma or allergic rhinitis, leading to the assumption that specific genes are associated with AE [2]. A great number of AE loci have been identified, notably on chromosome 5q31–33 which contains genes for the Th2 cytokines interleukin (IL)-3, IL-4, IL-5, IL-13 and GM-CSF [3]. Genetic studies identified a connection between AE and variants of the IL-13 coding region, functional mutations of the promotor region of RANTES (17q11) and gain-of-function polymorphisms in the α -subunit of the IL-4 receptor (16q12) [4]. Polymorphisms in the IL-4 receptor region could also be linked to a variant of AE, formerly termed 'intrinsic atopic eczema' and now termed 'eczema': patients with eczema show all clinical signs of AE in the absence of increased serum IgE levels and IgE sensitization to common aeroallergens [5]. A connection of genes on chromosome 11q13 encoding for the β -chain of the high-affinity receptor for IgE (Fc ϵ RI) has been controversially discussed [6]. Genes on chromosome 3q21 encoding the costimulatory molecules CD80 and CD86 have been proposed to be associated with AE in a genome-wide linkage study [7], whereas another study linked psoriasis and AE to loci on chromosomes 1q21 and 17q25 [8], proposing common candidate genes involved in skin inflammation. AE has also been associated with a low-producing transforming growth factor- β 1 (TGF- β 1) phenotype which might enhance skin inflammation due to the lacking anti-inflammatory properties of TGF- β 1 [9]. In view of the hygiene hypothesis, it is assumed that early contact with bacterial products might exert a protective effect against atopic diseases [10]. In this context, polymorphisms of Toll-like receptors, the principal receptor for bacterial endotoxin recognition, have been investigated. While some studies provide controversial results as to a connection between TLR4 polymorphisms and allergic asthma [11, 12], another recently published study linked a TLR2 R753Q polymorphism to a subgroup of AE patients with a severe phenotype [13].

Immunological Abnormalities

Systemic Immune Response

AE patients show peripheral blood eosinophilia and elevated serum IgE levels reflecting the predominant Th2 immune response in this disease. Moreover, serum levels of interferon (IFN)- γ have been shown to be decreased in AE patients, which might be related to a deficient production of the IFN- γ cytokine IL-18 by AE patients [14]. Furthermore, frequencies of allergen-specific T cells producing IL-4, IL-5 and IL-13 but low IFN- γ are elevated in AE patients, further contributing to the Th2 predominance [15]. In this context, the recently reported preferential apoptosis of circulating Th1 cells in AE patients might further accelerate this Th2 predominance [16]. Since the Th2 cytokines IL-4 and IL-13 are critically involved in inducing IgE isotype switching, they are of great importance. IL-5 plays a central role in the development and activation of eosinophils and also contributes to the prolonged survival of eosinophils in AE patients [17].

Cytokine Expression in Skin Lesions

Since it is well accepted that Th2 cytokines play a predominant role in systemic immune response in atopic individuals, many studies have analyzed their presence within AE skin lesions. In this context, comparative investigations of unaffected skin of AE patients versus skin of healthy nonatopic individuals could demonstrate increased mRNA for IL-4 and IL-13 in AE patients [18]. In acute skin lesions of AE patients, mRNA of the Th2 cytokines IL-4, IL-5 and IL-13 was elevated compared with unaffected skin of AE patients. In acute AE skin lesions, mRNA for Th1 cytokine IFN- γ and IL-12 was not significantly detectable, in contrast to chronic AE skin lesions where increased mRNA for IFN- γ and IL-12 but also IL-5 and GM-CSF could be demonstrated, leading to the assumption of a biphasic course of AE with a more marked Th2 profile during acute AE, whereas Th1 predominance is found in the chronic phase of AE [19]. An immunohistochemical study demonstrated elevated IL-17 in acute AE lesional skin while IL-11 was detected in chronic lesions. Both cytokines play a central role in tissue remodeling [20]. Another comparative study demonstrated decreased expression of IL-15 mRNA in acute and chronic AE skin lesions compared with psoriasis lesions. On IL-15, a Th1-like cytokine was shown to induce IFN- γ production and to suppress IgE synthesis, leading to the assumption that decreased IL-15 in AE patients might further contribute to the Th2 predominance [21]. Cytokine production was also examined during the early genesis of skin lesions using an atopy patch test (APT) con-

sisting in the application of aeroallergens to the skin in order to provoke an eczematous reaction. In this context, provocation with house dust mite led to increased expression of the Th2 cytokine IL-4 in the initial phase, while after 24–48 h the Th1 cytokine IFN- γ was found [22], providing further evidence for a biphasic nature of AE.

Antigen-Presenting Cells

Significant numbers of IgE-bearing Langerhans cells (LC) and inflammatory dendritic epidermal cells (IDEC) which express Fc ϵ RI are present in the lesional skin of AE patients [23, 24]. Both cell types belong to the group of myeloid dendritic cells (DC) and play a central role in the uptake and presentation of antigens or allergens to Th1 and Th2 cells [25]. In terms of antigen-focusing, allergens can be internalized via Fc ϵ RI and further processed for antigen presentation to T cells. Neither Fc ϵ RI+ IDEC nor Fc ϵ RI+ LC can be found in healthy skin [24]. Fc ϵ RI expression on LC and IDEC might result from high serum IgE levels, but could also be connected with a low TGF- β -producing phenotype as we could show recently that both conditions are capable of stabilizing Fc ϵ RI on LC and IDEC in vitro [26, 27]. Moreover, recent data provide evidence that Fc ϵ RI expression on DC in the skin might mirror a systemic immunological response to atopic disease as it could be shown that Fc ϵ RI+ LC are also present in unaffected skin of patients suffering from allergic rhinitis, allergic asthma and AE during the active phase of the disease [28]. Recent data provide evidence that LC and IDEC contribute differently to the development of AE. In this context, it has been shown that Fc ϵ RI+ LC are critical in the initiation of an eczematous skin reaction during atopic skin testing, which suggests that Fc ϵ RI+ LC play a central role in the initial phase of AE [25].

The clinical relevance of Fc ϵ RI+ LC is reflected by the observation that their presence is necessary to provoke an eczematous reaction after application of aeroallergens in the APT [29]. Further on we could show in vitro that Fc ϵ RI-activated LC-like DC release chemotactic signals and increase the migratory capacity of precursor cells of IDECs and naive T cells. Furthermore, Fc ϵ RI-activated IDEC-like DCs produce high amounts of proinflammatory cytokines as well as chemokines such as IL-1 and TNF- α and might thereby amplify the inflammatory immune reaction in AE patients. In addition, Fc ϵ RI-activated IDEC-like DC prime naive T cells into IFN- γ producing T cells and release IL-12 and IL-18, leading to the assumption that IDEC might be critically involved in the switch of Th2 to Th1 immune responses [25].

It has been suggested very recently that a second population of DC, the so-called plasmacytoid DC (pDC), are involved in pathophysiological mechanisms underlying AE. Upon activation, pDC are able to produce type-I interferons and are known to play a central role in viral defense. A recent publication reports that in contrast to other inflammatory skin diseases only very few pDC could be detected in AE lesions [30]. This might result from decreased expression of skin-homing molecules such as the cutaneous lymphocyte antigen (CLA) and the L-selectin CD62L which are both expressed in lower levels on pDC of AE patients [31]. Furthermore, pDC of AE patients expressed high levels of Fc ϵ RI and its aggregation impaired the surface expression of MHC molecules, induced the production of IL-10 and enhanced the apoptosis of pDC. Importantly, Fc ϵ RI-preactivated pDC produce less type-I interferons after stimulation with CpG motifs [31]. Thereby pDC might contribute to the enhanced susceptibility of patients with AE to viral infections (fig. 1).

Infiltration of Inflammatory Cells

Soluble factors predominate the cellular infiltrate in AE lesions. Increased expression of IL-16 attracting CD4+ T cells has been demonstrated in acute lesions [32]. Further on, the CC cytokine RANTES, MCP4 and eotaxin have been demonstrated in lesional skin of AE patients. Most likely they contribute to the chemotaxis of CCR3+ eosinophils as well as Th2 T cells [33, 34]. Keratinocytes of AE patients are capable of producing increased amounts of the chemokines TSLP as well as MDC and thereby contribute to the activating CD11c+ DC. These DC in turn produce large amounts of the chemokines MDC and TARC thereby favoring the selective recruitment of CCR4+ Th2 cells to the skin [20, 35, 36]. Very recently it has been reported that in AE, CCL18 is the most highly expressed chemokine among all known chemokines and that topical exposure to relevant allergen as well as to superantigens results in significant induction of CCL18 in AE [37]. During persisting inflammation, as seen in chronic skin lesions, increased levels of IL-5 and GM-CSF have been detected [38]. Both cytokines prolong the survival of eosinophils, macrophages, monocytes and LC [17]. Mechanical traumata of the skin, e.g. by scratching, lead to the release of many proinflammatory cytokines such as TNF- α and keratinocytes of AE patients produce increased quantities of RANTES in response to TNF- α [39].

Aeroallergens

It has been shown that bronchial or intranasal challenge with aeroallergens can lead to pruritus and eczematous skin lesions in AE patients and to the corresponding allergen-specific IgE. Moreover, epicutaneous application of aeroallergens (e.g. house dust mites, weeds, animal dander and moulds) via the APT on nonlesional skin of AE patients provokes an eczematous reaction in 30–50% of the cases. A very recently published multicenter study showed that from a clinical point of view, the APT was more specific than skin prick testing or detection of specific IgE. Nevertheless, APT is usually negative in healthy volunteers or patients with allergic respiratory diseases [40].

It has been shown that avoidance of house dust mite allergens results in a significant improvement of AE. A connection between the degree IgE sensitization to aeroallergens and the severity of AE could also be demonstrated. Furthermore, allergen-specific T cells to house dust mites isolated from lesional skin or APT sites of AE patients provide further evidence for the importance and relevance of aeroallergens in AE [2, 41].

Autoallergens

Specific IgE against human proteins are detectable in the serum of most AE patients [42]. Although the autoantigens characterized to date are intracellular proteins they have been detected in IgE immune complexes suggesting that autoallergens are released through mechanical trauma, e.g. scratching resulting in IgE sensitization and subsequently to a T-cell- and IgE-mediated immune response [43, 44]. This concept is further supported by the detectable decrease of specific IgE towards autoallergens after successful therapy of AE with cyclosporine [44, 45].

Colonization by *Staphylococcus aureus*

The skin of AE patients is colonized by *S. aureus* in over 90% of the cases. This phenomenon may be attributed to the recently reported reduced production of β -defensins in the skin of patients with AE. It is well accepted that these peptides produced by keratinocytes have high antibiotic properties. Further evidence for the importance of *S. aureus* is provided by the observation that in AE patients suffering from secondary infections, a combination therapy consisting of an antibiotic and a topical steroid is superior to a monotherapy with a steroid only [2].

Certain strains of *S. aureus* are known to produce enterotoxins, e.g. *S. aureus* enterotoxin A, B, C, D, E, G, and toxic shock syndrome toxin-1 (TSST-1). They can act as superantigens in an antigen-nonspecific manner, lead-

ing to substantial proliferation of T cells and may thereby contribute to amplification of the inflammatory reaction [46]. Moreover, specific IgE against these superantigens was detected in AE patients, leading to the suggestion of an antigen-specific reaction which might also be involved or further amplify skin inflammation [47]. Interestingly, in patients showing clinically all features of AE but displaying normal serum IgE levels and lacking any sensitization to common aeroallergens, significant amounts of specific IgE against *S. aureus* enterotoxin A, B, C, D, E, G, and TSST-1 could be detected [48]. Besides, specific IgE molecules against superantigens on mast cells can lead to the release of histamines in the skin [48]. Furthermore, it has been shown very recently that superantigens have a great impact on functional properties of CD4+/CD25+ T regulatory cells in AE patients. Thus, after stimulation with *S. aureus* enterotoxin B, CD4+/CD25+ T regulatory cells lose their suppressive properties. Furthermore, when T regulatory cells were mixed with CD4+CD25- cells and stimulated with *S. aureus* enterotoxin B, the suppressive function of T regulatory cells was reversed, leading to the assumption that superantigens may be involved in breaking tolerance and thereby contributing to inflammatory processes triggered by *S. aureus* enterotoxins [49].

Conclusion

Although much progress has been made in understanding AE, its pathophysiology remains enigmatic. However, AE is certainly a complex disease, resulting from multiple interactions between genes and environmental factors. Moreover, modern techniques of genetic investigation combined with a better definition of clinical phenotype will hopefully lead to the identification of genes responsible for the various forms of AE. Such new findings will have an important impact on our understanding of the immunological mechanisms underlying AE and on the development of more specific new therapeutic strategies.

References

- Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, Motala C, Ortega Martell JA, Platts-Mills TA, Ring J, Thien F, Van Cauwenberge P, Williams HC: Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol* 2004;113:832–836.
- Leung DY, Bieber T: Atopic dermatitis. *Lancet* 2003;361:151.
- Forrest S, Dunn K, Elliott K, Fitzpatrick E, Fullerton J, McCarthy M, Brown J, Hill D, Williamson R: Identifying genes predisposing to atopic eczema. *J Allergy Clin Immunol* 1999;104:1066.
- Kawashima T, Noguchi E, Arinami T, Yamakawa-Kobayashi K, Nakagawa H, Otsuka F, Hamaguchi H: Linkage and association of an interleukin 4 gene polymorphism with atopic dermatitis in Japanese families. *J Med Genet* 1998;35:502.
- Novak N, Kruse S, Kraft S, Geiger E, Kluken H, Fimmers R, Deichmann KA, Bieber T: Dichotomic nature of atopic dermatitis reflected by combined analysis of monocyte immunophenotyping and single nucleotide polymorphisms of the interleukin-4/interleukin-13 receptor gene: The dichotomy of extrinsic and intrinsic atopic dermatitis. *J Invest Dermatol* 2002;119:870–875.
- Cox HE, Moffatt MF, Faux JA, Walley AJ, Coleman R, Trembath RC, Cookson WO, Harper JI: Association of atopic dermatitis to the beta subunit of the high affinity immunoglobulin E receptor. *Br J Dermatol* 1998;138:182.
- Lee YA, Wahn U, Kehrt R, Tarani L, Businco L, Gustafsson D, Andersson F, Oranje AP, Wolkertstorfer A, Berg A, Hoffmann U, Kuster W, Wienker T, Ruschendorf F, Reis A: A major susceptibility locus for atopic dermatitis maps to chromosome 3q21. *Nat Genet* 2000;26:470–473.
- Cookson WO, Ubhi B, Lawrence R, Abecasis GR, Walley AJ, Cox HE, Coleman R, Leaves NI, Trembath RC, Moffatt MF, Harper JI: Genetic linkage of childhood atopic dermatitis to psoriasis susceptibility loci. *Nat Genet* 2001;27:372–373.
- Arkwright PD, Chase JM, Babbage S, Pravica V, David TJ, Hutchinson IV: Atopic dermatitis is associated with a low-producer transforming growth factor beta(1) cytokine genotype. *J Allergy Clin Immunol* 2001;108:281–284.
- Gehring U, Bolte G, Borte M, Bischof W, Fahlbusch B, Wichmann HE, Heinrich J: Exposure to endotoxin decreases the risk of atopic eczema in infancy: A cohort study. *J Allergy Clin Immunol* 2001;108:847–854.
- Fageras Bottcher M, Hmani-Aifa M, Lindstrom A, Jenmalm MC, Mai XM, Nilsson L, Zdolsek HA, Bjorksten B, Soderkvist P, Vaarala O: A TLR4 polymorphism is associated with asthma and reduced lipopolysaccharide-induced interleukin-12(p70) responses in Swedish children. *J Allergy Clin Immunol* 2004;114:561–567.
- Yang IA, Barton SJ, Rorke S, Cakebread JA, Keith TP, Clough JB, Holgate ST, Holloway JW: Toll-like receptor 4 polymorphism and severity of atopy in asthmatics. *Genes Immun* 2004;5:41–45.
- Ahmad-Nejad P, Mrabet-Dahbi S, Breuer K, Klotz M, Werfel T, Herz U, Heeg K, Neumair M, Renz H: The toll-like receptor 2 R753Q polymorphism defines a subgroup of patients with atopic dermatitis having severe phenotype. *J Allergy Clin Immunol* 2004;113:565–567.
- Higashi N, Gesser B, Kawana S, Thestrup-Pedersen K: Expression of IL-18 mRNA and secretion of IL-18 are reduced in monocytes from patients with atopic dermatitis. *J Allergy Clin Immunol* 2001;108:607–614.
- van Reijssen FC, Bruijnzeel-Koomen CA, Kalthoff FS, Maggi E, Romagnani S, Westland JK, Mudde GC: Skin-derived aeroallergen-specific T-cell clones of Th2 phenotype in patients with atopic dermatitis. *J Allergy Clin Immunol* 1992;90:184–193.
- Akdis M, Trautmann A, Klunker S, Daigle I, Kucuksezer UC, Deglmann W, Disch R, Blaser K, Akdis CA: T helper (Th) 2 predominance in atopic diseases is due to preferential apoptosis of circulating memory/effector Th1 cells. *FASEB J* 2003;17:1026–1035.
- Leung DY, Boguniewicz M, Howell MD, Nomura I, Hamid QA: New insights into atopic dermatitis. *J Clin Invest* 2004;113:651–657.
- Hamid Q, Naseer T, Minshall EM, Song YL, Boguniewicz M, Leung DY: In vivo expression of IL-12 and IL-13 in atopic dermatitis. *J Allergy Clin Immunol* 1996;98:225–231.
- Hamid Q, Boguniewicz M, Leung DY: Differential in situ cytokine gene expression in acute versus chronic atopic dermatitis. *J Clin Invest* 1994;94:870–876.
- Toda M, Leung DY, Molet S, Boguniewicz M, Taha R, Christodoulouopoulos P, Fukuda T, Elias JA, Hamid QA: Polarized in vivo expression of IL-11 and IL-17 between acute and chronic skin lesions. *J Allergy Clin Immunol* 2003;111:875–881.
- Ong PY, Hamid QA, Travers JB, Strickland I, Al Kerithy M, Boguniewicz M, Leung DY: Decreased IL-15 may contribute to elevated IgE and acute inflammation in atopic dermatitis. *J Immunol* 2002;168:505–510.
- Kerschenlohr K, Decard S, Przybilla B, Wollenberg A: Atopy patch test reactions show a rapid influx of inflammatory dendritic epidermal cells in patients with extrinsic atopic dermatitis and patients with intrinsic atopic dermatitis. *J Allergy Clin Immunol* 2003;111:869–.
- Bieber T, de la Salle H, Wollenberg A, Hakimi J, Chizzonite R, Ring J, Hanau D, de la Salle C: Human epidermal Langerhans cells express the high affinity receptor for immunoglobulin E (Fc epsilon RI). *J Exp Med* 1992;175:1285–1290.
- 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.
- Novak N, Valenta R, Bohle B, Laffer S, Haberstok J, Kraft S, Bieber T: Fc epsilon RI engagement of Langerhans cell-like dendritic cells and inflammatory dendritic epidermal cell-like dendritic cells induces chemotactic signals and different T-cell phenotypes in vitro. *J Allergy Clin Immunol* 2004;113:949–957.
- Novak N, Kraft S, Haberstok J, Geiger E, Allam P, Bieber T: A reducing microenvironment leads to the generation of Fc epsilon RI-high inflammatory dendritic epidermal cells (IDEC). *J Invest Dermatol* 2002;119:842–849.
- Allam JP, Klein E, Bieber T, Novak N: Transforming growth factor-beta1 regulates the expression of the high-affinity receptor for IgE on CD34 stem cell-derived CD1a dendritic cells in vitro. *J Invest Dermatol* 2004;123:676–682.
- Semper AE, Heron K, Woollard AC, Kochan JP, Friedmann PS, Church MK, Reischl IG: Surface expression of Fc epsilon RI on Langerhans' cells of clinically uninvolved skin is associated with disease activity in atopic dermatitis, allergic asthma, and rhinitis. *J Allergy Clin Immunol* 2003;112:411–419.
- Langeveld-Wildschut EG, Bruijnzeel PL, Mudde GC, Versluis C, Van Ieperen-Van Dijk AG, Bihari IC, Knol EF, Thepen T, Bruijnzeel-Koomen CA, van Reijssen FC: Clinical and immunologic variables in skin of patients with atopic eczema and either positive or negative atopy patch test reactions. *J Allergy Clin Immunol* 2000;105:1008–1016.
- Wollenberg A, Wagner M, Gunther S, Towarowski A, Tuma E, Moderer M, Rothenfusser S, Wetzel S, Endres S, Hartmann G: Plasmacytoid dendritic cells: A new cutaneous dendritic cell subset with distinct role in inflammatory skin diseases. *J Invest Dermatol* 2002;119:1096–1102.
- Novak N, Allam JP, Hagemann T, Jenneck C, Laffer S, Valenta R, Kochan J, Bieber T: Characterization of Fc epsilon RI-bearing CD123 blood dendritic cell antigen-2 plasmacytoid dendritic cells in atopic dermatitis. *J Allergy Clin Immunol* 2004;114:364–370.
- Reich K, Hugo S, Middel P, Blaschke V, Heine A, Gutgesell C, Williams R, Neumann C: Evidence for a role of Langerhans cell-derived IL-16 in atopic dermatitis. *J Allergy Clin Immunol* 2002;109:681–687.
- Yawalkar N, Ugucioni M, Scharer J, Braunwalder J, Karlen S, Dewald B, Braathen LR, Baggiolini M: Enhanced expression of eotaxin and CCR3 in atopic dermatitis. *J Invest Dermatol* 1999;113:43–48.

- 34 Morales J, Homey B, Vicari AP, Hudak S, Oldham E, Hedrick J, Orozco R, Copeland NG, Jenkins NA, McEvoy LM, Zlotnik A: CTACK, a skin-associated chemokine that preferentially attracts skin-homing memory T cells. *Proc Natl Acad Sci USA* 1999;96:14470–14475.
- 35 Galli G, Chantry D, Annunziato F, Romagnani P, Cosmi L, Lazzeri E, Manetti R, Maggi E, Gray PW, Romagnani S: Macrophage-derived chemokine production by activated human T cells in vitro and in vivo: Preferential association with the production of type 2 cytokines. *Eur J Immunol* 2000;30:204–210.
- 36 Kakinuma T, Nakamura K, Wakugawa M, Mitsui H, Tada Y, Saeki H, Torii H, Asahina A, Onai N, Matsushima K, Tamaki K: Thymus and activation-regulated chemokine in atopic dermatitis: Serum thymus and activation-regulated chemokine level is closely related with disease activity. *J. Allergy Clin. Immunol.* 2001;107:535–541.
- 37 Pivarcsi A, Gombert M, eu-Nosjean MC, Lauerman A, Kubitz A, Meller S, Rieker J, Muller A, Da CL, Haahtela A, Sonkoly E, Fridman W. H, Alenius H, Kemeny L, Ruzicka T, Zlotnik A, Homey B: CC chemokine ligand 18, an atopic dermatitis-associated and dendritic cell-derived chemokine, is regulated by staphylococcal products and allergen exposure. *J Immunol* 2004;173:5810–5817.
- 38 Taha RA, Leung DY, Ghaffar O, Boguniewicz M, Hamid Q: In vivo expression of cytokine receptor mRNA in atopic dermatitis. *J Allergy Clin Immunol* 1998;102:245–250.
- 39 Yamada H, Matsukura M, Yudate T, Chihara J, Stingl G, Tezuka T: Enhanced production of RANTES, an eosinophil chemoattractant factor, by cytokine-stimulated epidermal keratinocytes. *Int Arch Allergy Immunol* 1997;114(suppl 1):28.
- 40 Darsow U, Laifaoui J, Kerschenlohr K, Wollenberg A, Przybilla B, Wuthrich B, Borelli S Jr, Giusti F, Seidenari S, Drzimalla K, Simon D, Disch R, Borelli S, Devillers AC, Oranje AP, De RL, Hachem JP, Dangoisse C, Blondeel A, Song M, Breuer K, Wulf A, Werfel T, Roul S, Taieb A, Bolhaar S, Bruijnzeel-Koomen C, Bronnimann M, Braathen LR, Didierlaurent A, Andre C, Ring J: The prevalence of positive reactions in the atopy patch test with aeroallergens and food allergens in subjects with atopic eczema: A European multicenter study. *Allergy* 2004;59:1318–1325.
- 41 Novak N, Bieber T: Allergic and nonallergic forms of atopic diseases. *J Allergy Clin Immunol* 2003;112:252–262.
- 42 Valenta R, Maurer D, Steiner R, Seiberler S, Sperr WR, Valent P, Spitzauer S, Kapiotis S, Smolen J, Stingl G: Immunoglobulin E response to human proteins in atopic patients. *J Invest Dermatol* 1996;107:203–208.
- 43 Seiberler S, Bugajska-Schretter A, Hufnagl P, Binder BR, Stockl J, Spitzauer S, Valent P, Valenta R: Characterization of IgE-reactive autoantigens in atopic dermatitis. 1. Subcellular distribution and tissue-specific expression. *Int Arch Allergy Immunol* 1999;120:108–116.
- 44 Valenta R, Natter S, Seiberler S, Wichlas S, Maurer D, Hess M, Pavelka M, Grote M, Ferreira F, Szepefalusi Z, Valent P, Stingl G: Molecular characterization of an autoallergen, Hom s 1, identified by serum IgE from atopic dermatitis patients. *J Invest Dermatol* 1998;111:1178–1183.
- 45 Kinaciyan T, Natter S, Kraft D, Stingl G, Valenta R: IgE autoantibodies monitored in a patient with atopic dermatitis under cyclosporin A treatment reflect tissue damage. *J Allergy Clin Immunol* 2002;109:717–719.
- 46 Breuer K, Wittmann M, Bosche B, Kapp A, Werfel T: Severe atopic dermatitis is associated with sensitization to staphylococcal enterotoxin B (SEB). *Allergy* 2000;55:551–555.
- 47 Leung DY, Harbeck R, Bina P, Reiser RF, Yang E, Norris DA, Hanifin JM, Sampson HA: Presence of IgE antibodies to staphylococcal exotoxins on the skin of patients with atopic dermatitis. Evidence for a new group of allergens. *J Clin Invest* 1993;92:1374–1380.
- 48 Novak N, Allam JP, Bieber T: Allergic hyperreactivity to microbial components: a trigger factor of 'intrinsic' atopic dermatitis? *J Allergy Clin Immunol* 2003;112:215–216.
- 49 Ou LS, Goleva E, Hall C, Leung DY: T regulatory cells in atopic dermatitis and subversion of their activity by superantigens. *J Allergy Clin Immunol* 2004;113:756–763.