

Allergen uptake and presentation by dendritic cells

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Allergic diseases such as atopic dermatitis, rhinitis and asthma are thought to result from a dysregulated immune response to commonly encountered antigens in genetically predisposed individuals. This response leads to chronic eosinophil-rich allergic inflammation and is controlled by Th2 lymphocytes. The first step in the allergic immune response is the uptake and presentation of allergen by professional antigen presenting cells such as dendritic cells, macrophages and B lymphocytes. Immature dendritic cells reside in the epithelia of the skin, upper and lower airways and gut and have the potential to sense foreign antigens and non-specific inflammatory tissue damage. Following recognition and uptake of Ag, mature dendritic cells migrate to the T-cell rich area of draining lymph nodes, display an array of Ag-derived peptides on the surface of major histocompatibility complex molecules and acquire the cellular specialization to select and activate naive Ag-specific T cells. By the nature of the signals they provide to naive T cells, mature dendritic cells are critical for polarizing Th0 helper cells into either Th1 or Th2 effector cells and for inducing long-lived memory Th cells. This article reviews recent information implying dendritic cells in the pathogenesis of allergic disease.

Curr Opin Allergy Clin Immunol 1:51–59. © 2001 Lippincott Williams & Wilkins.

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Current Opinion in Allergy and Clinical Immunology 2001, 1:51–59

Abbreviations

CCR	CC-chemokine receptor
MHC	major histocompatibility complex
MIP	macrophage inflammatory protein

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1528-4050

Introduction

Immunological research into the mechanisms of allergy has identified cytokine production by Th2 effector lymphocytes as being critical for orchestrating allergic inflammation. Upon recognition of their cognate antigen, Th2 lymphocytes produce cytokines that regulate IgE synthesis, growth and activation of eosinophils and mast cells and expression of endothelial cell-adhesion molecules. Despite the wealth of experimental data implicating allergen-specific Th2 cells as critical effector cells in the allergic response, less information is available on the generation of these cells from naive Th0 precursors. The first step towards generation of a T helper lymphocyte response is the recognition and uptake of Ag by professional antigen presenting cells that have the capacity to digest Ag into short peptides that associate with major histocompatibility complex (MHC) molecules and to provide costimulation for naive T cells. Research over the past 25 years has identified a family of dendritic cells as being the most potent antigen presenting cells for inducing and regulating the primary immune response *in vivo* and *in vitro* [1•].

Immature dendritic cells reside in the periphery to take up antigen

The skin and mucosae of the body are continually exposed to foreign antigens. Dendritic cells represent a significant proportion of cells lining these barriers. Even though it has been estimated that Langerhans cells represent only 1–3% of epidermal cells, the extension of cellular processes between keratinocytes ensures that 25–30% of the skin barrier area is covered by them. Similarly, the mucosa of the mouth, nose, airway, gut and genitourinary tract is covered with an extensive network of dendritic cells which reside in the para- and intercellular channels surrounding the basal epithelial cells. In the lung, the lateral intercellular space is sealed from the outside environment by epithelial tight junctions [2]. To interact with dendritic cells, potential aeroallergens must cross the lung epithelium and gain access to this space. In confluent airway epithelial cells, the enzymatic activity of Der p 1 – one of the major allergens of the house dust mite – led to the cleavage of the tight junction protein occludin and to effective breakdown of the epithelial barrier function [3•]. In all non-lymphoid tissues, dendritic cells are in a resting, so-called immature state that is specialized for antigen uptake by three dominant mechanisms. First, antigenic material can be acquired via receptor-mediated endocytosis involving clathrin-coated pits. Immature dendritic

cells express a plethora of specialized cell receptors for patterns associated with foreign antigens, such as the C-type lectin carbohydrate receptors (langerin, DC-SIGN, dectin, macrophage mannose receptor, and the unique carbohydrate receptor DEC-205) [4•,5•,6,7,8•]. Lectin-receptor mediated uptake by dendritic cells results in an approximately 100-fold more efficient presentation to T cells than with antigens internalized via fluid phase [8•,9]. Interestingly, langerin is a C-type lectin displaying mannose-binding specificity and is exclusively expressed by dendritic cells that display Birbeck granules, such as lung dendritic cells and skin Langerhans cells. Pollen starch granules were shown to bind to C-type lectin receptors on alveolar macrophages and dendritic cells, although internalization occurred only in macrophages [10]. A second mechanism of antigen uptake is constitutive macropinocytosis that involves the actin skeleton-driven engulfment of large amounts of fluid and solutes (approximately one cell volume/hour) by the ruffling membrane of the dendritic cell followed by concentration of soluble antigen in the endocytic compartment [11•]. Macropinocytosis seems to be a dominant mechanism involved in the uptake of recombinant Bet v 1 and Phl p 1 pollen allergens by Langerhans cells, and can be inhibited by cytochalasin D and amiloride [12•]. Thirdly, immature Langerhans cells and cultured dendritic cells have been shown to phagocytose particulate antigens such as latex beads and even whole bacteria, as well as apoptotic cells, and could be the dominant mechanism of uptake of particulate allergens [1•].

The antigens that are taken up by any of the above mechanisms accumulate in the endocytic compartment, where they are loaded on newly synthesized and recycling MHC class II molecules but may also be transported into the cytosol, where they become accessible to the class I antigen presentation pathway [11•,13•]. Within the endocytic compartment, antigen is cleaved into short immunogenic peptides by proteolytic enzymes of the cathepsin family. Antigen loading on MHC class II molecules occurs in an acidic cellular compartment rich in newly synthesized MHC class II molecules, called the MIIC compartment [14]. It is located at the intersection of the biosynthetic (endoplasmic reticulum, Golgi complex, secretory granules) and endocytic pathway of vesicle transport within the cell and contains the MHC II-related HLA-DM peptide exchanger that is essential for loading high affinity antigenic peptides on MHC II [8•,15,16•]. Alternatively, there is a pathway of peptide loading onto pre-formed MHC II molecules that have been internalized into mildly acidic endosomal vesicles after being expressed on the cell-surface [8•,17,18]. Surprisingly, proteolysis of antigen by immature dendritic cells can also occur extracellularly through secreted proteases,

generating peptides that can be loaded onto empty cell surface-expressed MHC class II [19•].

At present it is unclear how allergens are loaded onto MHC class II molecules by dendritic cells. In sensitized individuals, internalization of allergens via receptor-mediated endocytosis by multivalent crosslinking of the high affinity IgE receptor (FcεRI) on immature dendritic cells targets the antigen to the MIIC compartment [20,21,22•]. In contrast, the generation of peptide-MHC complexes derived from macropinocytosis of Bet v 1 and Phl p 1 pollen allergens was shown to be inhibited only partly when the pH of the endosomes was altered, suggesting that part of the molecules were not metabolized in the lysosomal MIIC compartment [12•].

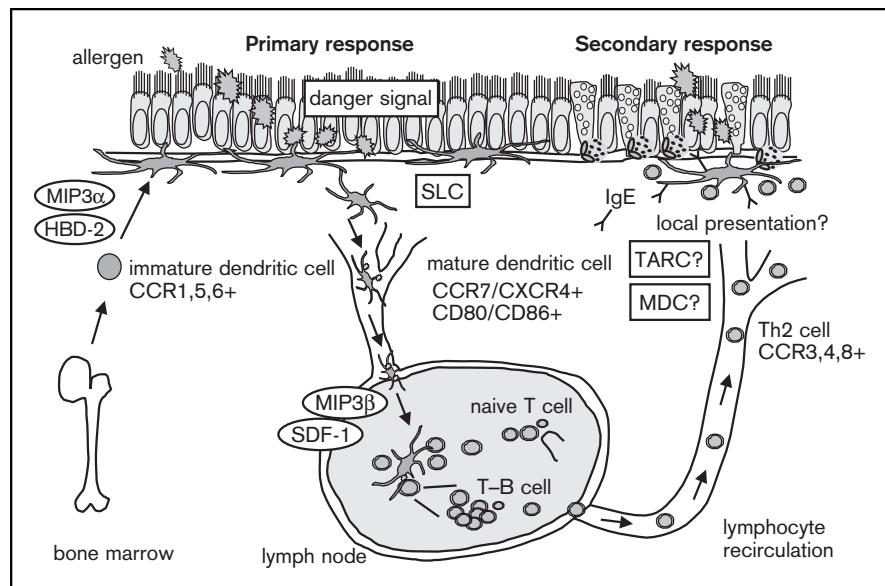
Dendritic cells migrate to the draining lymph nodes to stimulate naive T cells

The differential expression of chemokine receptors explains the complicated migration behaviour of dendritic cells (Fig. 1). Immature dendritic cells express CC chemokine receptor (CCR)-1, CCR5 and most importantly CCR6, and are attracted into sites where inflammatory chemokines are expressed. Macrophage inflammatory protein (MIP)-3α is the CCR6 ligand that is expressed in normal skin keratinocytes and venular endothelial cells, the epithelium overlaying tonsil and Peyer's patch crypts and probably lung epithelium, where it is involved in constitutive trafficking of CCR6⁺ dendritic cells [23•,24•,25,26,27•]. More importantly, MIP3α is strongly upregulated in keratinocytes of inflamed skin and inflammatory tonsil crypts, and is the determining chemokine attracting immature Langerhans cells into these sites of inflammation [28•]. Another CCR6 ligand that is induced by lipopolysaccharide and TNF-α is the epithelial beta-defensin HBD-2 that can attract immature dendritic cells *in vitro* [29•].

A critical event in the induction of cellular immunity is for dendritic cells to migrate from the infected peripheral tissues to the draining lymphoid organ, bearing antigens from the infecting agent [30•]. This migration has to occur against the chemotactic gradient that attracts immature dendritic cells. As part of the maturation program that is induced by contact with pathogens or tissue damage, the expression of CCR6 is shut down whereas that of CCR7 and CXCR4 is increased, explaining why maturing dendritic cells direct their interest towards afferent lymphatics and T cell area of draining lymph nodes where the CCR7 ligands secondary lymphoid chemokine (6C-kine) and MIP3-β and the CXCR4 ligand stromal cell-derived factor-1 are expressed [26,30•]. The stimulation of the CCR7 is crucial for entry of Langerhans cells into skin lymphatic vessels, migration to the draining lymph nodes, and for

Figure 1. The proposed role of dendritic cells in the primary and secondary immune response to allergen, with the lung as an example

During the primary response, bone marrow derived dendritic cells are attracted by inflammatory chemokines [macrophage inflammatory protein (MIP)3 α] into peripheral tissues, where they capture allergen. The recognition of allergen constitutes a danger signal that induces the maturation of dendritic cells. They become responsive to sinusoidal lining cell, expressed at the afferent lymphatic endothelium, and to MIP3 β , expressed in the T cell area of lymph nodes. In the lymph node they strongly express major histocompatibility complex (MHC) II-peptide and costimulatory molecules and attract and interact with naive T cells to induce the primary immune response, generating effector Th2 cells and regulatory T cells that control immunoglobulin IgE switching by B cells. Effector Th2 cells will in their turn migrate via the efferent lymphatics to recirculate in the bloodstream. Upon repeated or sustained encounter of allergen, these effector Th2 cells are poised to migrate into inflammatory sites and can probably be stimulated by local dendritic cells that carry IgE⁺ via the Fc ϵ RI receptor to generate eosinophilic airway inflammation, goblet cell hyperplasia and bronchial hyperreactivity. Dendritic cells have the capacity to produce MDC and TARC that are chemotactic for recirculating Th2 cells. HBD-2, human beta defensin; MDC, monocyte derived chemokine; SDF, stromal cell derived factor; SLC, secondary lymphoid chemokine; TARC, thymus and activation regulated chemokine.



generation of contact hypersensitivity and delayed type hypersensitivity reactions, as illustrated in mice with a targeted deletion of CCR7 or treated with antibodies against secondary lymphoid chemokine [31•,32•,33•].

Mature dendritic cells interact with naive T cells in the lymph node to induce T cell activation

When dendritic cells have reached the T cell area of draining lymph nodes, the antigen uptake capacity has been shut down completely and cellular specializations to stimulate naive T cells are acquired. They produce chemokines for naive T cells (MIP3- β , DCCK-1) and resting T cells (monocyte-derived chemokine, thymus and activation regulated chemokine), that make up the 'scent of the T cell zone' [30•]. Attraction of naive T cells may help to ensure that dendritic cells interact rapidly with multiple T cells, allowing efficient scanning for cells that recognize the antigen. Naive T cells repeatedly engage and disengage contact with antigen bearing dendritic cells via interaction of adhesion molecules such as DC-SIGN and CD54 interacting with intercellular adhesion molecule-3 and CD11a/CD18 [5•,34•]. These non-specific interactions approximate the two cell types and allow the initial screening and serial triggering of the low affinity T cell receptor for recognition of its specific peptide-MHC [35•]. As part of their maturation program, dendritic cells that have migrated from the periphery express surface MHC II-peptide complexes and costimulatory molecules such as CD80 and CD86 for CD28 on the naive T cell [16•,18].

In T cells, a successful and sustained peptide-MHC/TCR interaction together with CD28 ligation induces supramolecular activation complexes consisting of lipid rafts that efficiently polarize and concentrate triggered TCRs, CD28 and signal transduction machinery towards the site of interaction with the dendritic cell – the immunological synapse [36]. Similarly, dendritic cells concentrate CD86 and peptide-MHC complexes in lipid rafts on their membrane surface, towards sites of T cell contact [16•,37•]. Triggered by these mechanisms, activated T cells express CD40L and TRANCE that lead to increased survival and terminal maturation of dendritic cells by upregulating CD80, CD86 and cytokine production, further sustaining the cognate interaction [1•]. The end result is that the induction of T cell division by antigen-loaded dendritic cells is very rapid *in vivo* and that, 2 days after injection of dendritic cells, some antigen specific T cells have already divided twice. A further 24–48 hours later, divided cells have acquired effector phenotype and migrate from the draining node to the periphery [38•].

Dendritic cells determine T helper cell polarization

As dendritic cells are the vehicle of immunity after exposure to foreign antigens, they also unsurprisingly determine the polarization of T helper responses after arrival in the draining nodes. This issue has received considerable attention in the most recent literature [39•,40•,41]. Various pathways of regulation are opera-

tive to induce an optimum T cell response. Immature dendritic cells can be instructed by the characteristics of the antigen or its accompanying adjuvant to induce either a Th1, a Th2 or an undifferentiated Th0 response (Table 1). The microbe-derived pattern molecules inducing Th1 responses do so by enhancing the production of bioactive IL-12 p70 in dendritic cells, via triggering of ancient innate immune receptors expressed on dendritic cells [58]. The TOLL-like receptors are widely expressed on dendritic cells and mediate lipopolysaccharide-induced IL-12 production by enhancing the cellular levels of NF- κ B transcription factors [59]. However, the paradigm that dendritic cells exposed to microbial factors are stable inducers of Th1 immunity is gradually shifting. Indeed, microbial products need additional host-derived microenvironmental instruction – in the form of interferon-gamma or even IL-4 – to induce stable IL-12 production in dendritic cells [60]. Moreover after activation by lipopolysaccharide, monocyte-derived human dendritic cells produce IL-12 only transiently and become refractory to further IL-12 production upon interaction with CD40L⁺ T cells. Soon after stimulation dendritic cells prime strong Th1 responses, whereas at later time points the same cells preferentially prime Th2 and nonpolarized T cells [47]. Not only does the production of IL-12 decrease, but there is also a gradual decrease in the number of dendritic cells reaching the draining lymph nodes. When

dendritic cells stimulate naive T cells at low stimulator/responder ratios, Th2 polarization is favored despite the presence of IL-12 [50].

Recently it was proposed that different developmental lineages of dendritic cells could induce either Th1 or Th2 responses, hence the terminology DC1 or DC2 (Table 1) [41,54]. In the original description, monocyte-derived DC-1s (i.e. myeloid dendritic cells) induced IL-12-dependent Th1 responses, whereas DC-2s derived from IL3R α ⁺ CD4⁺ CD3[−] CD11c[−] plasmacytoid precursor cells (i.e. lymphoid dendritic cells) induced IL-4-independent Th2 responses preferentially [54,61]. However, follow-up studies have shown that additional levels of regulation determine the outcome of T helper differentiation by myeloid dendritic cells (Table 1). Also, it was shown that mo-DCs could be separated into a CD1a⁺ or CD1a[−] subpopulation, inducing Th1 or Th2 responses respectively. Although both subsets express similar levels of costimulatory molecules, IL-12 production is completely lacking in CD1a[−] mo-DCs, even after stimulation with anti-CD40, lipopolysaccharide and interferon-gamma [56]. The discussion as to whether dendritic cell lineage contributes to T helper differentiation is also relevant to the murine system where CD8 α ⁺ lymphoid dendritic cells were initially thought to be biased towards Th1 and CD8 α [−] and myeloid dendritic cells to Th2 induction (i.e. opposite to the human

Table 1. Factors influencing T helper polarization by dendritic cells

Type of variable	Favouring Th1	Favouring Th2	
Antigen			
dose	high dose	low dose	[42]
characteristics	<i>Candida albicans</i> yeasts Toxoplasma Ag	<i>Candida albicans</i> hyphae Filarial nematode products Allergens ?	[43] [44,45]
adjuvant factors	CpG oligodesoxynucleotides Gram positive cell wall early after lipopolysaccharide stimulation	late after lipopolysaccharide stimulation Cholera toxin	[46] [47,48]
MHC–TCR interaction	high affinity short interaction high stimulator/responder	low affinity sustained interaction low stimulator/responder	[42] [49] [50]
Costimulatory molecules	low expression CD80/86 ICAM-1 CD40	OX40-L ICOS-L (B7RP-1 or -2)	[51] [52] [53]
Dendritic cell heterogeneity			
maturation	mature	immature	
lineage	monocyte-derived dendritic cell macrophage derived dendritic cell CD1a ⁺ myeloid dendritic cell	lymphoplasmacytoid dendritic cell CD1a [−] myeloid dendritic cell mucosal dendritic cell	[54] [55] [56] [57]
localization			
Cytokine production	high IL-12 low IL-10	low IL-12 (PGE ₂ -exposed) high IL-10 high IL-6	[40]

ICAM, intercellular adhesion molecule; ICOSL, inducible costimulator ligand; MHC, major histocompatibility complex; PGE, prostaglandin; TCR, T cell receptor

situation) [39•]. In conclusion, priming of T helper responses by dendritic cells is very flexible, allowing the simultaneous generation of Th1, Th2 and Th0 responses.

Dendritic cells in animal models of allergy

It is only recently that dendritic cells have been studied in murine models of allergy, such as the rodent asthma model of ovalbumin-induced eosinophilic airway inflammation. In early studies, Holt *et al.* demonstrated that rat airway dendritic cells can be rapidly recruited to sites of inflammation, capture inhaled ovalbumin and process it into an immunogenic form on MHC class II molecules. The function of lung dendritic cells is suppressed by secreted products of alveolar macrophages (e.g. nitric oxide) that keep them in an immature antigen-capturing mode [62•]. These immature myeloid dendritic cells do not produce IL-12 and induce Th2-dependent immunoglobulin production after intravenous transfer into naive rats [57]. After transfer of ovalbumin-pulsed bone-marrow derived dendritic cells into the trachea, we have recently shown that mice and rats can be sensitized to develop eosinophilic airway inflammation and goblet cell hyperplasia, controlled by IL-4 and IL-5 producing Th2 CD4⁺ cells [63•,64]. The sensitization process occurred after migration of immature dendritic cells into the draining mediastinal lymph nodes [38•]. Primary exposure to ovalbumin via the respiratory route is normally a tolerogenic event. However, when endogenous airway dendritic cells were activated by transgenic expression of GM-CSF or by concomitant viral infection with influenza virus, tolerance was avoided and eosinophilic airway inflammation ensued [65,66•]. From these models, it appears that dendritic cells are responsible for sensitization to inhaled allergen. More importantly, dendritic cells are also attracted from the bone marrow and the bloodstream into sites of eosinophilic airway inflammation during the secondary immune response to ovalbumin and are functionally important for the maintenance of eosinophilic airway inflammation and IgE synthesis in sensitized mice, identifying the dendritic cell as a target for therapeutic intervention (Fig. 1) [67–69].

Dendritic cells in human allergy

From the above discussion it seems likely that human dendritic cells are implicated in Th2 sensitization to common allergens in genetically predisposed individuals. It has been proposed that during the neonatal period and early infancy – the peak period of sensitization – dendritic cells are functionally immature, failing to counterbalance the default Th0/Th2 priming to common allergens at this age [70]. Failure to educate the immune system because of reduced exposure to environmental microbial load – a consequence of the western lifestyle – could explain why dendritic cells are not instructed to produce IL-12 and fail to counteract Th2 responses.

Alternatively, an intrinsic deficiency in IL-12 production has been described in blood monocytes (i.e. precursors of dendritic cells) of patients with atopic dermatitis and atopic asthma, although this could be the consequence of the allergic phenotype rather than its origin and recent data suggest that there is no difference in IL-12 production in mo-DCs between atopic and non-atopic individuals [71,72••]. Another explanation could be the nature of the allergen exposure. Chronic low-level exposure to inhaled allergens could lead to low levels of dendritic cells continuously migrating to the lymph nodes and inducing sustained TCR ligation at low stimulator/responder ratios, conditions known to bias towards Th2 responses [47••,50••]. Administration of allergen-pulsed dendritic cells to humans to prove that they elicit sensitization is unethical. However, dendritic cells have been used as therapeutic vaccines for immunotherapy of melanoma and other cancers. There has been one report of induction of novel Th2-dependent sensitization to bovine serum albumin – used in the autologous dendritic cell preparation – after repeated injection of dendritic cells, which led to anti-bovine albumin IgE and anaphylactic reactions [73].

The function of dendritic cells in patients with established allergic disease is more relevant from a therapeutic perspective. Increased numbers of CD1a⁺ dendritic cells can be found in the nose of patients with atopic rhinitis, in lesional skin of patients with atopic dermatitis and in the bronchial epithelium of patients with stable atopic asthma [74–76,77•,78,79]. Out of season topical allergen challenge to the nose of patients with atopic rhinitis is accompanied by a further recruitment of intraepithelial CD1a⁺ dendritic cells as well as recruitment of distinct lamina propria CD4⁺ IL3R α ⁺ (CD123⁺) CD11c[–] CD1a[–] plasmacytoid dendritic cells (precursor DC-2s, see above) [80,81••]. The latter cells expressed high levels of L-selectin and were shown to accumulate together with naive T cells at endothelial venules expressing the L-selectin ligand peripheral node addressin. Interestingly, IL3R α ⁺ plasmacytoid dendritic cells did not accumulate in nasal polyps or other mucosal inflammatory lesions, suggesting that they are specifically associated with atopic rhinitis [81••].

The function of dendritic cells in patients with or without atopic diseases has been studied *in vitro*. It was shown that immature mo-DCs from individuals with atopic asthma have an enhanced allostimulatory function and higher levels of CD11b and HLA-DR than non-atopic patients, although others have refuted this idea [72••,82]. When mo-DCs were pulsed with relevant allergen (Der p 1 and 2, Bet v 1) and cultured with autologous naive or memory T cells, they induced both Th1 and Th2 cytokines – but predominantly Th2 when atopic donors were used – despite similar IL-12

production [72^{••},83,84]. The further addition of rIL-12 induced a separate interferon-gamma producing subset without decreasing the IL-5 producing subset. However, the addition of anti-IL-12 reduced bulk interferon-gamma production without affecting IL-4 production. Interestingly, culture of dendritic cells on collagen type I strongly enhanced IL-12 production in those cells and induced interferon-gamma and reduced IL-5 in allergen specific T cells [85[•]]. These data confirm that dendritic cells can efficiently stimulate human allergen-specific memory Th2 cells to produce Th2 cytokines and maybe contribute to ongoing allergic inflammation [68,86]. Consistent with this idea, Hammad *et al.* were able to show in a humanized SCID mouse model that human mo-DCs pulsed with Der p 1 significantly enhanced the cellular infiltration of human allergen-specific T cells in the lungs of challenged mice and boosted the formation of allergen-specific IgE [87^{••} and unpublished data].

The CD1a⁺ Langerhans cells in the skin of patients with atopic dermatitis and dendritic cells in the nose and bronchi of patients with atopic rhinitis and atopic asthma contain the high affinity IgE receptor FcεRI [78,88]. Despite the fact that the alpha chain of this receptor is expressed intracellularly on most Langerhans cells of control and atopic individuals, the surface expression is highly upregulated in atopic patients and correlates with the level of serum IgE [22^{••},88]. At least in patients with atopic dermatitis and atopic rhinitis, the Langerhans cells are covered with monomeric IgE which suggests that FcεRI functions as an allergen-focusing molecule and that allergens are more efficiently taken up, processed and presented to T cells following targeting via FcεRI [75,80]. By critically lowering atopic individuals' threshold to mount allergen-specific T cell responses, this would result in the perpetuation of allergen-specific IgE production (type I reactions) and perhaps even in the occurrence of T-cell-mediated delayed-type hypersensitivity reactions in allergen-exposed tissues. It was recently reported that only those atopic patients with IgE on their Langerhans cells develop eczematous skin lesions upon epicutaneous application of aeroallergens [89]. Reducing the levels of allergen-specific IgE, either by non-anaphylactogenic anti-IgE monoclonals (E25) or by allergen avoidance can, therefore, be seen as a therapeutic strategy that extends beyond its effects on IgE-mediated effector mechanisms (i.e. mast cell degranulation).

Finally, our current standard therapy of allergic diseases – the regular use of corticosteroids – has profound effects on the function of dendritic cells within inflamed tissues. It has been shown that the regular use of inhaled corticosteroids reduces the number of dendritic cells in the airways and nose of patients with atopic asthma and atopic rhinitis [76,90,91]. Systemic and inhaled steroids

inhibit the differentiation and maturation process of and induce the apoptosis of lung dendritic cells [92[•],93,94]. Interestingly, exposure of immature mouse and human dendritic cells to steroids leads to a phenotype that induces T suppressor cells that could downregulate Th1-mediated inflammation [95,96]. More studies are needed to address the effects of current and future therapeutics on human dendritic cells *in vivo*. Clearly the use of humanized SCID models could prove to be very valuable for development of new drugs aimed at interfering with dendritic cell function.

Conclusion

Recent advances in cell biology and in animal models of allergy have identified dendritic cells as the principal antigen presenting cells involved in the induction and maintenance of Th2 allergic responses. It can be foreseen that studies on the functional role of these cells in humans will shortly lead to increased insight into the pathogenesis of allergic diseases and hopefully to better strategies for preventing and treating these conditions.

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