

News from dendritic cells in atopic dermatitis

Knut Schäkel and Anja Hänsel

Department of Dermatology, University Hospital
Heidelberg, Heidelberg, Germany

Correspondence to Professor Dr Knut Schäkel, MD,
Department of Dermatology, University Hospital,
Voßstr. 2, 69115 Heidelberg, Germany
Tel: +49 6221 568447; fax: +49 6221 568449;
e-mail: knut.schaekel@med.uni-heidelberg.de

**Current Opinion in Allergy and Clinical
Immunology** 2011, 11:000–000

Purpose of review

Dendritic cells are essential for the generation of innate and adaptive immune responses, which makes them stay on center stage when studying the immunopathogenesis of atopic dermatitis. This review will discuss recent findings on the role of dendritic cells subsets in atopic dermatitis and will report novel findings on how the microenvironment conditions dendritic cells to fuel atopic dermatitis.

Recent findings

Several microenvironmental factors characteristic for atopic dermatitis and with direct relevance for the disease have been defined. We now increasingly understand how thymic stromal lymphopoietin and histamine contribute to the disease by modulating the function of dendritic cells. We have learned much about the pathogenesis of atopic dermatitis by the studies on inflammatory dendritic epidermal cells. However, the current analysis on the functional and phenotypic heterogeneity of dendritic cells in eczematous skin lesions may lead to the definition of additional dendritic cell types relevant in the pathogenesis of atopic dermatitis. In this respect, it appears interesting to further discuss the parallels and differences in atopic dermatitis and psoriasis.

Summary

Understanding the heterogeneity of dendritic cells and their functional alteration by local factors in the inflamed skin will provide essential clues to the immunopathogenesis of atopic dermatitis.

Keywords

atopic dermatitis, dendritic cells, thymic stromal lymphopoietin, histamine, dermal dendritic cells

Curr Opin Allergy Clin Immunol 11:000–000
© 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins
1528-4050

Introduction

Dendritic cells stand out by their unique capacity of priming naive T cells to become effector cells. In order to function as professional antigen presenting cells, dendritic cells have an efficient machinery to present high levels of major histocompatibility complex (MHC) molecules charged with antigenic peptides, which serves as the antigen-specific signal 1. In addition, the expression of very high levels of costimulatory molecules enables dendritic cells to activate naive T cells and provides the second signal. The cytokine production of dendritic cells and the balance between the expression of different costimulatory and inhibitory molecules (signal 3) determines the quality of the stimulation and thereby determines the differentiation of T cells in more or less functionally fixed subsets, Th1, Th2, regulatory T cells (Treg), Th17 and others.

In a broader view, DCs orchestrate immune responses for the defence of our body against invading pathogenic micro-organisms. In the steady state, regulatory mech-

anisms of epithelial cells are keeping up with low level activating signals. In chronic inflammatory diseases, dendritic cells can become misguided by a stimulatory microenvironment and drive harmful immune responses. This may also apply to atopic dermatitis, a chronic inflammatory skin disease affecting many children (10–20%) and adults (1–3%). The local skin microenvironment in atopic dermatitis is the result of epidermal barrier defects and genetically fixed immune abnormalities. An important component of the epidermal barrier is filaggrin. During the maturation of keratinocytes, filaggrin aggregates keratin filaments into keratin fibrils. When filaggrin is proteolytically degraded, it serves as an osmolyte and accounts for the corneocyte hydration. Epidemiologic studies have shown that mutations in filaggrin pose an increased risk of early onset, severe, persistent atopic dermatitis and an increased risk of asthma [1]. It is on the one hand that a defective skin barrier allows allergens as well as pathogenic microbes to penetrate it. Once the epidermal barrier is conquered, allergens can induce immune activation by their enzymatic activity and allergens as well as microbes activate the innate immune defence by

their stimulation of pattern recognition receptors like toll-like receptors (TLR). However, this TLR-triggered immune response appears deficient in patients with atopic dermatitis. Many patients carry TLR-2 polymorphisms and show a reduced clearance of *Staphylococcus aureus* from the skin. This is in line with in-vitro observations of a reduced production of proinflammatory cytokines when the patient's macrophages are stimulated with toll-like receptor 2 ligands. Furthermore, when compared with psoriasis, the expression of antimicrobial peptides is reduced in atopic dermatitis and can lead to an increased bacterial colonization. We also have to take into account that the skin in atopic dermatitis is severely damaged by the scratching due to excessive pruritus. This mechanical damage often completely disrupts the epidermal barrier, creates inflammation by generating additional autologous danger signals and stimulates keratinocytes to produce the proallergic cytokine thymic stromal lymphopoietin (TSLP) [2,3^{*}]. So even in the absence of an ongoing local antigen-specific and T cell-mediated immune response, the skin microenvironment in atopic dermatitis is highly stimulatory for dendritic cells. Dendritic cells are built to integrate these signals and they have an extensive inherent functional plasticity. Dendritic cells are heterogeneous and individual dendritic cell subtypes, are differentially distributed in tissues, express distinct sets of pattern recognition receptors and also differ in their capacity to program naive T cells.

Epidermal dendritic cells

Langerhans cells are located in the epidermis and are the first line of a cellular immune defense in the skin. Here they form a network of cells that sample antigens getting through the skin barrier. Langerhans cells are CD1a⁺ and contain characteristic Langerin⁺ Birbeck granules [4]. Chorro *et al.* [5] recently reported on the precursors of Langerhans cells. They could show that Langerhans cell precursors (CD115⁺, CD135⁺, CD11b⁺, CD45⁺, CX₃CR1⁺) in mice enter the epidermis before birth and acquire a dendritic morphology and the expression of MHC II, CD11c, and Langerin immediately after birth. These cells undergo a massive burst of proliferation between day 2 and 7 after birth, expanding their numbers by 10–20-fold. A low level of Langerhans cell proliferation (3–4%) was also evident in human epidermis of adults. Interestingly, the authors also studied two patients with atopic dermatitis in which they could demonstrate a three to four times increased percentage of proliferating Langerhans cells. Schuster *et al.* [6] found that CD45⁺HLA-DR^(high)CD1c⁺ dendritic cells are already present in the epidermis and dermis at 9 week estimated gestational age and that transforming growth factor β1 production precedes Langerin and CD1a expression on CD45⁺CD1c⁺ Langerhans cell precursors.

Key points

- We now increasingly understand how thymic stromal lymphopoietin contribute to the disease by modulating the function of dendritic cells.
- Histamine signaling through the histamine receptor 1 and histamine receptor 4 on dendritic cells results in a strong anti-inflammatory activity and promotes Th2 programming.
- The functional and phenotypic heterogeneity of dendritic cells in eczematous skin lesions is increasingly recognized.

In atopic dermatitis, Langerhans cells express the high-affinity IgE receptor (FcεRI), and internalize IgE-bound allergens for their presentation to T cells [7].

The number of Langerhans cells (CD207⁺, CD1a⁺) appear similar in healthy skin and in atopic dermatitis [8]. Atopic dermatitis harbours a population of CD1a⁺, CD207⁺ dendritic cell inflammatory dendritic epidermal cells as reported by Schuller *et al.* [9]. These cells are identified by flow cytometry in epidermal/dermal cell suspensions by their expression of CD1a and the absence of CD207. Although initially described by Schuller *et al.* in the epidermis, some authors regard them rather as a population of inflammatory dermal dendritic cells [8,10]. This cell type is found in atopic dermatitis but not in significant number in psoriasis or healthy skin.

Little is known about the traffic of Langerhans cells to the inflamed epidermis and dermis. Gros *et al.* [11] studied shave biopsies from chronic atopic dermatitis skin lesions as well from skin lesions developing after cutaneous application of house dust mite allergen (atopy patch test). During the development of an allergen-induced eczematous skin lesion, they observed a decrease in the Langerhans cell numbers. The number of CD1a⁺, CD207⁺ dendritic cells increased. Among the chemokine receptors tested, a strong expression CCR5 and CCR6 was found.

Acanthosis is a hallmark in atopic dermatitis and particularly in psoriasis. IL-22 is held responsible for inducing acanthosis in psoriasis [12–15]. Also in atopic dermatitis IL-22-producing CD4⁺ and CD8⁺ T cells were found. Nograles *et al.* [16] provided evidence that Langerhans cells are strong inducers of IL-22-producing T cells [17]. These IL-22-producing T cells were either CD4 or CD8 positive and the majority of them lacked the production of IL-17, IFN-γ, and IL-4 and are, therefore, regarded as T22 cells [18].

Dermal dendritic cells

Based on the expression of a number of surface markers we can now differentiate between different populations

of myeloid dendritic cells. They can be identified by their expression of CD11c and the expression of either CD1c⁺ or CD14⁺. The population of CD1c⁺ dendritic cells were termed resident dendritic cells, as their frequency remains fairly constant in healthy skin and in lesional psoriasis [19]. CD14⁺ dendritic cells primed CD4⁺ T cells into cells that induce naive B cells to switch isotype and become plasma cells. With the help of slan (6-sulfo LacNAc)-specific monoclonal antibodies, our group has identified an additional population of myeloid dendritic cells in healthy skin and psoriasis (Günther *et al.* submitted), [20]. These cells appear to differ from the other dendritic cells so far described in the skin as they lack expression of CD1c and CD14 as well as the haemoglobin scavenger receptor CD163. CD163 is used as a marker for macrophages [20]. The role of CD1c⁺ dendritic cells, CD14⁺ dendritic cells or slan-dendritic cells in atopic dermatitis is yet to be determined.

An in-depth phenotypic analysis of dendritic cells in skin lesions of patients with atopic dermatitis was performed by Guttman-Yassky *et al.* [10]. Dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin (DC-SIGN) was the most abundantly expressed dendritic cell/macrophage marker in the dermis. DC-SIGN positive cells also expressed the mannose receptor (CD206) and may represent a population of macrophages or dendritic cells. These cells may be relevant for stimulating a local inflammatory immune response as they were outnumbering CD3⁺ T cells in the inflamed skin. In psoriasis DC-SIGN⁺, CD206⁺, CD163⁺ macrophages were shown to frequently express TNF- α in situ and thereby appear to be important for stimulating the local inflammatory response [21]. These dendritic cell/macrophage-like cells were found scattered throughout the dermis in atopic dermatitis [10]. Only few mature CD83⁺, DC-Lamp⁺ dendritic cells were identified in atopic dermatitis and they strictly localized in clusters also containing T cells. Although interesting as an observation, we unfortunately know very little about the topography of immune cells in the dermis so far.

Plasmacytoid dendritic cells

Plasmacytoid dendritic cells (pDCs) are characterized as CD123⁺, BDCA-2⁺, CD11c⁻ cells [22]. They are distributed in peripheral tissues and lymph nodes and present antigens to T cells [23]. pDCs appear important for the defence against viral infections, as they produce high amounts of type I IFNs (IFN- α/β) when stimulated with viral nucleic acids through TLR7 and TLR9 [24]. Type I IFNs have been implicated in the pathogenesis of systemic lupus erythematosus and psoriasis, in which pDCs have been described [25,26].

In atopic dermatitis, the frequency of pDCs in the dermis is increased as determined by staining skin section for BDCA-2 or CD123 [8,10]. pDCs were absent in the epidermis but accounted for roughly one-third of the dermal dendritic cells. A significant proportion of these cells (20–40%) were activated as revealed by their expression of CD80, CD86 and CD40. The role of pDCs in atopic dermatitis is not completely understood. pDCs from patients with atopic dermatitis were shown to express Fc ϵ RI occupied by IgE. Cross-linking of IgE on pDC largely attenuated their proinflammatory capacity. Specifically, it induced the production of IL-10, reduced the levels of IFN- α/β and supported a Th2 response [27]. This is true for dendritic cells activated by TLR9 ligands, a pattern recognition receptor for DNA-viruses, and were basically reproduced and extended by a recent study by Gill *et al.* [28^{*}] using Fc ϵ RI⁺ pDCs from patients with allergic asthma, stimulated with TLR7-ligands derived from influenza virus. This Fc ϵ RI-dependent inhibition of IFN- α production of pDCs in patients with atopic dermatitis may in part explain the risk of patients with severe atopic dermatitis to develop widespread herpes simplex infection.

Lessons from the microenvironment: thymic stromal lymphopoietin, histamine and IL-31

Severe pruritus is a hallmark of atopic dermatitis. Scratching in response to pruritus leads to wounding and severe mechanical injury of the skin. Antigen application to skin mechanically injured by tape stripping is known to result in Th2-dominated skin inflammation in mice. In this model, Oyoshi *et al.* [29^{*}] now provided the direct link between the mechanical injury, the induction of TSLP, and the programming of Th2 cells by dendritic cells exposed to TSLP in the tape stripped skin. Therefore, scratching in patients with atopic dermatitis can serve as adjuvants for the induction of Th2-responses to antigens present in the skin.

Hulse *et al.* [30^{**}] could show that in-vitro generated monocyte derived dendritic cells express only low levels of the TSLP-receptor. TSLP in their hands exerted only weak Th2-promoting effects. Interestingly, TSLP-receptor expression was strongly induced by cross-linking of Fc ϵ RI. Consequently, targeting the antigen to Fc ϵ RI in the presence of TSLP led to a strong induction of Th2 cells. Therefore, this study establishes an important proallergic role for TSLP, especially in the context of dendritic cells conditioned by cross-linking of their Fc ϵ RI by allergens.

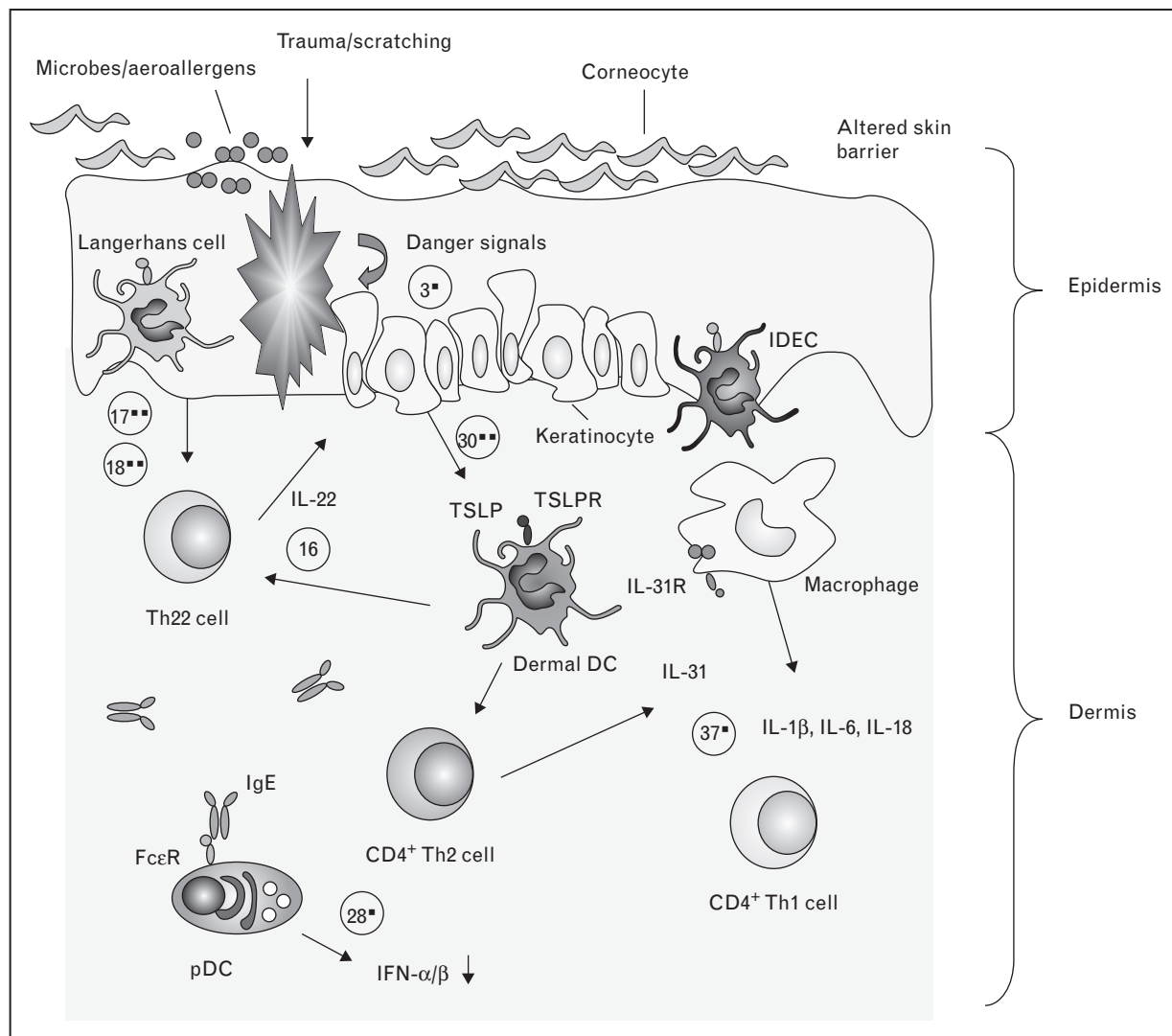
TSLP may also be induced by an air-borne pollutant, as revealed by Shigeno *et al.* [31]. These authors show that dibutyl phthalate when used as a solvent for an allergen [fluoresceinisothiocyanat (FITC)] induced TSLP. This

solvent-induced TSLP production served as a critical bias for the induction of a Th2-dependent contact allergic response.

An inhibition of the proallergic TSLP-function was described by Jung *et al.* [32]. They could show that agonists of the peroxisome proliferator-activated receptor gamma (PPAR γ) inhibited proinflammatory effects of TSLP. In their experiments, the PPAR γ agonist rosiglitazone prevented the onset and exacerbation of atopic dermatitis in NC/Tnd mice. These effects could be attributed to the action PPAR γ agonists on the level of dendritic cells.

Histamine is a long studied and classic mediator of allergic skin inflammation mainly released by mast cells and basophils. Both cell types as well as histamine are increased in atopic dermatitis. Histamine mediates its effects through four receptors (histamine Receptors 1–4). Vanbervliet *et al.* [33] studied the relevance of the histamine receptor 1(HR1) in the context of dendritic cells and skin inflammation. They demonstrated that histamine signaling through the HR1 on dendritic cells in mice is an important early event in the induction of an atopic-like dermatitis. Specifically, they could show that the lack of HR1 expression on dendritic cells led to

Figure 1 Network of dendritic cell-subsets in atopic dermatitis



Trauma and scratching lead to a disrupted skin barrier and enable allergens and microbes to enter the skin in atopic dermatitis patients. Flagellin and host-derived danger signals (RNA, DNA) induce the expression of TSLP in keratinocytes [3*]. A simultaneous stimulation of dendritic cells with allergen targeted to Fc ϵ R1 and TSLP enhance the Th2-response [30**]. Langerhans cells as well as dermal dendritic cells preferentially induce Th22 cells [17,18]. IL-22 delays keratinocyte differentiation and causes acanthosis [16]. Besides Langerhans cells and IDECs, pDCs express the high-affinity Fc ϵ R1. Moreover, IgE cross-linking prior to viral challenge results in an abrogated IFN- α release by pDCs and a diminished viral-induced TLR7-upregulation in pDCs [28*]. IL-31, a cytokine released by T cells following activation, induced the production of proinflammatory cytokines in macrophages [37*].

diminished IL-12, upregulated IL-23, and IL-6 production upon allergen stimulation.

Other studies focussed on the relevance of the histamine H4 receptor being strongly expressed on dendritic cells. The histamine receptor 4 (HR4) mediates strong immune regulatory effects in that it modulates cytokine production, chemotaxis and chemokine expression. Cowden *et al.* [34[•]] have studied the role of the HR4 in a model of FITC-mediated contact allergy model, a Th2-cell-mediated mouse inflammation model that mimics features of atopic dermatitis. Blocking HR4-signalling with two different HR4-antagonist had a strong anti-inflammatory activity with reduced dendritic cell migration to lymph nodes and reduced IL-4, IL-5 and IL-17 levels when restimulating lymph node T cells. In-vitro stimulation of the HR4 is known to result in chemotaxis and a reduced IL-12 production of in-vitro generated monocyte derived dendritic cells. Gschwandtner *et al.* [35] now studied a population of proinflammatory native human dermal dendritic cells. These dendritic cells are best characterized by their expression of slan (6-sulfo LacNAc), which is expressed on the P-selectin glycoprotein ligand 1 [36]. Interestingly, the HR4 was upregulated in atopic dermatitis in response to IFN- γ . Stimulation of HR4 on slan-dendritic cells induced a substantial downregulation of TNF- α and IL-12. These data strengthen the role of the HR4 as a therapeutic target in atopic dermatitis.

A study by Kasraie *et al.* [37[•]] provides a new link between staphylococcal colonization and the sensitivity for IL-31. IL-31 is a T cell-derived cytokine associated with atopic dermatitis [38,39]. Mice overexpressing IL-31 developed skin inflammation, pruritus and severe dermatitis [40]. Focussing on human monocytes and macrophages, the authors could show that staphylococcal exotoxins significantly upregulated IL-31RA expression on monocytes and macrophages. Furthermore, IL-31 stimulation of monocytes pretreated with staphylococcal exotoxins strongly enhanced the secretion of IL-1 β , IL-6 and IL-18 and upregulated the expression of the costimulatory molecule CD86.

Conclusion

Atopic dermatitis is one of the most important dermatologic diseases with a complex, not completely understood immunopathology.

Acquired and genetically fixed reductions of the skin barrier together with local trauma due to scratching predispose to an abnormal microclimate in the skin. These local changes lead to an increased recruitment and functional modulation of different subsets of dendritic cells and macrophages (Fig. 1) [3[•],16–18,28[•],30^{••},37[•]]. The

responsiveness of dendritic cell to TSLP, histamine and their expression of the high-affinity IgE receptor (Fc ϵ RI) are characteristic features of dendritic cells in atopic dermatitis that foster the Th2-dominated allergic inflammation. Although the functional heterogeneity of dendritic cells in atopic dermatitis as well as in other diseases such as psoriasis is increasingly recognized, more work is required to define how dendritic cells as a whole orchestrate the chronic inflammation in atopic dermatitis.

Acknowledgements

This work was supported in part by grants from the German Research Council (DFG) SFB 938 to K.S.

Conflicts of interest

There is no conflict of interest.

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

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

- 1 Rodriguez E, Baurecht H, Herberich E, *et al.* Meta-analysis of filaggrin polymorphisms in eczema and asthma: robust risk factors in atopic disease. *J Allergy Clin Immunol* 2009; 123:1361–1370.
- 2 Ganguly D, Chamilos G, Lande R, *et al.* Self-RNA-antimicrobial peptide complexes activate human dendritic cells through TLR7 and TLR8. *J Exp Med* 2009; 206:1983–1994.
- 3 Le TA, Takai T, Vu AT, *et al.* Flagellin induces the expression of thymic stromal lymphopoietin in human keratinocytes via toll-like receptor 5. *Int Arch Allergy Immunol* 2011; 155:31–37.
- This article described Flagellin as a further trigger for the release of TSLP in keratinocytes via TLR5, which is enhanced by Th2/TNF cytokines.
- 4 Seiji M, Fitzpatrick TB, Birbeck MS. The melanosome: a distinctive subcellular particle of mammalian melanocytes and the site of melanogenesis. *J Invest Dermatol* 1961; 36:243–252; 243–252.
- 5 Chorro L, Sarde A, Li M, *et al.* Langerhans cell (LC) proliferation mediates neonatal development, homeostasis, and inflammation-associated expansion of the epidermal LC network. *J Exp Med* 2009; 206:3089–3100.
- 6 Schuster C, Vaculik C, Fiala C, *et al.* HLA-DR⁺ leukocytes acquire CD1 antigens in embryonic and fetal human skin and contain functional antigen-presenting cells. *J Exp Med* 2009; 206:169–181.
- 7 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.
- 8 Stary G, Bangert C, Stingl G, *et al.* Dendritic cells in atopic dermatitis: expression of Fc epsilon RI on two distinct inflammation-associated subsets. *Int Arch Allergy Immunol* 2005; 138:278–290.
- 9 Schuller E, Teichmann B, Haberstick J, *et al.* In-situ expression of the costimulatory molecules CD80 and CD86 on langerhans cells and inflammatory dendritic epidermal cells (IDEC) in atopic dermatitis. *Arch Dermatol Res* 2001; 293:448–454.
- 10 Guttman-Yassky E, Lowes MA, Fuentes-Duculan J, *et al.* Major differences in inflammatory dendritic cells and their products distinguish atopic dermatitis from psoriasis. *J Allergy Clin Immunol* 2007; 119:1210–1217.
- 11 Gros E, Bussmann C, Bieber T, *et al.* Expression of chemokines and chemokine receptors in lesional and nonlesional upper skin of patients with atopic dermatitis. *J Allergy Clin Immunol* 2009; 124:753–760.
- 12 Zheng Y, Danilenko DM, Valdez P, *et al.* Interleukin-22, a T(H)17 cytokine, mediates IL-23-induced dermal inflammation and acanthosis. *Nature* 2007; 445:648–651.
- 13 Sa SM, Valdez PA, Wu J, *et al.* The effects of IL-20 subfamily cytokines on reconstituted human epidermis suggest potential roles in cutaneous innate defense and pathogenic adaptive immunity in psoriasis. *J Immunol* 2007; 178:2229–2240.

- 14 Boniface K, Guignouard E, Pedretti N, *et al.* A role for T cell-derived interleukin 22 in psoriatic skin inflammation. *Clin Exp Immunol* 2007; 150:407–415.
 - 15 Ma HL, Liang S, Li J, *et al.* IL-22 is required for Th17 cell-mediated pathology in a mouse model of psoriasis-like skin inflammation. *J Clin Invest* 2008; 118:597–607.
 - 16 Nograles KE, Zaba LC, Guttman-Yassky E, *et al.* Th17 cytokines interleukin (IL)-17 and IL-22 modulate distinct inflammatory and keratinocyte-response pathways. *Br J Dermatol* 2008; 159:1092–1102.
 - 17 Nograles KE, Zaba LC, Shemer A, *et al.* IL-22-producing 'T22' T cells account for upregulated IL-22 in atopic dermatitis despite reduced IL-17-producing TH17 T cells. *J Allergy Clin Immunol* 2009; 123:1244–1252.
 - 18 Fujita H, Nograles KE, Kikuchi T, *et al.* Human Langerhans cells induce distinct IL-22-producing CD4⁺ T cells lacking IL-17 production. *Proc Natl Acad Sci U S A* 2009; 106:21795–21800.
 - 19 Zaba LC, Fuentes-Duculan J, Eungdamrong NJ, *et al.* Identification of TNF-related apoptosis-inducing ligand and other molecules that distinguish inflammatory from resident dendritic cells in patients with psoriasis. *J Allergy Clin Immunol* 2010; 125:1261–1268.
 - 20 Hänzel A, Günther C, Ingwersen J, *et al.* Human slan (6-sulfo LacNAc) dendritic cells are inflammatory dermal dendritic cells in psoriasis and drive strong TH17/TH1 T-cell responses. *J Allergy Clin Immunol* 2011; 127:787–794.
 - 21 Fuentes-Duculan J, Suarez-Farinas M, Zaba LC, *et al.* A subpopulation of CD163-positive macrophages is classically activated in psoriasis. *J Invest Dermatol* 2010; 130:2412–2422.
 - 22 Shortman K, Liu YJ. Mouse and human dendritic cell subtypes. *Nat Rev Immunol* 2002; 2:151–161.
 - 23 Ito T, Amakawa R, Inaba M, *et al.* Plasmacytoid dendritic cells regulate Th cell responses through OX40 ligand and type I IFNs. *J Immunol* 2004; 172:4253–4259.
 - 24 Gilliet M, Cao W, Liu YJ, *et al.* Plasmacytoid dendritic cells: sensing nucleic acids in viral infection and autoimmune diseases. *Nat Rev Immunol* 2008; 8:594–606.
 - 25 Lande R, Gregorio J, Facchinetti V, *et al.* Plasmacytoid dendritic cells sense self-DNA coupled with antimicrobial peptide. *Nature* 2007; 449:564–569.
 - 26 Pascual V, Farkas L, Banchereau J, *et al.* Systemic lupus erythematosus: all roads lead to type I interferons. *Curr Opin Immunol* 2006; 18:676–682.
 - 27 Novak N, Allam JP, Hagemann T, *et al.* Characterization of FcεpsilonRI-bearing CD123 blood dendritic cell antigen-2 plasmacytoid dendritic cells in atopic dermatitis. *J Allergy Clin Immunol* 2004; 114:364–370.
 - 28 Gill MA, Bajwa G, George TA, *et al.* Gruchalla RS: counterregulation between the FcεpsilonRI pathway and antiviral responses in human plasmacytoid dendritic cells. *J Immunol* 2010; 184:5999–6006.
- This article demonstrated the link between FcεRI and IFN-α pathways.
- 29 Oyoshi MK, Larson RP, Ziegler SF, *et al.* Mechanical injury polarizes skin dendritic cells to elicit a T(H)2 response by inducing cutaneous thymic stromal lymphopoietin expression. *J Allergy Clin Immunol* 2010; 126:976–984.
- This article showed that mechanical injury upregulates TSLP in the skin and polarize skin dendritic cells to elicit a Th2 response via the induction of IL-10.
- 30 Hulse KE, Reefer AJ, Engelhard VH, *et al.* Targeting allergen to FcγRIII reveals a novel T(H)2 regulatory pathway linked to thymic stromal lymphopoietin receptor. *J Allergy Clin Immunol* 2010; 125:247–256.
- The authors described a novel T(H)2 regulatory pathway linking FcγRI signaling to TSLP receptor upregulation.
- 31 Shigeno T, Katakuse M, Fujita T, *et al.* Phthalate ester-induced thymic stromal lymphopoietin mediates allergic dermatitis in mice. *Immunology* 2009; 128:e849–e857.
 - 32 Jung K, Tanaka A, Fujita H, *et al.* Peroxisome proliferator-activated receptor gamma-mediated suppression of dendritic cell function prevents the onset of atopic dermatitis in NC/Tnd mice. *J Allergy Clin Immunol* 2011; 127:420–429.
 - 33 Vanbervliet B, Driss-Vermare N, Massacrier C, *et al.* The inducible CXCR3 ligands control plasmacytoid dendritic cell responsiveness to the constitutive chemokine stromal cell-derived factor 1 (SDF-1)/CXCL12. *J Exp Med* 2003; 198:823–830.
 - 34 Cowden JM, Zhang M, Dunford PJ, *et al.* The histamine H4 receptor mediates inflammation and pruritus in Th2-dependent dermal inflammation. *J Invest Dermatol* 2010; 130:1023–1033.
- This article offers a new way for the treatment of Th2-mediated skin disorders by administering a H(4)R antagonist, which significantly inhibited the pruritus.
- 35 Gschwandtner M, Schäkel K, Werfel T, *et al.* Histamine H(4) receptor activation on human slan-dendritic cells down-regulates their pro-inflammatory capacity. *Immunology* 2011; 132:49–56.
 - 36 Schäkel K, Kannagi R, Kniep B, *et al.* 6-Sulfo LacNAc, a novel carbohydrate modification of PSGL-1, defines an inflammatory type of human dendritic cells. *Immunity* 2002; 17:289–301.
 - 37 Kasraie S, Niebuhr M, Werfel T, *et al.* Interleukin (IL)-31 induces pro-inflammatory cytokines in human monocytes and macrophages following stimulation with staphylococcal exotoxins. *Allergy* 2010; 65:712–721.
- A new link between staphylococcal colonization and the worsening of inflammation via IL-31 is described in this article.
- 38 Sonkoly E, Muller A, Lauerma AI, *et al.* IL-31: a new link between T cells and pruritus in atopic skin inflammation. *J Allergy Clin Immunol* 2006; 117:411–417.
 - 39 Bilsborough J, Leung DY, Maurer M, *et al.* IL-31 is associated with cutaneous lymphocyte antigen-positive skin homing T cells in patients with atopic dermatitis. *J Allergy Clin Immunol* 2006; 117:418–425.
 - 40 Dillon SR, Sprecher C, Hammond A, *et al.* Interleukin 31, a cytokine produced by activated T cells, induces dermatitis in mice. *Nat Immunol* 2004; 5:752–760.