

Dendritic cells and atopic eczema/dermatitis syndrome

Dagmar von Bubnoff, Susanne Koch and Thomas Bieber

Purpose of review

The manifestation of atopic eczema/dermatitis syndrome is believed to result from a complex interrelationship of environmental factors, pharmacological abnormalities, skin barrier defects, and immunological phenomena. Although we are only beginning to understand the molecular basis of this disease, much progress has been made in defining key events leading to the manifestation of allergic inflammation. Here, we review recent findings that underscore the importance of dendritic cells as being central to shape these proinflammatory responses.

Recent findings

Evidence for a differential regulation of the high affinity receptor for IgE, FcεRI, on the surface of atopic dendritic cells compared with non-atopic dendritic cells became apparent. In atopic donors, in contrast to non-atopic donors, the intracellular expression of the γ-chains of FcεRI is sufficient, thus leading to the assembly with the α-chain and surface expression of the receptor. This finding is of considerable interest for an understanding of the pathophysiology of IgE-mediated dendritic cell functions in atopic eczema/dermatitis syndrome. In addition, it has been shown that keratinocytes from the epidermal skin of individuals with atopic eczema/dermatitis syndrome express human thymic stromal lymphopoietin, which activates dendritic cells to attract T helper type 2 cells into the skin. Furthermore, these activated dendritic cells prime naïve T cells into T helper type 2 cells.

Summary

The past few years have seen a remarkable process of refocusing in atopy. Dendritic cells in particular have been at the centre of this process. It has become unequivocally clear that these cells have the power of shaping the allergic response.

Keywords

antigen-presenting cells, atopic eczema/dermatitis syndrome, FcεRI

Abbreviations

AEDS	atopic eczema/dermatitis syndrome
APC	antigen-presenting cell
DC	dendritic cell
ER	endoplasmic reticulum
IDEC	inflammatory dendritic epidermal cell
LC	Langerhans cell
MHC	major histocompatibility complex
TSLP	thymic stromal lymphopoietin

© 2003 Lippincott Williams & Wilkins
1528-4050

Introduction

In Western societies, approximately 20% of the population suffers from allergic diseases such as allergic rhinitis, allergic asthma and the atopic eczema/dermatitis syndrome (AEDS). The current immune homeostasis and genetic composition of the individual predominantly influence the immunological events that follow antigen exposure. Histologically, AEDS is characterized by increased numbers of Langerhans cells (LCs), inflammatory dendritic epidermal cells (IDECs), macrophages, basophils, eosinophils, T helper type 2 cells, and dermal dendritic cells (DCs).

The very first event after an allergen encounter is the event that seems to regulate the immune response. Whereas mast cells and other cells of anaphylaxis mediate the effector phase of the allergic response, DCs seem to be of crucial importance in determining the allergic response. Under normal circumstances, allergen challenge results in specific T-cell hyporesponsiveness, the process of which requires (a series of) efficient immunological responses. Under different circumstances, the same proteins are able to elicit a T helper type 2 biased allergic reaction.

In this review we will focus on the central role of DCs in AEDS. We attempt to present the current knowledge about the molecular events leading to allergic inflammation, and to relate this information to the pathophysiology of AEDS.

Atopic eczema/dermatitis syndrome

The atopic eczema/dermatitis syndrome is a highly pruritic skin disease characterized by alternating periods of inflammation and remission. Major features are eczematous lesions, especially in the large skin folds of the joints. Worldwide, 10–20% of children and approximately 1–2% of adults are affected but there are reports about an increasing prevalence of AEDS, especially in industrialized countries [1,2•]. It is believed that

Curr Opin Allergy Clin Immunol 3:353–358. © 2003 Lippincott Williams & Wilkins.

Department of Dermatology, Friedrich-Wilhelms-University of Bonn, 53105 Bonn, Germany

Correspondence to Thomas Bieber, Department of Dermatology, Friedrich-Wilhelms-University of Bonn, 53105 Bonn, Germany
Tel: +49 228 287 4338; fax: +49 228 287 4881;
e-mail: thomas.bieber@ukb.uni-bonn.de

Current Opinion in Allergy and Clinical Immunology 2003, 3:353–358

changes in the environment such as improved hygiene and fewer infections during childhood are responsible for this increase [3•,4]. Infectious diseases such as hepatitis or tuberculosis, which are far less common today, may serve to activate the innate immune system and balance the T helper type 2 biased immune system present during early life [5•]. Several groups have demonstrated the hypothesis that newborns are poorly equipped to respond to microbial assault and must therefore rely on exogenous factors for immunity. It has been found, for example, that reduced soluble CD14 levels, a protein that interacts with lipopolysaccharide from bacteria, in maternal amniotic fluid and breast milk is associated with the development of atopy and eczema in infants [6].

Genetics alone cannot explain the rapid increase of AEDS, although several chromosomal regions have been identified that are pathophysiologically relevant for AEDS. Most of the AEDS susceptibility loci consist of polymorphisms of T helper type 2 cytokine genes, e.g. the T allele of the -590C/T polymorphism of the IL-4 gene promoter region [7]. This allele is associated with an increased activity of the IL-4 gene promoter and is frequently above average in AEDS.

Two types of AEDS are currently recognized [8•]. The extrinsic form of AEDS results from specific IgE-mediated sensitization to allergens and affects approximately 70–80% of patients. Patients with the intrinsic type of AEDS do not show increased IgE levels to frequent (aero) allergens such as house dust mites or pollen. This form of AEDS represents approximately 20–30% of patients. The mechanism of the allergic response that distinguishes the intrinsic form from the extrinsic form of AEDS is far from being understood but is being intensively investigated. Therefore, most of the progress made in understanding the pathophysiological mechanism of AEDS is related to the extrinsic form.

Dendritic cells and atopic eczema/dermatitis syndrome

Antigen-presenting cells (APCs) constitute a heterogeneous group of cells with the common task of presenting antigens in the context of the major histocompatibility complex (MHC). Among professional APCs, epidermal LCs and DCs are unique in their ability to prime naive T cells, and are thus responsible for the primary immune response (i.e. the sensitization phase of allergy).

Origin and characteristics of dendritic cells

Professional APCs are mainly divided into 2 systems: the DCs, including blood and tissue DCs and epidermal LCs, and the monocyte-macrophage system. All these cell types originate from pluripotent bone marrow CD34⁺ haematopoietic progenitor cells.

Langerhans cells

Epidermal LCs are components of the DC line and are located in the epidermis and in mucosal tissues. They are increased in number in atopically affected skin [9]. LCs are the only cells of the epidermis that constitutively express MHC class II, CD1a and Langerin on their cell surface. They lack the monocyte-macrophage marker CD14. LCs differ ultrastructurally from other DCs by the presence of Birbeck granules, which constitute a subdomain of the endosomal-recycling compartment of the cell [10•]. Langerin is a transmembrane type II Ca²⁺-dependent lectin, which is involved in the biosynthesis of Birbeck granules.

As immediate precursors of epidermal LCs in human dermal skin have been morphologically characterized, knowledge of their life cycle has been elucidated [11•]. Epidermal LCs seem to be maintained by a stable precursor population in the dermis under steady-state conditions. With inflammation, however, blood-borne LC precursors are actively attracted to the epidermis under the influence of the CCR2 chemokine receptor.

Dendritic cells

Two distinct DC precursor cells have been characterized in the blood: DC1 cells carry the myeloid surface antigen CD11c and plasmacytoid DCs or DC2s are CD11c negative [12]. DC2 cells are characterized by a unique surface phenotype: CD4⁺CD3⁻IL-3R α ⁺⁺⁺HLA-DR⁺. These DCs produce large amounts of IFN-1 (IFN- α and IFN- β) in response to a viral infection. Interestingly, plasmacytoid DCs can be found in increasing numbers in specific skin infiltrates, such as Lichen ruber or lupus erythematosus, whereas in AEDS, DC2s are present in very low numbers [13•]. In addition, human activated plasmacytoid DCs respond to histamine by downregulating their capacity to secrete IFN [14]. These findings may help explain the increased susceptibility observed in atopic individuals to viral skin infections such as eczema herpeticum.

Peripheral blood monocyte precursors of immature DC1 cells have been designated pDC1. They give rise to myeloid DC1 upon culture with granulocyte macrophage colony-stimulating factor and IL-4. The surface markers of DC1 mirror their origin from myeloid precursors: CD11c⁺CD33^{+/−}CD1a⁺MHC class II⁺CD80⁺CD86⁺. After maturation with CD40 ligand or endotoxin, the cells produce large amounts of IL-12. CD11c-positive DCs and LCs represent key cells for the activation of T cells in lymph nodes after they have emigrated and matured during antigen uptake [15].

Inflammatory dendritic epidermal cells

IDECs are a distinct DC population that is mainly found in inflammatory skin diseases such as AEDS, contact

dermatitis or psoriasis [16]. In the lesional skin of AEDS, the number of IDECs exceeds the number of LCs, whereas normal skin does not contain IDECs [17*]. In epidermal cell suspensions, IDECs can be distinguished from CD1a-positive LCs on the basis of the surface density of the high affinity receptors for IgE, FcεRI, and the expression of CD11b: LCs are CD1a⁺⁺⁺CD11b⁻FcεRI⁺ and IDECs are CD1a⁺CD11b⁺⁺⁺FcεRI⁺⁺⁺. Morphologically, IDECs resemble LCs, but in contrast to these cells IDECs lack the typical Birbeck granules and are Langerin negative.

After the successful topical treatment of atopic lesions, the number of IDECs in epidermal skin decreases below the detection level, suggesting substantial involvement in atopic inflammation of this cell type.

Recently, an in-vitro model using reducing agents such as mercaptoethanol was developed to generate FcεRI^{high} IDECs from FcεRI-positive atopic monocytes [18]. Apparently, reducing agents are able to stabilize the redox-sensitive disulfide dimers of the γ-chain, which are essential for FcεRI surface expression (see below).

The high-affinity receptor for IgE, FcεRI

One of the hallmarks of APCs in AEDS-affected skin is the presence of the high-affinity receptor for IgE, FcεRI, on the cell surface [19]. FcεRI is central in mediating immunoregulatory signals into the cell upon ligation by complexed IgE. In addition, as the binding of allergen-IgE complexes on FcεRI represents the very first event of the immune cascade, this receptor provides a key to the onset and propagation of allergic diseases. Upon binding of polyvalent antigens by receptor-bound IgE, FcεRI forms aggregates and triggers cellular activation. Distinct mediators are subsequently released that critically determine the outcome of the immune response (see Fig. 1).

Structure of FcεRI

On effector cells of anaphylaxis such as mast cells and basophils, the 'classic' tetrameric FcεRI consisting of an α-chain, one β-chain and two disulfide linked γ-chains, is constitutively expressed. By contrast, a trimeric form of FcεRI (αγ₂) is variably expressed on LCs, IDECs, DCs and monocytes. The α-chain of FcεRI allows the binding of IgE, the β-chain increases stability and maturation and increases the signalling capacity of the receptor. The γ-chain dimer, which is also shared by other Fc receptors, has a common immunoreceptor tyrosine-based activation motif with the β-chain and is thought to be involved in signal transduction. Although the receptors on APCs lack the β-chain, they are fully functional [20].

Regulation of FcεRI surface expression

FcεRI surface expression on APCs is positively associated with the atopic status of the individual. It is

expressed on in-vitro generated DCs from atopic donors, whereas on DCs from non-atopic donors it is nearly absent. Recently, evidence for a differential expression of the γ-chain of FcεRI in the DCs of atopic versus non-atopic donors could be established [21**]. For trimeric FcεRI surface expression intracellular assembly of the α- and γ-chains of the receptor seems to be of major importance. In the endoplasmic reticulum (ER), folding and core glycosylation of an immature FcεRIα-chain occurs followed by cleaving of the terminal glucose residues. The transport of immature FcεRIα-chains from the ER to the Golgi compartment is influenced by the proper cleaving after glycosylation and combining with the γ-chains. In non-atopic donors, intracellular expression of the γ-chains is weak, leading to the accumulation of immature α-chains in the ER. In atopic donors, expression of the γ-chains is sufficiently upregulated allowing combination with the α-chain and FcεRI surface expression. This finding is of considerable interest for elucidating the pathophysiology of IgE-mediated DC functions in AEDS. In addition, the modulation of FcεRIγ-chain expression in DCs may lead to possible treatment options for atopic diseases.

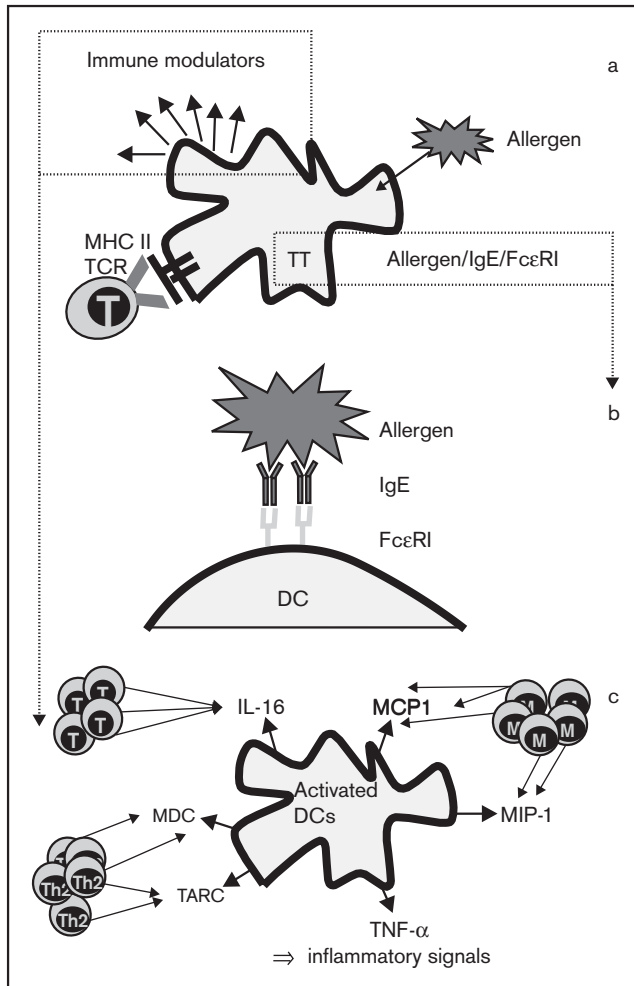
Dendritic cells and the sensitization phase

After encountering an allergen, 2 distinct phases can be distinguished. First is the sensitization phase, where DCs take up the allergen for the first time and migrate to regional lymph nodes. There they prime naïve T cells, which develop into effector cells and T memory cells. The second phase is the elicitation phase, in which, on a second encounter of an allergen, induction of inflammatory and regulatory reactions take place.

Role of FcεRI during antigen uptake

In the phase of sensitization, DCs take up allergen for the first time and migrate to regional lymph nodes. To internalize high molecular weight molecules of pollens or dust mites, receptor-mediated endocytosis or unspecific macropinocytosis is probably used by DCs [22]. FcεRI on LCs and DCs may play an important role during the sensitization phase besides its role in the effector phase of IgE-mediated hypersensitivity reactions. The complex of allergen-specific IgE is fixed on FcεRI of APCs and internalized for efficient processing [23]. In the process of intracellular degradation and assembly, the unmasking of hidden epitopes of this allergen may arise and lead to a variety of antigenic peptides. Some of these unmasked peptides may share molecular homology to peptides from unrelated allergens, a process called molecular mimicry. Subsequently, DCs or LCs might activate naïve T cells with a different T-cell receptor repertoire. This in turn may lead to a widening of the IgE spectrum because of the homology of epitopes, or may lead to the crossreactivity of IgE between different allergens.

Figure 1. Immunomodulatory consequences of dendritic cell activation in donors with atopic eczema/dermatitis syndrome



(a) Dendritic cells (DCs) are activated upon FcεRI crosslinking by allergen-bound IgE. This causes enhanced presentation of allergen peptides to T cells, and leads to the secretion of immunomodulatory cytokines. (b) FcεRI crosslinking by allergen-bound IgE. (c) Activated DCs from an atopic genetic background seem to exert their pro-inflammatory role twofold: matured DCs polarize naïve T cells into T helper type 2 cells and chemotactic cytokines selectively attract T helper type 2 cells to inflammatory sites. M, Monocytes; MCP-1, monocyte chemoattractant protein 1; MDC, macrophage-derived cytokine; MHC, major histocompatibility complex class II; MIP-1, macrophage inhibitory protein 1; TARC, thymus and activation-regulated chemokine; TCR, T-cell receptor.

Migration

The migration of leukocytes to and from inflammatory sites depends on a cascade of discrete events, partly mediated by chemokines and their receptors [24]. Chemokines are mainly released from activated APCs themselves and from surrounding keratinocytes. Immature DCs express a chemokine receptor profile (CCR1, CCR2, CCR5 and CCR6) that reacts with chemokines released at the inflammatory site [25]. Maturing DCs that have captured antigens upregulate constitutively

expressed chemokine receptors such as CXCR4, CCR4, and CCR7 [26]. Concomitantly, the downregulation of cognate receptors occurs.

LC-derived IL-16 has been found to be produced in skin from AEDS patients, where it acts as a strong migratory signal for CD4 T helper type 2 cells into the epidermis [27•]. The engagement of FcεRI on LCs further upregulates IL-16 production of these cells and thus contributes to the inflammation in AEDS. Importantly, only recently it has been shown that human keratinocytes from the epidermal skin of AEDS patients express human thymic stromal lymphopoietin (TSLP), a protein that activates CD11c-positive DCs to produce thymus and activation-regulated chemokine (or CCL17) and macrophage-derived chemokine (MDC or CCL22), which directly attract T helper type 2 cells [28•]. In addition, TSLP is involved in the activation and emigration of LCs from the epidermis. It also plays a role in the recruitment of LC precursors into the dermis because the production of TSLP is associated with the appearance of dermal Langerin-positive DCs. The migration of LC precursors into the epidermis seems to be selectively regulated by macrophage inflammatory protein 3α [29•]. These data provide evidence for a tight interaction of human epithelial cells, DCs and T helper type 2 cells in triggering allergic inflammation in AEDS.

Dendritic cells and lymphocyte responses in the atopic eczema/dermatitis syndrome

T helper type 2 cells and DCs are implicated in playing key roles in the upstream steps of allergic inflammation, whereas mast cells, basophils, and eosinophils are effector cells. Atopic individuals show an inherited preference for T helper type 2 responses. The exact molecular mechanisms, however, and cellular events enabling DCs to achieve this polarization are unknown [30].

Recently, investigations shed new light on the mechanism whereby atopic tissues contribute to the pathophysiology of allergic inflammation. Keratinocytes in AEDS lesions activate DCs via TSLP, which results in the strong proliferation and activation of naïve T cells [28•]. These T cells are primed to produce high amounts of IL-13, IL-15 and TNF-α, moderate levels of IL-4, and no or very low levels of IL-10 and IFN-γ. IL-13 acts as a possible differentiation factor towards T helper type 2 cells in the cutaneous microenvironment [31•]. The production of IL-10 in airway inflammation is associated with the development of allergen-specific regulatory T cells and not necessarily with the presence of classic T helper type 2 cells [32]. In addition, these regulatory IL-10-producing T cells confer protection against airway inflammation instead of inducing it. Taken together, TSLP-activated DCs seem to play a key role for the polarization and attraction of pro-allergic T cells.

Apart from these functions that are exerted on T cells, IL-4 and IL-13 are principal mediators promoting B-cell antibody class switching to IgE, and are therefore key initiators of IgE-mediated diseases [33]. Allergen-specific IgE binds to FcεRI on effector cells of anaphylaxis and on APCs in the epidermis–dermis and airway mucosa.

It was believed that after an initial acute phase of AEDS involving mainly T helper type 2 cells, a switch to IFN-γ-producing T helper type 1 cells occurs in chronically affected skin. A new concept arises if the above-described TSLP-activated CD11c-positive DCs are taken into account. In addition to facilitating the proliferation of CD4 T cells, naïve CD8 T cells also respond to this signal [34•]. The triggering of TSLP-activated DCs by CD40L seems to induce cytolytic CD8 T cells that produce large amounts of IFN-γ. Therefore, CD40L-expressing DCs activated by TSLP may participate in the chronicity of AEDS and cause tissue damage by the generation of IFN-γ.

The elicitation phase

After a second encounter of an allergen, memory T cells and IgE bound to FcεRI on tissue APCs and effector cells rapidly respond to known antigenic structures. FcεRI^{high} IDECs are known to respond with large quantities of chemoattractive and inflammatory cytokines after receptor crosslinking occurs [17•]. Monocyte chemoattractant protein 1, macrophage inflammatory protein 1, TNF-α and others are released that attract more APCs to the site of inflammation [35]. In addition to other known FcεRI-facilitated effector mechanisms such as antigen uptake, antigen presentation and an increase in APC stimulatory capacity, DC activation in allergy results from various sources and surrounding stromal cells seem to be critically involved.

Conclusion

The activation of DCs appears to be a critical step in the pathogenesis of T helper type 2-mediated allergic inflammation such as AEDS. The high affinity receptor for IgE, FcεRI, as well as defined mediators of epithelial cells seem to be critically involved in this step. The blocking of important mediators or functionally relevant structures linked to the pathophysiology of AEDS should lead to successful strategies for attenuating the severity of allergic disease.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

- 1 Schultz-Larsen F, Hanifin JM. Epidemiology of atopic dermatitis. *Immunol Allergy Clin North Am* 2002; 22:1–24.
- 2 Leung D, Bieber T. Atopic dermatitis. *Lancet* 2003; 361:151–160.
- An excellent and comprehensive review about atopic dermatitis with current data.
- 3 Cookson W. Genetics and genomics of asthma and allergic diseases. *Immunol Rev* 2002; 190:195–206.
- This review is extraordinarily informative about the inheritability of AEDS.
- 4 Sherrif Q, Golding J, Alspac Study Team. Hygiene levels in a contemporary population cohort are associated with wheezing and atopic eczema in preschool infants. *Arch Dis Child* 2002; 87:26–29.
- 5 Akbari O, Stock P, DeKruyff R, et al. Mucosal tolerance and immunity: regulating the development of allergic disease and asthma. *Int Arch Allergy Immunol* 2003; 130:108–118.
- T-cell tolerance against allergens is mediated by regulatory T cells. ICOSL (inducible costimulatory molecule ligand) and B7.2 co-stimulatory signalling in DCs preferentially leads to the production of IL-10 from DCs. These events induce regulatory T cells, which downregulate T helper types 1 and 2 function.
- 6 Jones C, Holloway J, Popplewell E, et al. Reduced soluble CD14 levels in amniotic fluid and breast milk are associated with the subsequent development of atopy, eczema, or both. *J Allergy Clin Immunol* 2002; 109:858–866.
- 7 Forrest S, Dunn K, Elliott K, et al. Identifying genes predisposing to atopic eczema. *J Allergy Clin Immunol* 1999; 104:1066–1070.
- 8 Novak N, Kruse S, Kraft S, et al. 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.
- This paper shows that extrinsic and intrinsic atopic dermatitis individuals may differ genetically.
- 9 Kraft S, Wessendorf JH, Haberkost J, et al. Enhanced expression and activity of protein-tyrosine kinases establishes a functional signaling pathway only in FcεRI^{high} Langerhans cells from atopic individuals. *J Invest Dermatol* 2002; 119:804–811.
- 10 Dermott R, Ziyhan U, Spehner D, et al. Birbeck granules are subdomains of endosomal recycling compartment in human epidermal Langerhans cells, which form where Langerin accumulates. *Mol Biol Cell* 2002; 13:317–335.
- The authors demonstrate that Birbeck granules are not endocytotic structures, but subdomains of the endosomal recycling compartment that forms where Langerin accumulates.
- 11 Merad M, Manz M, Karsunky H, et al. Langerhans cells renew in the skin throughout life under steady-state conditions. *Nat Immunol* 2002; 3:1135–1141.
- The authors show that LCs, in the absence of inflammation, are maintained locally in the skin. Upon inflammation, however, LC precursors renew in the skin within 2 weeks and are recruited from blood.
- 12 Soilleux EJ, Morris LS, Leslie G, et al. Constitutive and induced expression of DC-SIGN on dendritic cell and macrophage subpopulations *in situ* and *in vitro*. *J Leukoc Biol* 2002; 71:445–457.
- 13 Wollenberg A, Wagner M, Gunther S, et al. Plasmacytoid dendritic cells: a new cutaneous dendritic cell subset with distinct role in inflammatory skin diseases. *J Invest Dermatol* 2002; 119:1096–1102.
- This is a demonstration that plasmacytoid DCs seem to be absent in skin from AEDS lesions.
- 14 Mazzoni Q, Leifer CA, Mullen GE, et al. Cutting edge: histamine inhibits IFN-α release from plasmacytoid dendritic cells. *J Immunol* 2003; 170:2267–2273.
- 15 Wollenberg A, Bieber T. Antigen-presenting cells. In: Bieber T, Leung DYM, editors. *Atopic dermatitis*. New York: Marcel Dekker; 2002. pp. 267–283.
- 16 Wollenberg A, Mommaas M, Oppel T, et al. Expression and function of the mannose receptor on epidermal dendritic cells in inflammatory skin diseases. *J Invest Dermatol* 2002; 118:327–334.
- 17 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; 111:869–874.
- This investigation clearly demonstrated that IDECs are main players of AEDS.
- 18 Novak N, Kraft S, Haberkost J, et al. A reducing microenvironment leads to the generation of FcεRI^{high} inflammatory dendritic epidermal cells (IDEC). *J Invest Dermatol* 2002; 119:842–849.
- 19 Novak N, Kraft S, Bieber T. Unraveling the mission of FcεpsilonRI on antigen-presenting cells. *J Allergy Clin Immunol* 2003; 111:38–44.
- 20 Kraft S, Novak N, Katoh N, et al. Aggregation of the high-affinity IgE receptor FcεRI on human monocytes and dendritic cells induces NF-κB activation. *J Invest Dermatol* 2002; 118: 830–837.

- 21 Novak N, Tepel C, Koch S, *et al.* Evidence for a differential expression of the •• FcεR1γ chain in dendritic cells of atopic and nonatopic donors. *J Clin Invest* 2003; 111:1047–1056.

This is the first demonstration that FcεR1γ-chain expression is altered in atopic individuals, which accounts for elevated receptor surface expression.

- 22 Maurer T, Heit A, Hochrein H, *et al.* CpG-DNA aided cross-presentation of soluble antigens by dendritic cells. *Eur J Immunol* 2002; 32:2356–2364.
- 23 Galli E, Cicconi R, Rossi P, *et al.* Atopic dermatitis: molecular mechanisms, clinical aspects and new therapeutical approaches. *Curr Mol Med* 2003; 3:127–138.
- 24 Sebastiani S, Albanesi C, Nasorri F, *et al.* Nickel-specific CD4(+) and CD8(+) T cells display distinct migratory responses to chemokines produced during allergic contact dermatitis. *J Invest Dermatol* 2002; 118:1052–1058.
- 25 Vanbervliet B, Homey B, Durand I, *et al.* Sequential involvement of CCR2 and CCR6 ligands for immature dendritic cell recruitment: possible role at inflamed epithelial surfaces. *Eur J Immunol* 2002; 32:231–242.
- 26 Ardeshtna KM, Pizzey AR, Walker SJ, *et al.* The upregulation of CC chemokine receptor 7 and the increased migration of maturing dendritic cells to macrophage inflammatory protein 3β and secondary lymphoid chemokine is mediated by the p38 stress-activated protein kinase pathway. *Br J Haematol* 2002; 119:826–829.
- 27 Reich K, Hugo S, Middel P, *et al.* Evidence for a role of Langerhans cell-derived IL-16 in atopic dermatitis. *J Allergy Clin Immunol* 2002; 109:681–687.

See Ref. [28••].

- 28 Soumelis V, Reche P, Kanzler H, *et al.* Human epithelial cells trigger dendritic •• cell-mediated allergic inflammation by producing TSLP. *Nature Immunol* 2002; 3:673–680.

These two papers [27••,28••] provide direct evidence that LCs and keratinocytes of lesional AEDS skin contributes substantially to the recruitment of allergen-specific T helper type 2 cells into the epidermis.

- 29 Caux C, Vanbervliet B, Massacrier C, *et al.* Regulation of dendritic cell • recruitment by chemokines. *Transplantation* 2002; 73(1 Suppl.):S7–S11. This is a direct demonstration of how LC precursors are selectively attracted by macrophage inflammatory protein 3α.

- 30 Larche M, Robinson DS, Kay AB. The role of T lymphocytes in the pathogenesis of asthma. *J Allergy Clin Immunol* 2003; 111:450–463.

- 31 Herrick CA, Xu L, McKenzie AN, *et al.* IL-13 is necessary, not simply • sufficient, for epicutaneously induced Th2 responses to soluble protein antigen. *J Immunol* 2003; 170:2488–2495.

This study demonstrates the requirement of the cytokine IL-13 for the recruitment of antigen-specific T helper type 2 cells into the epidermis.

- 32 Zuany-Amorim C, Sawicka E, Manlius C, *et al.* Suppression of airway eosinophilia by killed *Mycobacterium vaccae*-induced allergen-specific regulatory T-cells. *Nat Med* 2002; 8:625–629.

- 33 Tangye SG, Ferguson A, Avery DT, *et al.* Isotype switching by human B cells is division-associated and regulated by cytokines. *J Immunol* 2002; 169:4298–4306.

- 34 Gilliet M, Soumelis V, Watanabe N, *et al.* Human dendritic cells activated by •• TSLP and CD40L induce proallergic cytotoxic T cells. *J Exp Med* 2003; 196:1059–1063.

The authors provide an explanation for the observed increase of IFN-γ in chronic lesions of AEDS. CD40L-expressing DCs activated by TSLP seem to induce cytolytic CD8 T cells, thus promoting tissue damage by the production of IFN-γ.

- 35 Eglite S, Morin JM, Metzger H. Synthesis and secretion of monocyte chemotactic protein-1 stimulated by the high affinity receptor for IgE. *J Immunol* 2003; 170:2680–2687.