

## EDITORIAL

# Myeloid dendritic cells make it to the top

### Introduction

Dendritic cells (DCs) are professional antigen-presenting cells that form a dense network in antigen-exposed tissues including the nasal and bronchial mucosa and lung interstitium [1]. They are endowed with so-called pattern recognition receptors and efficiently take up antigens for presentation to naïve T cells, following their migration to the draining lymph nodes of the lung [2–4]. In these nodes DCs have the capacity to direct the development of CD4<sup>+</sup> T cells into differentiated Th1 or Th2 effector cells with an immediate capacity to control inflammation and to clear dangerous pathogens [5–7]. At the same time, some CD4<sup>+</sup> T cells are induced to become central memory T cells (T<sub>CM</sub>), providing a rapid new wave of effector cells during immune recall responses to the same pathogen. Airway DCs have also been implicated in the homeostasis of the pulmonary immune response. Under some conditions, DCs induce functional tolerance to inhaled antigen either through CD4<sup>+</sup> T regulatory (T<sub>reg</sub>) cells, or deletional tolerance [8].

The role of these cells in controlling the response to inhaled allergens is becoming increasingly clear (for review see [9]). In animal models, a critical role for DCs in the induction and maintenance of eosinophilic airway inflammation is now fairly established [6,10]. Human studies on the role of DCs in allergen presentation are relatively scarce. *In vitro* it was shown that cultured human DCs are highly capable of processing and presenting allergens to syngeneic naïve or memory T cells of atopic individuals with a bias towards Th2 cytokine production in these cultures [11–14].

### Dendritic cells are recruited to the airways following local allergen challenge of atopic asthmatics

In this issue, Upham and colleagues expand our knowledge on the role of DCs in human asthma by demonstrating for the first time a reduction of circulating HLA-DR<sup>+</sup> CD33<sup>+</sup> DCs following relevant allergen challenge to the airways of ragweed and house dust mite (HDM)-sensitive patients. The accumulation is very rapid and occurs as early as 3 h post-exposure, and lasting at least 24 h. It is furthermore reported that the baseline level of myeloid DCs is not different between normal individuals and those with asthma, although no data are shown to support this [15]. This interesting paper should be read simultaneously with a recent paper by Jahnsen et al. describing a rapid accumulation of airway myeloid DCs following local bronchial challenge with relevant allergen in atopic asthmatics [16]. In the latter study, a dramatic increase in the number of CD1a<sup>+</sup> HLA-DR<sup>+</sup> DCs were observed in the lamina propria of the larger bronchi after allergen challenge compared with baseline (22.4 vs. 7.8 cells/mm<sup>2</sup>). The rapid tissue accumulation

(within 4–5 h) of these cells together with a reduction in circulating HLA-DR<sup>+</sup> CD33<sup>+</sup> DCs as reported in the Upham paper strongly suggests that DCs are directly recruited from the bloodstream to the airways following bronchial allergen challenge in allergic asthmatic patients [16].

What is not clear from both studies is whether the recruitment of DCs to the airways is due to the exposure to allergen *per se* or due to the allergic status of the challenged individual. No experiments were described in which atopic subjects were challenged with an irrelevant allergen, or in which healthy controls were exposed to allergens. It is indeed possible that allergen extracts are contaminated with trace amounts of lipopolysaccharide (LPS) or other contaminants. Studies in the rat and mouse have indeed demonstrated that these bacterial compounds lead to a rapid and dramatic increase in the number of airway DCs [17,18]. Therefore, the current studies do not exclude a non-specific effect of allergens or their contaminants on the numbers of airway DCs. Despite these methodological drawbacks, it is however, likely that allergen challenge leads to recruitment of airway DCs in a specific manner. In support of this, relevant ovalbumin (OVA) allergen challenge in OVA-sensitized rats and mice is a clear stimulus for DC recruitment to the airways, even in the absence of LPS contamination [18–20]. Studies in humanized severe combined immunodeficiency mice (huSCID) reconstituted with peripheral blood mononuclear cells (PBMCs) of HDM-allergic patients furthermore showed that DCs are exquisitely sensitive to airway challenge with Der p 1, the major allergen of HDM, being attracted towards sites of eosinophilic airway inflammation. In these studies, allergen challenge also led to the migration of DCs towards lymph nodes [21].

### Not all dendritic cells are attracted to the airways

Recent years have seen a growing interest in the heterogeneity of DCs [22]. This reflects our increasing knowledge about the differential origins of DC subsets from haematopoietic precursors and circulating blood precursors (see Fig. 1). Myeloid DCs have a lineage relationship in common with monocytes and macrophages and express some common surface myeloid markers such as CD33 and CD13, also expressed on the blood circulating DCs reported in the Upham paper [15]. The prototypical myeloid DC is generated *in vitro* by culturing CD14<sup>+</sup> peripheral blood monocytes in the presence of GM-CSF and IL-4, a protocol often used to generate large numbers of DCs for adoptive immunotherapy [23]. Another commonly used protocol to generate myeloid DCs is from CD34<sup>+</sup> haematopoietic stem cells purified from cord blood, bone marrow or peripheral blood, and grown in the presence of GM-CSF and TNF- $\alpha$  [24]. These cultures generate Langerhans cells through a CD1a<sup>+</sup>

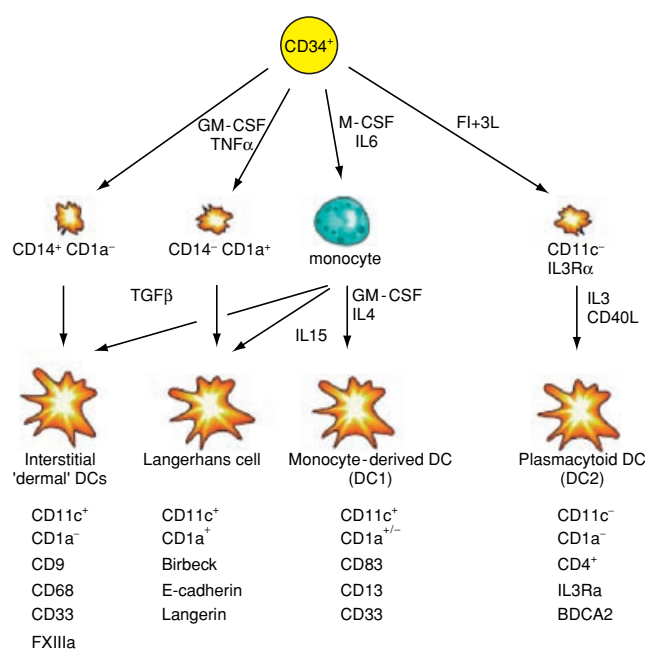


**Fig. 1.** Dendritic cell heterogeneity. Various types of DCs can be generated *in vitro* from CD34<sup>+</sup> haematopoietic stem cells under the influence of cytokines and growth factors. Interstitial dermal DCs, Langerhans cells and monocyte derived DCs belong to the myeloid lineage and share many markers with monocytes and macrophages. Plasmacytoid DCs are of lymphoid lineage and express markers commonly seen on T and B cells.

intermediate cell or 'dermal' DCs through a CD14<sup>+</sup> monocyte-like intermediate cell. Although these culture methods lead to the outgrowth of DCs after a few days of culture, it is not at all clear how physiological they are for the generation of DCs that are present in the various tissues. However, one dogma that has emerged from these studies is that monocytes can now be regarded as the immediate precursors of tissue DCs, similar to the observation that they are also precursors for tissue macrophages. Monocytes might become DCs or macrophages depending upon the milieu in which they reside following extravasation or depending upon the function they fulfil during antigen recognition [25]. However, it remains to be proven whether DCs in the airways are derived from a circulating or tissue dwelling monocyte. It has long been established that bronchoalveolar lavage fluid macrophages from atopic asthmatics have a clearly different and activated phenotype, expressing the RFD-1 marker, originally described as a DC marker, as well as some costimulatory molecules [26–28]. Although these data suggest that activated alveolar mononuclear cells might constitute an immediate precursor for DCs in asthma, the paper by Upham suggests that at least some lung DCs are derived from a circulating CD33<sup>+</sup> myeloid DC precursor. Studies in the mouse also suggest that tissue DCs derive from a circulating immature DC precursor, rather than from circulating monocytes [29].

The second subset of DCs is called the (lympho)plasmacytoid DC, because of its morphological resemblance to plasma cells, and expression of markers commonly seen during lymphoid development [30]. These cells have only been described recently. The precursor for these cells develops from a CD34<sup>+</sup> haematopoietic precursor and expresses the CD123  $\alpha$ -chain of

the receptor for IL-3, while lacking the CD11c marker expressed on myeloid DCs. A physiological function for these cells is suggested to occur during viral infections, when they are massively recruited to the site of infection and serve as an important source of antiviral IFN- $\alpha$  [31]. Others have suggested that these cells have a role in inducing peripheral tolerance in CD4 and CD8 cells [32,33].

When cultured together with naïve T cells *in vitro*, the plasmacytoid subset of DCs gives rise to Th2 development, hence the name DC2, whereas myeloid monocyte-derived DCs induce Th1 responses, hence their name DC1 [34]. Although the fact that a particular DC subset induces a particular Th response is probably an oversimplification, the original description of DC2s as Th2-inducers has generated interest into whether patients with allergy have changes in the number and/or function of DC2s. There have been some contradicting reports that patients with atopy have a slightly enhanced percentage of plasmacytoid DC2s under baseline conditions, while the percentage of CD11c<sup>+</sup> CD123<sup>-</sup> myeloid DC1s is reduced, although in one report this does not reach statistical significance [35,36]. The reason for the increase in CD11c<sup>-</sup> CD123<sup>+</sup> DCs in atopic individuals was suggested to be decreased sensitivity to the normal IL-4-induced apoptosis in DC2s of allergic individuals [36]. Although the paper by Upham does not mention the DC2 subset, it is specifically stated that the number of myeloid DC1s is not different between normals and atopic asthmatics in the absence of relevant allergen challenge. Similarly, we have unpublished data to suggest that there is no gross difference in the DC1:DC2 ratio between atopic and non-atopic individuals. One possible caveat that needs to be born in mind is the fact that DC2s are very sensitive to the action of steroids and this could confound the counting of DC2s when the period of steroid washout is not long enough [37].

The strongest evidence for an involvement of DC2s in the pathogenesis of allergy is in allergic rhinitis [38]. Patients with silent nasal allergy were challenged topically with relevant allergen daily for 7 days. Biopsy specimens as well as blood samples were obtained before and during such provocation, and DC2s were identified by their high expression of CD123. It was shown that DC2s were present in low and variable numbers in normal nasal mucosa but increased dramatically during the allergic reaction. This accumulation concurred with the expression of the L-selectin ligand peripheral lymph node addressin on the mucosal vascular endothelium. The latter observation was particularly interesting in view of the high levels of L-selectin on circulating DC2 precursors and of previous reports suggesting that these cells can enter organized lymphoid tissue via high endothelial venules (which express peripheral lymph node addressin constitutively). Although previous reports had demonstrated an increase in CD1a<sup>+</sup> HLA-DR<sup>+</sup> DCs following out of season allergen challenge to the nose, these CD1a<sup>+</sup> DCs are clearly different from DC2s and probably represent myeloid Langerhans cells [38,39]. However, despite initial enthusiasm that DC2s might be essential during all allergic reactions, studies of allergen challenge in atopic asthmatics by the same author have failed to demonstrate an accumulation of DC2s in challenged bronchi [16]. Upham et al. also state in their discussion that the short-term allergen challenge might prove to be insufficient for the recruitment of DC2s to the airway lumen, and that increases could be predicted after longer periods of allergen challenge. Another explanation might be that DC2s

have a different chemokine responsiveness, with some chemokines being produced in allergen-challenged nasal tissues specifically attracting these cells [40]. Also, there could be minute changes in the expression of cell adhesion molecules (for example peripheral node addressin) on the endothelial cells of the nasal mucosa compared with bronchial mucosa which could be the reason for a selective attraction of DC2s to the nose. The bottom line is that DC2s in atopic asthma should be studied more carefully before conclusions about their functional role can be drawn.

### Myeloid dendritic cells on top of the allergic cascade?

The fact that myeloid DCs are attracted to the airways at times of allergen challenge in atopic asthmatics suggests a critical role for these cells in the late-phase cellular immune response. This is supported by data from mouse models. We have previously shown that the removal of DCs during allergen challenge of sensitized mice completely abolishes Th2 cytokine production, IgE synthesis and, more importantly, cellular infiltration of eosinophils and goblet cell hyperplasia [10]. Recently it was shown that lung myeloid DCs in the mouse have the capacity to retain allergens for a prolonged period of time and are the prime cells presenting allergen to specific T cells for effector generation, even 8 weeks after allergen challenge [41]. Therefore, DCs could be essential for maintaining low levels of inflammation despite maximal allergen avoidance. This maintenance of low level inflammation might be facilitated by the presence of specific IgE bound to the high affinity receptor for IgE, present on circulating and bronchial mucosal DCs of allergic subjects, and significantly lowering the threshold for allergen recognition [42,43].

If DCs really have a critical role to play in the late-phase response, the question then arises where the interaction between allergen, DC and T cells occurs. The interaction between aero-allergens and lung DCs is allowed only if these allergens cross the lung epithelium. Der p 1, one of the major allergens of the house dust mite *Dermatophagoides pteronyssinus*, displays a cysteine protease enzymatic activity responsible for the cleavage of the tight junction protein occludin, thus increasing the accessibility of DCs residing beneath the epithelial barrier [44]. The papers by Upham and Jahnsen and the work in animal models suggest that DCs are furthermore recruited to the site of allergen deposition [15,16]. The recruitment is most likely induced by the production of chemokines by resident cells such as epithelial cells or mast cells. Der p 1 has been shown to induce the epithelial release of such chemokines as CXCL8 (IL-8), and mast cells release many chemokines such as CCL2 (MCP-1), CCL7 (MCP3), CCL17 (TARC), CCL20 (MIP-3 $\alpha$ ) and CCL22 (MDC) upon *in vitro* cross-linking of the IgE receptor [45]. The chemokine most closely linked to the attraction of immature DCs to sites of inflammation in the lung is CCL20 (MIP-3 $\alpha$ ); the CCR6 receptor for this chemokine was first cloned from lung DCs [46]. Other chemokinetic substances involved could be CCL2 (MCP-1), CCL13 (MCP-4), CCL11 (eotaxin), but also neuropeptides and complement cleavage products [18,47]. The exact chemokines attracting DCs to the lung following allergen challenge remain to be determined however, and could clearly be different from the chemokines that recruit DCs to the lung under baseline conditions [48].

An important question that arises next is whether the recruited DCs present the allergen locally to T cells or whether DCs migrate to the draining nodes to stimulate recirculating central memory T cells (see Fig. 2). Others believe, like us, that both scenarios occur simultaneously. In a very important paper, it was recently shown by Harris et al. that lung DCs stimulate effector function (i.e. induction of eosinophilia) in primed Th2 cells in the peripheral lung compartment without inducing proliferation in these cells. At the same time, some DCs migrate to the draining nodes to stimulate effector function in recirculating memory Th2 cells by first inducing their proliferation and expansion [49]. This proliferative phase is probably necessary to replete peripheral tissues with new rounds of effector cells. It seems from these mouse studies that part of the secondary response therefore occurs in the draining nodes. In a previous work performed in SCID mice, we showed that Der p 1 could act directly on DCs from allergic patients introduced into the trachea of the animals and induce their migration towards mediastinal lymph nodes. The allergen-induced migration could be explained by an up-regulation of CCR7, the receptor

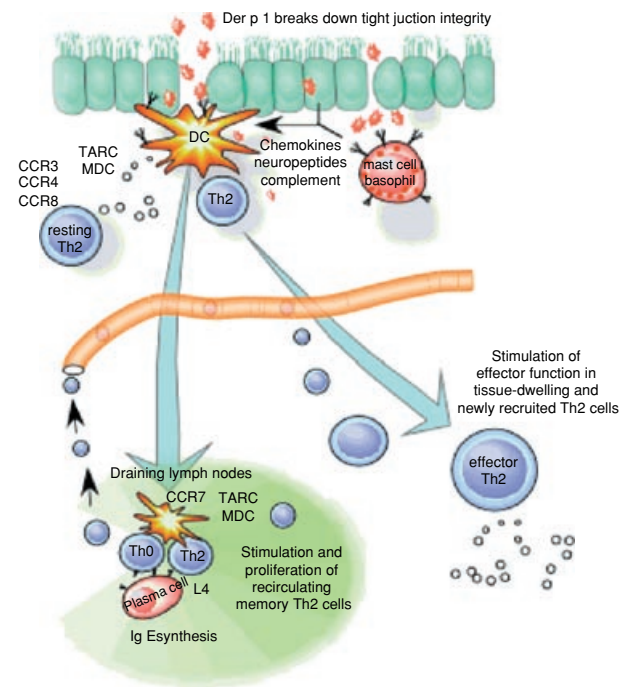


**Fig. 2.** Myeloid DCs on top of the allergic cascade. When an allergen has the potential to breach the epithelial tight junction barrier, the first cells that recognize this antigen are DCs, epithelial cells and mast cells. These cells can all bind allergen-specific IgE either through Fc $\epsilon$ R1 or CD23, possibly enhancing the recognition of the allergen. The allergens induce the release of chemokines, neuropeptides and complement breakdown products which attract circulating DCs to the mucosa and influence DC function. At the same time, the allergen also activates DCs to produce TARC and MDC preferentially in allergic subjects, leading to the local attraction of Th2 cells expressing CCR3, CCR4 and CCR8. These attracted Th2 cells can directly exert their effector function when activated by APCs, but fail to proliferate locally. The allergen also induces the migration of allergen-loaded DCs to the draining lymph nodes by increased expression of the CCR7 receptor, necessary for homing to the T cell area. In this area, DCs attract recirculating resting central memory Th2 cells and possibly some naïve allergen-specific T cells and induce their proliferation. After a few rounds of division, effector Th2 cells are generated that are now biased to migrate to the inflamed lung tissue, where they collaborate with locally activated Th2 cells to orchestrate the eosinophilic inflammation.

for the chemokines CCL21 (secondary lymphoid chemokine) and CCL19 (MIP-3 $\beta$ ) which are constitutively expressed in afferent lymph endothelium and T cell area of lymph nodes, respectively [50]. In the mediastinal lymph nodes, DCs issued from HDM-sensitive patients could restimulate autologous Th2 cells to become effector cells (Hammad, Lambrecht et al. unpublished data).

Irrespective of the site of interaction between DCs and memory Th cells, it is possible that Th cells have to be attracted to the DC, possibly through the release of Th1- or Th2-attracting chemokines. Some chemokines were demonstrated to be specifically involved in the recruitment of Th1 and Th2 cells into inflamed tissues [51]. For example, CCL17 (TARC) and CCL22 (MDC) attract CD4<sup>+</sup> CD45RO<sup>+</sup> cells polarized to produce Th2 cytokines [52]. In contrast, CXCL10 (IP-10) preferentially attracts Th1-polarized cells. The selective attraction of these cells by particular chemokines is best explained by the differential expression of chemokine receptors between Th1 and Th2 cells [53]. Indeed, CXCR3 and CCR5 are preferentially expressed by Th1 cells, whereas Th2 cells preferentially express CCR3, CCR4 and possibly CCR8. In the airways, both TARC and MDC were shown to play a crucial role in the establishment of an inflammatory allergic reaction by attracting Th2 cells to the site of inflammation. In a murine model of asthma, MDC was involved in the recruitment of antigen-specific Th2 cells to the lung, thus allowing the enhancement and maintenance of the pulmonary inflammatory reaction [54]. In humans also, TARC and MDC are strongly expressed in the bronchial epithelium of asthmatic patients and in the nasal mucosa of patients suffering from allergic rhinitis [55]. In these models, epithelial cells are often described as the major source of Th2-attracting chemokines. However, in mice and in humans, TARC and MDC can also be produced by DCs [52], indicating that DCs themselves could also contribute to the enhancement of the inflammatory response. To clarify this point, we investigated whether DCs from both allergic patients and healthy donors could preferentially produce Th1- or Th2-attracting chemokines following a stimulation with the allergen Der p 1

**Table 1.** Effect of *in vitro* exposure of human monocyte derived DCs to the house dust mite allergen Der p 1. DCs were obtained by culturing blood monocytes from allergic and nonallergic donors in GM-CSF and IL-4 and were exposed to Der p 1 for 16 h

|                            | Allergic DCs | Non-allergic DCs |
|----------------------------|--------------|------------------|
| <b>Cytokines</b>           |              |                  |
| IL-10                      | Increased    | No effect        |
| IL-12                      | No effect    | Increased        |
| TNF- $\alpha$              | Increased    | No effect        |
| IL-1 $\beta$               | Increased    | No effect        |
| IL-6                       | Increased    | No effect        |
| <b>Chemokines</b>          |              |                  |
| MDC                        | Increased    | No effect        |
| TARC                       | Increased    | No effect        |
| IP-10                      | No effect    | Increased        |
| RANTES                     | Increased    | Increased        |
| MIP-1 $\alpha$             | Increased    | Increased        |
| <b>Chemokine receptors</b> |              |                  |
| CCR7                       | Increased    | No effect        |

(see Table 1 for summary). The results show that Der p 1-pulsed DCs from allergic patients increased TARC and MDC production without modifying IP-10 release. On the contrary, Der p 1-pulsed DCs from healthy donors increased only IP-10 secretion. However, in response to Der p 1, the production of other non-specific chemokines such as CCL5 (RANTES) and CCL3 (MIP-1 $\alpha$ ) was similarly increased when DCs were issued from healthy donors or from allergic patients. The functional significance of chemokine release by DCs was furthermore studied using chemotactic assays with long-term Th1 and Th2 clones. The selective recruitment of Th2 clones by supernatants from Der p 1-pulsed DCs of allergic patients was specifically inhibited by anti-TARC and anti-MDC neutralizing antibodies. Supernatants of Der p 1-pulsed DCs from healthy donors attracted Th1 clones selectively, a process inhibited by blocking anti-IP-10 antibodies [56]. In allergic patients, the up-regulation of TARC and MDC production by DCs exposed to Der p 1 may contribute to the recruitment of early activated Th2 cells expressing CCR4. This would mean that in HDM-sensitive patients, DCs through the production of chemokines closely associated with the specific recruitment of Th2 cells, such as TARC and MDC, may participate in the enhancement of the allergic reaction.

In conclusion, the paper by Upham illustrates that myeloid DCs are attracted very rapidly to the bronchial epithelium after exposure to relevant allergen. Recent data furthermore suggest that myeloid DCs through their attraction of Th2 cells and stimulation of effector function in Th2 cells might well be essential for orchestrating the secondary immune response and are therefore on top of the allergic cascade.

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