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The master regulators of allergic inflammation: dendritic cells in Th2 sensitization

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The development of Th2 responses to inhaled proteins represents a malfunction of the adaptive immune system in that protein antigens are not microbial in nature and should not elicit an adaptive immune reaction. This derailing of the immune system may result from false alarms generated by the innate immune system, resulting in unexpected dendritic cell (DC) maturation after exposure to allergens. Conditions in the local microenvironment during DC maturation may also result in the preferential induction of Th2 responses. Recent progress has been made in our understanding of the role of DCs in both Th2 sensitization to aeroallergens and the regulation of Th2 and Th1 immunity.

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Abbreviations

DC	dendritic cell
IL	interleukin
LN	lymph node
LPS	lipopolysaccharide
PAMP	pathogen-associated molecular pattern
Th	T helper

Introduction

Atopic asthma is an allergic disorder of the airways in which environmental protein antigens trigger T helper type 2 (Th2) pulmonary inflammation, resulting in infiltration of eosinophils into the lung, airway hyperreactivity, mucus hypersecretion and the production of IgE. Despite the clear role of Th2 cells in the pathogenesis of asthma, less is known about what factors are required to generate Th2 immunity to inhaled environmental antigens.

The dendritic cell (DC) is an essential factor in CD4⁺ T cell priming and is thought to be important in T cell differentiation. The central role of activated DCs is supported by their potency in T cell priming and their optimal distribution for antigen surveillance in the periphery [1,2]. The maturation of DCs represents a key

regulatory step in T cell activation. Conserved microbial structures or ‘pathogen-associated molecular patterns’ (PAMPs) constitute a principal group of DC maturation factors [3]. Recognition of PAMPs takes place through pattern recognition receptors including Toll-like receptors (TLRs), which thereby represent a link between the innate and adaptive immune systems [4]. Many of the ligands for TLRs have been shown to have both a positive and a negative effect on allergic airway disease. How the interaction between DCs and microbial stimuli influences Th2 sensitization is, however, less clear.

The role of DCs in the induction of Th1 immunity has been relatively well characterized (Figure 1). Uptake of antigen in peripheral tissues by a DC in the context of a PAMP leads to DC maturation and migration to lymph nodes (LNs; [2,5]). This is associated with the cessation of antigen phagocytosis, which in turn prevents the presentation of bystander or self-antigens on activated DCs. In the LNs, antigen presentation on MHC class II molecules, coupled with expression of co-stimulatory molecules by mature DCs, results in the activation of naïve CD4⁺ T cells. Concomitant production of IL-12 results in Th1 differentiation.

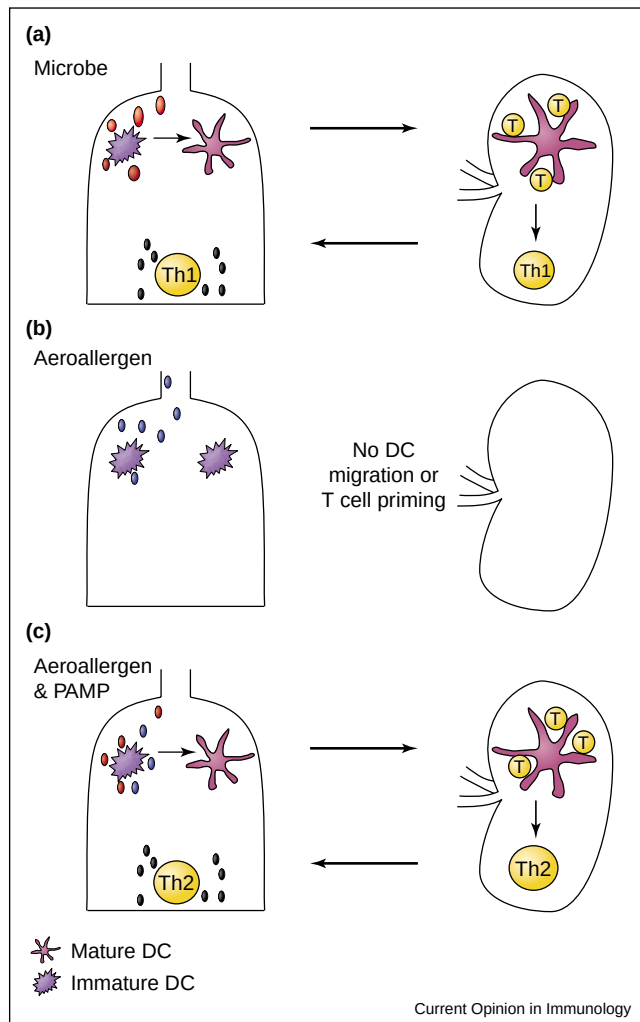
Although this conventional model of T cell priming adequately accounts for Th1 sensitization, the induction of Th2 responses is less well understood. Work done in the past five years has clearly established the central role of DCs in the induction and re-elicitation of Th2-mediated airway inflammation in asthma; however, two major questions remain. First, how do DCs acquire an activated phenotype after inhalation of protein antigens? Second, why are Th2 cells, rather than Th1 cells, induced after allergen exposure in the lung?

Here we review recent advances on the role of DCs both in Th2 sensitization to aeroallergens and in the differential regulation of Th2 and Th1 immunity.

Activated dendritic cells are imperative in allergic airway disease

Numerous studies have established the central role of DCs in the induction of Th2-mediated allergic responses. Studies of individuals with atopic disease and animal models of asthma have shown that DCs are recruited to the airways during allergen provocation and that these DCs have a tendency to stimulate Th2 responses *ex vivo*, as compared with pulmonary DCs from healthy controls [6–8]. Furthermore, DCs have been shown to be necessary for re-eliciting disease and maintaining chronic

Figure 1



Activation of pulmonary dendritic cells and sensitization to aeroallergens. Immature DCs in the lung sample the local microenvironment and, given the proper stimuli, mature. Maturation induces DC migration to the draining LNs, where CD4⁺ T-cell priming and differentiation occurs. Activated T cells migrate back to sites of antigen exposure. In the case of microbes (a), PAMPs initiate this highly regulated process, which usually results in Th1 immunity. By contrast, most inhaled protein antigens are inert (b) and would not be expected to induce the DC maturation process; therefore, T-cell immunity would not be expected. But aeroallergens are associated with robust Th2 immunity and thus another signal must be initiating DC maturation. Several studies have found that various PAMPs can account for this concomitant signal (c).

pulmonary inflammation [9,10]. Finally, the strongest evidence for a direct role of DCs in allergen sensitization has recently come from DC transfer experiments showing that antigen-loaded DCs are sufficient to induce Th2 sensitization [11[•],12].

DC migration to secondary lymphoid organs is integral to the initiation of an immune response. Chemokines and

their receptors direct cellular migration and tissue localization [5]. CCR7, a key chemokine receptor responsible for DC localization to the LNs, has been found to be important in eliciting Th2 allergic inflammation in the lungs of humanized severe combined immunodeficient (SCID) mice after adoptive transfer of DCs [11[•]]. Recent work from our laboratory has found that the lipopolysaccharide (LPS) associated with protein antigens is also an important factor in inducing DC migration to the draining LNs [13[•]]. In the absence of DC migration, Th2 cell sensitization to inhaled antigens does not occur; therefore, in contrast to previous hypotheses in which DCs with a more immature phenotype were thought to favor Th2 induction, it now seems clear that DC maturation and migration are key steps in Th2 sensitization [14].

PAMPs are crucial for dendritic cell activation, even in allergy

The activation of DCs is a rate-limiting step in T-cell priming, as co-stimulatory molecule expression and antigen presentation on MHC II are significantly induced only during the DC maturation process [15,16]. The recognition of PAMPs by TLRs results in DC maturation [4], and initially these DC maturation factors were thought to induce Th1 responses exclusively because of their propensity to induce production of IL-12 [17]. Only recently has the link between the innate immune system and the Th2 arm of the adaptive immune system been evaluated.

Recent studies have shown that protein allergens do not activate APCs *in vivo* or *in vitro* in the absence of a PAMP [13[•],18[•],19]. Furthermore, without this DC maturation stimulus, allergens cannot induce Th2 sensitization. Thus, the necessity for DC maturation via signals provided by the innate immune system seems to be a universal requirement for both Th1 and Th2 activation. Therefore, immunity to aeroallergens may result from concomitant exposure to PAMPs (or other innate signals), which results in DC activation and, eventually, in Th2 priming (Figure 1).

Nature versus nurture: are dendritic cells pre-committed to Th1 or Th2 differentiation?

Subsets of DCs have been identified in humans and mice on the basis of differences in their expression of cell-surface markers, tissue distribution and cytokine production profiles [20]. Specific DC subsets, termed DC1 and DC2, were initially thought to be fixed in their ability to induce Th1 and Th2 responses, respectively [20–22]. Whether these DC1 and DC2 subtypes arise from a common precursor or distinct lineages has not been resolved.

Recent advances have clarified the role of DC commitment in Th cell differentiation. In support of DC specialization, human DC subsets have been found to

express distinct repertoires of TLRs [23]. Recently, Boonstra *et al.* [24**] found that plasmacytoid and myeloid DCs from mice also show differences in TLR expression. When stimulated with the appropriate TLR ligand, however, both subtypes of DCs are capable of inducing Th1 responses. Furthermore, our laboratory has also found that the production of IL-12 by murine bone marrow DCs differs depending on the dose of PAMP that the DC experiences. This differential production of IL-12 is correlated with the generation of Th1, rather than Th2, immunity to inhaled antigens [13*].

The notion of pre-programmed DC1s or DC2s has been further challenged by recent studies highlighting their flexibility to induce either Th1 or Th2 responses depending on the presence of different activating stimuli [25*,26–29]. De Jong *et al.* [30**] found that different microbial compounds induced either DC1s or DC2s from human peripheral blood mononuclear cells. Similarly, Boonstra *et al.* [24**] found that both murine myeloid and plasmacytoid DCs could be induced to drive Th1 differentiation, depending on the presence of specific PAMPs. Either subset could also induce Th1 or Th2 differentiation in the presence of a high or low dose of antigen, respectively. Thus, under the appropriate conditions, subsets thought to induce exclusively Th2 responses can induce Th1 responses and vice versa.

Rather than supporting the idea that specialized DC subsets are pre-committed to induce one type of Th cell response, these studies highlight the flexibility of DCs to respond to environmental conditions (Table 1). Thus, a single subtype of DC may be able to initiate Th1 or Th2 responses to subsets of immune stimuli, thereby providing the immune system with both flexibility and specificity in its response to an environmental challenge.

Dendritic cell determination of Th2 immunity: Th2 by default or a third signal?

The above studies clearly demonstrate that DC maturation and migration are necessary steps in Th2 priming to

aeroallergens. Furthermore, DC subsets do not seem to have pre-programmed phenotypes that determine T cell lineage commitment, but rather DCs seem to respond to environmental instruction. Given this plasticity, how DCs selectively induce Th2 responses is not clear. One possibility is that once the prerequisite DC maturation signals (MHC class II and co-stimulatory molecules) are accomplished, Th2 differentiation occurs by default in the absence of Th1-inducing stimuli. Alternatively, a 'third signal' hypothesis has been proposed in which DCs must actively participate in Th2 differentiation [31]. Below we consider recent evidence in support of these two alternatives.

Th2 immunity by default

Traditionally, the induction of Th1 responses has been thought to depend on IL-12 production by DCs, although related Th1-inducing cytokines have been recently identified (IL-23 and IL-27) [32–35]. It is plausible that the only difference between the induction of Th1 versus Th2 responses after activated DCs have delivered signals one and two is the production of IL-12. Indeed, several recent clinical and animal studies have identified an inverse relationship between IL-12 and Th2-mediated lung disease.

For example, Rieder *et al.* [7] found that DCs from individuals with atopy produced less IL-12 than did healthy individuals, and work from our laboratory [13*] found increased IL-12 production from DCs under conditions that elicited Th1, rather than Th2, airway inflammation in a murine system. Although these studies establish that Th2 differentiation may result in the absence of IL-12, the possibility that another DC-derived signal is required to actively generate Th2 responses cannot be ruled out.

Alternatively, a lower ratio of DCs to T cells in the LNs has been proposed as a mechanism by which Th2 polarization is favored [36,37]. Again, it may be that DCs must provide signals one and two for T cell activation and, in

Table 1

Summary of pathogen or inflammation-derived signals known to favor the development of either Th1- or Th2-inducing dendritic cells.

	Th1-inducing dendritic cell	Th2-inducing dendritic cell
Microbial products	Pertussis toxin [30**]	Cholera toxin [30**] Filarial glycoprotein [29]
Microbial constituents	Poly(I:C) [30**] <i>Candida</i> yeasts [27] <i>Aspergillus</i> conidia [26] <i>Toxoplasma</i> extract [37]	<i>Schistosoma</i> egg antigens [30**] <i>Candida</i> hyphae [27] <i>Aspergillus</i> hyphae [26] <i>Mycobacterium</i> protein derivative [37]
Microbial dose	High-dose LPS [13*]	Low-dose LPS [13*]
Others	IFN- γ [28]	PGE ₂ [28] TSLP [52]

Abbreviations: IFN, interferon; PGE₂, prostaglandin E₂; TSLP, thymic stromal lymphopoietin.

the absence of significant DC migration to the draining LNs, Th2 differentiation is the default response. It should be noted, however, that these studies evaluated DC-to-T cell ratios *in vitro*, and it is uncertain how this effect will be related to T cell priming *in vivo*.

A third signal

DCs express a myriad of accessory molecules, many of which may actively influence Th2 differentiation after ligation of the T cell antigen receptor and could therefore represent a third signal provided by the DCs during T cell activation. The quality and intensity of co-stimulatory molecule expression on DCs has been proposed as one way of controlling the differential induction of Th1 and Th2 responses and thus is an essential factor to consider in Th2 sensitization. In response to maturation signals, DCs can express several types of co-stimulatory molecules on their surface, including OX40L, CD40 and members of the B7 family.

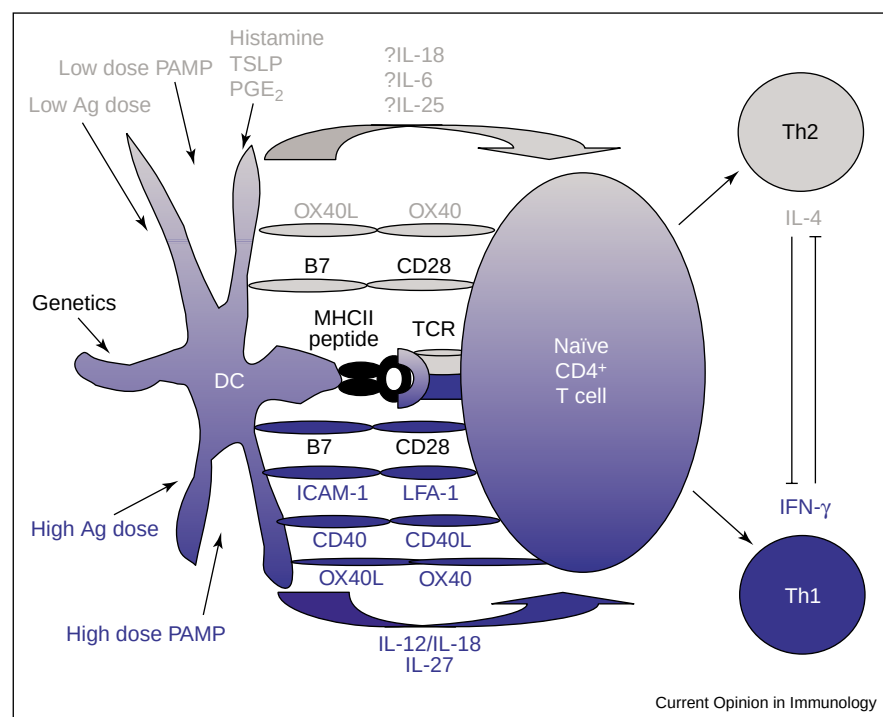
The role of traditional B7 family members, CD80 and CD86, in Th2 responses is well established [16]. Another family member, B7h, and its ligand, ICOS, were thought to preferentially induce Th2 responses. Recent studies have shown, however, that B7h and ICOS may be important for both Th1 and Th2 responses, and may

not have a primary role in the induction phase of T cell immunity [38].

OX40L has been implicated in the induction of allergic responses and is expressed on the surface of DCs in a manner that seems to depend on CD28 signals. In initial studies, lung eosinophilia, mucus production and airway hyperresponsiveness were all significantly reduced in the absence of OX40 [39,40]. More recent *in vivo* studies have suggested that OX40 and OX40L are essential specifically during sensitization to allergens [40]. *In vitro*, OX40L has been shown to be a mechanism by which DC2s activate Th2 cells in an IL-4-independent manner [30^{••}]. Other studies suggest, however, that the role of OX40L may extend to Th1 immunity as well [41,42].

Another co-stimulatory molecule that is induced on the surface of DCs upon maturation is CD40. Engagement of CD40 by CD40L is thought to be important for IL-12 production and thus for the preferential induction of Th1 responses in several systems [43]. By contrast, studies using CD40L-deficient mice or the transfer of antigen-pulsed bone marrow DCs have demonstrated that CD40 is needed for DC-induced Th2 responses to *Schistosoma mansoni* [44[•],45]. Few studies have been carried out on the role of CD40 in allergic disease. However, one recent

Figure 2



The differential regulation of Th1 and Th2 induction by dendritic cells. Th2 differentiation is induced by DCs at low doses of antigen (Ag) or PAMPs, whereas Th1 differentiation is induced by DCs at high doses of antigen or PAMPs. Under both conditions, the upregulation of MHC class II and B7 molecules by DCs is essential for priming naïve CD4⁺ T cells. Proposed signals used by DCs to selectively favor Th1 or Th2 differentiation are indicated. ICAM-1, intercellular adhesion molecule 1; LFA-1, leukocyte function-associated antigen 1.

study has suggested that the proteolytic activity of the allergen Der p1 cleaves CD40, resulting in a reduced production of IL-12 and a shift towards Th2 responses *in vitro* [46]. Whether CD40 can account for DC1, as opposed to DC2, status in allergic sensitization *in vivo* remains to be fully elucidated.

Finally, IL-4 and several other cytokines, including IL-13, IL-18, IL-25 and IL-6, have been implicated in the induction of Th2 responses. The novel cytokine IL-25 was found to induce the production of Th2 cytokines in models of both infectious and pulmonary allergic disease [47,48]. IL-6 is a cytokine produced by DCs and other cell types and has recently discovered roles in the abrogation of tolerance and in Th2 induction in several non-allergic models of disease [49,50]. In addition, the production of IL-6 by pulmonary DCs may favor Th2 differentiation by inhibiting Th1 responses [51].

Although many of the above DC-derived stimuli have been shown to induce Th2 responses, there is obviously no clear picture of a strictly Th2-inducing cytokine or cell-surface molecule. Although DC induction of Th2 responses might be a passive process dependent on the absence of Th1-specific signals such as IL-12 or CD40, the role of OX40L, IL-25 and other molecules in Th2-mediated inflammation provides support for a potentially active, Th2 skewing process in allergic disease (Figure 2). Moreover, additional factors, such as thymic stromal lymphopoietin, histamine and complement, have been identified as possibly having a role in Th2 differentiation and thus may also contribute to a third differentiating signal [52–55].

Conclusions

The immune system is constantly faced with the challenge of mounting a potent defense to pathogenic organisms while maintaining tolerance to self and innocuous environmental antigens. Failure to maintain this balance has pathological implications for the host, such as autoimmunity, allergy and impaired resistance to infections. The generation of an appropriate CD4⁺ T cell response is therefore a pivotal component of this process.

Genetic background, site of antigen exposure and dose of antigen have all been proposed to determine the initiation of Th2 responses in allergic disorders. Without the proper environmental stimuli, however, allergen exposure should result in either tolerance or ignorance, as is the case for most of the population. Recent work has advanced the hypothesis that PAMPs associated with allergen exposure are crucial for DC maturation and migration, thereby unifying the pathways by which Th1 and Th2 adaptive responses are generated. Further studies have clarified how DCs may provide a 'third signal' during T cell priming, thereby directing T cell differentiation. Indeed, a number of new cytokines and

cell-surface molecules have been identified that are induced during DC maturation that can determine Th1 versus Th2 differentiation.

Therefore, rather than the type of DC that presents antigen to naïve T cells, as was previously thought, it may be instead the conditions that are present during DC maturation (such as the nature of microbial infection) that dictate which arm of the adaptive immune response is used. Future work focusing on the role of DCs in atopic disease will need to elucidate the specific signals DCs utilize to favor Th2 differentiation during sensitization to allergens. Modulation of DC function can thus have a significant impact on control of allergic responses and other diseases mediated by T cells.

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