

Dendritic Cell and Epithelial Cell Interactions at the Origin of Murine Asthma

Bart N. Lambrecht^{1,2,3} and Hamida Hammad^{1,2}

¹Unit Immunoregulation and Mucosal Immunology, VIB Inflammation Research Center, Ghent, Belgium; ²Department of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium; and ³Department of Pulmonary Medicine, ErasmusMC, Rotterdam, The Netherlands

Abstract

Dendritic cells (DCs) are ideally placed in the airways and lungs to capture inhaled allergens. Different subsets of DCs perform different tasks. Migratory conventional DCs (cDCs) expressing CD11b mediate Th2 priming to respiratory allergens, whereas cDCs expressing CD103 mediate tolerance to them. Monocyte-derived DCs are poorly migratory antigen-presenting cells that mainly produce proinflammatory chemokines and are necessary for maintaining allergic airway inflammation once initiated. The function of the airway DC network is closely controlled

by cytokines released from airway epithelial cells. Airway epithelial cells react to pathogen-associated molecular patterns and damage-associated molecular patterns released on allergen inhalation by producing pro-Th2 polarizing cytokines and chemokines that attract and activate DCs. This conceptual framework of epithelial and DC collaboration is very helpful in explaining the process of allergic sensitization and how this is influenced by genetics and environment.

Keywords: dendritic cells; epithelial cells; barrier function; cytokines

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Correspondence and requests for reprints should be addressed to Bart N. Lambrecht, M.D., Ph.D., VIB Inflammation Research Center, Ghent University, Technologiepark 927, B-9052 Zwijnaarde, Belgium. E-mail: bart.lambrecht@dmb.vib-ugent.be

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Constant exposure of the immune system to many antigens means that it has to distinguish between pathogens and innocuous antigens. Dendritic cells (DCs) act as sentinels that continuously monitor the environment for microorganisms and other substances. These professional antigen-presenting cells (APCs) take up foreign antigens and present them to naive T cells in the draining lymph nodes to initiate immune responses. It is very established how DCs initiate a protective Th1, Th17, and/or cytotoxic T lymphocyte immune response against pathogens, tailored to clear the inciting pathogen (1). By expressing pattern recognition receptors for foreign

antigens, and by expressing a plethora of antigen uptake receptors, DCs can sense the nature of the pathogen and process a large variety of antigens for presentation to naive T cells. In this process they display peptide–major histocompatibility complex complexes on their surface (signal 1 for T cell activation), display costimulatory molecules (signal 2), and produce the polarizing cytokines (signal 3) for driving the expansion and differentiation of various T cell subsets. Not surprisingly, mice lacking DCs have strong defects in antibacterial, antifungal, and antiviral immunity that depend on Th1, Th17, and cytotoxic T lymphocyte response (2, 3). It has been much more

controversial if and how DCs have a central role in the Th2-type inflammation that develops in response to environmental allergens such as house dust mite (HDM), cockroach allergen, tree and grass pollen, fungal spores, and animal dander (4, 5). Th2-type inflammation that is commonly seen in allergic inflammation is typically rich in eosinophils, mast cells, basophils, and alternatively activated macrophages (M2 macrophages) and is controlled by adaptive Th2 immune cells that produce IL-4, IL-5, and IL-13 in collaboration with innate lymphoid type II cells (ILC2), which produce mainly IL-5 and IL-13 (Figure 1) (6). Here we review the role of antigen-presenting DCs in

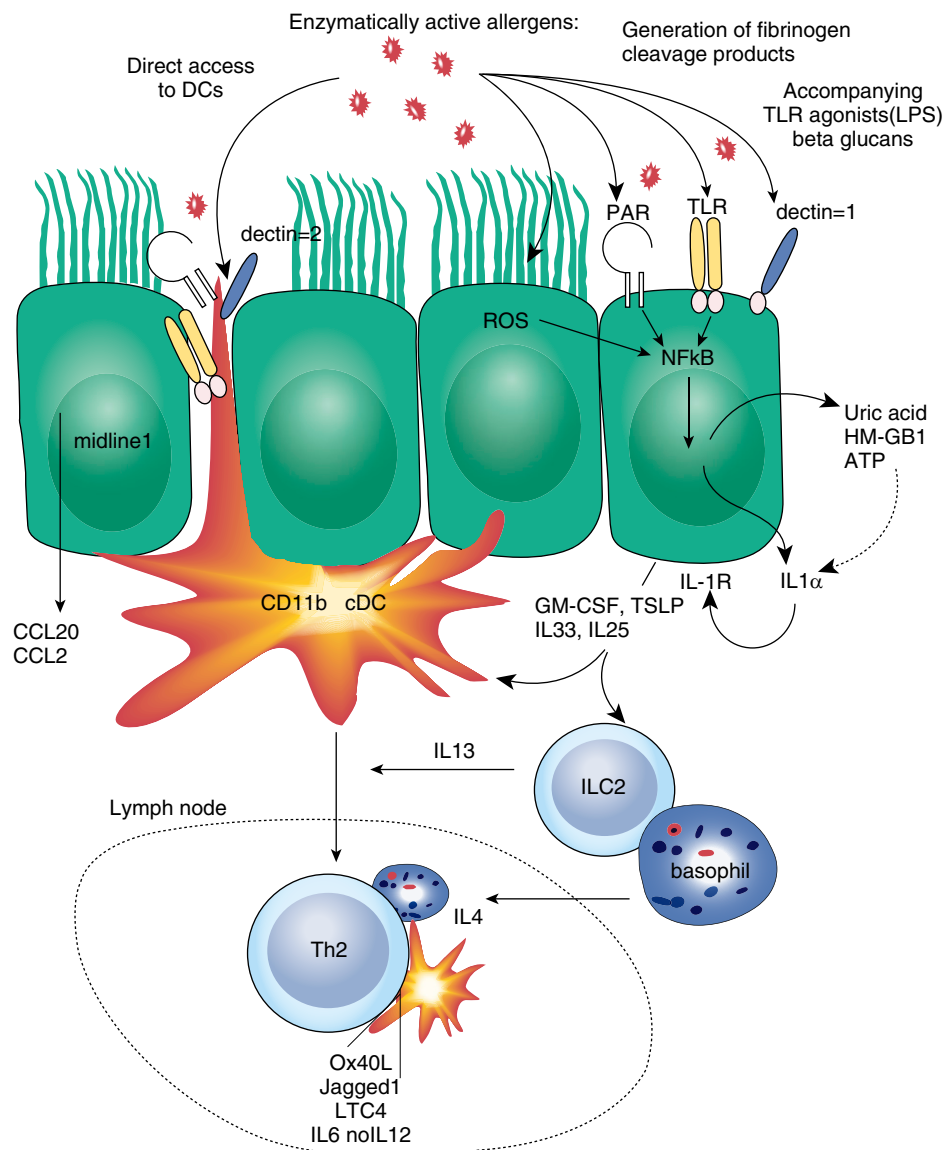


Figure 1. Crosstalk between dendritic cells (DCs) and epithelial cells leading to Th2 sensitization. Allergens that are inhaled can either directly activate DCs that express pattern recognition receptors (Toll-like receptors [TLRs], protease-activated receptors [PARs], and dectin 2) on their surface. Triggering of these pathogen recognition receptors leads to activation of DCs that migrate to the lymph nodes. Alternatively, allergens can first be recognized by bronchial epithelial cells that express the same types of receptors. Activation of epithelial cells occurs via reactive oxygen species (ROS) generation and via activation of transcription through the transcription factor nuclear factor (NF)- κ B. In epithelial cells, this leads to production of endogenous danger signals like uric acid, high mobility group box 1 (HMGB1), and ATP. These endogenous danger signals amplify IL-1 α , which in its turn activates production of cytokines granulocyte-macrophage colony stimulating factor (GM-CSF) and thymic stromal lymphopoietin (TSLP) and IL-33 to boost that activation of DCs. The DCs that are thus activated and migrate to the lymph nodes have a peculiar phenotype in that they lack the production of IL-12 yet are activated enough to induce Th2 immunity. This often occurs in a manner requiring IL-6 and the cell surface molecule Ox40L. Differentiation to Th2 immune cells is facilitated by the early presence of IL-4 and IL-13, which is made by innate immune cells like innate lymphoid cell (ILC)2s and basophils that also migrate to the lymph nodes.

causing the initial activation of Th2 cells to inhaled allergens during the process of sensitization, as well as their role in activation of effector Th2 cells in established allergic disease. We focus on the interaction of these cells with nearby epithelial cells. Although nonatopic

asthma shares many features with atopic asthma and is often exacerbated by chronic viral infections, we will not discuss this in further detail. More information on the involvement of DCs in respiratory viral infections can be found in a recent review (6).

DCs Are Necessary and Sufficient for Induction of Th2 Immunity

The contribution of DCs to the induction of Th2 immune responses has mainly been studied in models of asthma and allergic

rhinitis (6) as well as in models using the proteinase papain (7–9). Exposure to certain antigens causes allergic individuals to develop a Th2-dominated inflammatory immune response to the antigen in question, whereas healthy individuals mount a balanced Th1 and Treg response (10, 11). Allergic asthma is caused by continuous inhalation of allergens, which leads to chronic inflammation rich in eosinophils, metaplasia of goblet cells, and airway hyperresponsiveness. This eventually causes airway obstruction. Among the characteristics of asthma are IgE synthesis, eosinophil expansion and activation, mucus overproduction, and hyperreactivity of smooth muscle cells, and the IL-4, IL-5, and IL-13 produced by Th2 lymphocytes can control many of these features (12, 13).

To reach the immune cells circulating in the central lymphoid organs, an allergen must first penetrate the natural barriers of the body, namely the skin and mucus membranes. At the mucosal surfaces, allergens commonly come in contact with DCs (14, 15). In the lungs, intestine, and skin, DCs located on the basolateral side of epithelial cells sample luminal antigens by extending dendrites through the epithelial barrier (16–19). In humans and in mice, DCs in the lungs and gut express tight junction proteins and therefore might form tight junctions with epithelial cells to preserve the integrity of the epithelial barrier during antigen sampling (20–22, 23).

After taking up antigen, DCs migrate to the draining lymph nodes, where they present the processed antigen to T cells of the adaptive immune system. This presentation triggers clonal expansion of antigen-specific T cells. A central role for DCs in the induction of allergy would not be surprising, because allergy is dominated by an adaptive Th2 lymphocyte response. Indeed, strong evidence has proven this notion. When bone marrow–derived DCs or splenic DCs are cultured with granulocyte-macrophage colony stimulating factor (GM-CSF) and loaded with antigen and then injected in the lungs of mice, they can cause sensitization and lead to a Th2-driven inflammation and features of asthma when the mice are challenged with the antigen (24, 25). Some induction of Th17 cells also occurs in this adoptive transfer model, reflecting the mixed Th2/Th17 profile seen in human

asthma (25). Moreover, repeated injection of DCs into the lungs induces irreversible airway remodeling involving subbasement membrane deposition of components of the extracellular matrix (26). Likewise, when DCs from the lungs of mice exposed to allergen are transferred to naive recipients, they can induce sensitization and features of asthma (27–29).

The studies described above demonstrate the ability of DCs to induce Th2 immunity in the lung. Recent studies have also demonstrated that induction of Th2 immunity, bronchial hyperreactivity, and goblet cell metaplasia in response to allergens all require lung DCs. These manifestations were abolished when lung DCs were depleted in CD11c-DTR–transgenic mice when they were first exposed to the inhaled allergen HDM (29). Studies using sensitization models based on the use of the enzymatic model allergen papain or on helminth allergens indicate that DCs are required for a proper Th2 immune response (7–9, 30). Whether innate ILC2 and DCs interact functionally in asthma has not been studied. In a recent paper, Halim and colleagues show that in *Rora*^{sg/sg} mice (lacking ILC2s, but not Th2 cells), both the early innate and late Th2-mediated heightened eosinophilic and IgE response to inhalation with papain were abolished, pointing to an enforcing role for ILC2s in adaptive Th2 immunity (31). The most striking observation of the paper is that ILC2s promote Th2 immunity not through IL-4 (which they hardly produce) but by provision of IL-13. Th2 immunity to papain in *Rora*^{sg/sg} mice is restored by wild-type ILC2s but not by IL-13–deficient ILC2s. IL-13 stimulates migration of activated DCs to the lung draining nodes, pointing out for the first time that ILC2s and DCs cooperate to promote adaptive Th2 immunity.

In the context of allergy, it has been repeatedly suggested that basophils and eosinophils are also capable of antigen presentation and that they alone might be able to induce allergic responses (7, 32–34). However, an antibody to the high-affinity IgE receptor FcεRI was used in these studies to deplete basophils, and it is possible that DCs were depleted as well (29). Direct evidence for the ability of human basophils to present antigen and trigger Th2 immune responses is scanty (35). More likely, basophils cooperate with DCs to prime for Th2 immunity, possibly

by providing IL-4 at an early stage (29, 36). When lung eosinophils were directly compared with DCs, they did not demonstrate a strong antigen presentation function, except maybe for primed Th2 cells (37, 38).

Different Subtypes of DCs Induce Th2 Immunity

The different functions of DCs are believed to be performed by different subsets, a concept that is also slowly emerging in the field of lung immunity. DCs can be subdivided according to development from the bone marrow, tissue distribution pattern, expression of surface markers, and function (39). Human and murine DCs in the steady state are broadly grouped as conventional (c)DCs and plasmacytoid (p)DCs. The latter express Siglec-H, the bone marrow stromal antigen-1, B220, and Ly6C, and they can produce large amounts of type I interferons in the presence of viral infection. cDCs constitute the main group, which can be subclassified into lymphoid tissue–resident CD8⁺ and CD8[−] CD11b⁺ cDCs, and the nonlymphoid CD103⁺ and CD11b⁺ cDCs, found also in lungs, skin, and gut, and migrate to the draining nodes when encountering a foreign antigen. Both CD8⁺ and CD103⁺ cDCs depend on the transcription factors IRF8, Batf3, and Myc-L and are effective cross-presenters of exogenous antigens to CD8⁺ T cells and in generating short-lived T effector memory cells (40–42). The CD11b⁺ cDCs depend on the transcription factor IRF4 and Notch/RBPjk and excel in presentation to CD4 T cells and in generation of T central memory responses. These DC subgroups are present during the steady state, but during inflammation monocytes migrate to the local tissue to form moDCs (inflammatory DCs); this changes the picture (39, 43).

There has been recent interest in whether lung DC subsets induce Th1, Th17, or Th2 responses in different ways. Subsets of CD103⁺ and CD11b⁺ cDCs sorted *ex vivo* and stimulated with the model allergen ovalbumin induced Th1 and Th2 responses, respectively (44). This issue was also investigated *in vivo*, but sorting subsets during inflammation is daunting. Monocyte-derived DCs are rapidly recruited to the inflammation site in a CCR2-dependent way. The monocytic

marker Ly6C is commonly used to differentiate between CD11b⁺ MoDCs and CD11b⁺ cDCs. But because Ly6C is down-regulated when moDCs enter inflamed tissue, conventional surface marker staining could not distinguish between moDC and CD11b cDCs. Better markers are needed, and we and other researchers recently reported that moDCs express FcεRI (recognized by MAR-1), CD64, and MerTK, but CD11b cDCs do not (28). This approach was used to sort DC subsets from the lymph nodes of HDM-sensitized mice. Both CD11b⁺ cDCs and CD64⁺ moDCs could sensitize acceptor mice after adoptive intratracheal transfer, but CD103⁺ DCs could not. Mice deficient in Flt3L lacked all cDC subsets and also failed to induce Th2 immunity to low doses of HDM allergen. However, *Flt3l*^{-/-} mice still mounted Th2 immunity when a high dose of HDM was used, thus recruiting moDCs to the lung. Depletion of CD103⁺ in langerin-DTR mice did not abolish the hallmarks of asthma, confirming the redundancy of the role of CD103⁺ DCs in the HDM-driven asthma model (28). Recent findings indicate that CD103⁺ cDCs might even be tolerogenic toward inhaled allergens (45–48). The fact that CD11b⁺ cDCs seem to be necessary for Th2 immunity was also recently confirmed in *CD11cCre* × *Irf4*^{fl/fl} mice that selectively lack this subset of cDCs. These mice failed to mount Th2 immunity driven by ovalbumin and the Th2 adjuvant alum (49).

After injection of papain in the skin, basophils collaborate with DCs to induce Th2 immunity (Figure 1) (7, 33). Papain is captured by CD11b⁺ cDCs that also express macrophage galactose type C-type lectin 2 (CD301b) in the skin and various mucosae (50). Using the promoter of this gene to drive expression of the diphtheria toxin receptor, it was shown that conditional depletion of CD301b⁺ CD11b⁺ cDCs abolished the early generation of IL-4-producing Th2 cells to papain as well as to alum and to *Nippostrongylus brasiliensis*, although IgE responses to the parasite were intact (8). Similarly, *CD11cCre* × *Irf4*^{fl/fl} mice lack PDL-1⁺ CD301b⁺ cDCs in the skin-draining lymph nodes, and there was a defect on Th2 response generation to papain (9). Despite these reports, others have shown that DCs are not necessary to mount Th2 immunity to papain. The

most likely explanation is that with very high doses of allergen, there might be other APCs that come into play (33). For most allergens, including spores of the fungus *Alternaria* or cockroach allergens, there might be a spectrum of innate immune cells that come into play at various time points after allergen exposure. The relative contribution of these innate immune cells to induction of Th2 immunity in the lung depends on the dose of extract used, the presence of contaminating microbial products in the allergen extracts, and the timing of the experimental observations. This has created a lot of confusion in the field.

DCs Are Also Required for Effector Th2 Immune Responses to Allergens

It has been adequately demonstrated that DCs are both necessary and sufficient for inducing Th2 immunity in naive animals, but studies in mice from which DCs can be conditionally depleted have shown that they are also crucial during the allergen challenge period and when primed mice repeatedly encounter inhaled allergens (26, 51, 52). In areas of eosinophil-rich type 2 inflammation, DCs have an activated phenotype expressing higher levels of costimulatory molecules OX40L, CD80, CD86, PDL-1, and PDL-2 (51). In a secondary immune response, DCs are found very close to effector T cells and T resident memory (T_{rm}) cells in the regions of airways and large blood vessels (23, 53, 54). At these sites they might secrete chemokines to attract effector T cells or they might restimulate T_{rm} cells by providing costimulatory molecules (28, 55). Allergen-specific IgE and IgG1, by stimulating FcεRI and FcγRIII, respectively, provide strong enhancement because they target inhaled allergens to DCs in primed mice; this further boosts Th2 immunity (56, 57).

Though adoptively transferred moDCs can induce Th2 immunity, they more likely play a more important role during the effector phase of the immune response. MoDCs do not express CCR7 and thus do not migrate well to the draining nodes, so they likely interact with effector Th2 cells that migrate back to the lung or with T_{rm} cells (58). The observed attraction of effector Th2 cells by chemokines produced by moDCs provides support for this model

(28, 55, 59). They are also the predominant APC expressing FcεRI and RγRIII. The exact role of PDL-2 expression on DCs is currently unclear. PDL-2 was identified as a marker for the IRF-4-dependent Th2-inducing DCs of the skin (9).

DCs Activated Directly after Exposure to Allergen

Steady-state DCs are immature and must be activated and undergo maturation before they can migrate to the lymph nodes (in a CCR7-dependent manner) and initiate an immune response. DCs sense their environment via pathogen recognition receptor, such as Toll-like receptors (TLRs), nucleotide oligomerization domain (NOD)-like receptors, retinoic acid-inducible gene (RIG)-I-like receptors, and C-type lectin receptors (60, 61). Pattern recognitions receptors can detect various molecular patterns on microbes, called pathogen-associated molecular patterns (PAMPs), as well as molecules released by necrotic cells, called damage-associated molecular patterns. DCs also produce different cytokine receptors that can induce activation after they are secreted in an autocrine or paracrine manner. There is evidence that most allergens can activate different classes of pathogen recognition receptors, but the actual Th immune response might depend on the allergen, again creating some confusion in the field (60, 61). For example, glycans in the peanut glycoallergen ara h 1 can mediate DC activation and Th2 induction through DC-SIGN; in contrast, triggering DC-SIGN by the HDM allergen Der p 1 promotes Th1 immunity instead (62, 63). The mannose receptor on DCs mediates the uptake of various allergens through their carbohydrate moieties, leading to Th2 polarization (64). Triggering of the C-type lectin receptor dectin-2 on DCs by HDM induces the production of cysteinyl-leukotrienes (CysLT), Th2 attractive chemokines, and costimulatory molecules (59, 65). CysLTs then affect DC functioning in an autocrine manner through positive effects on the CysLT(1)R receptor and negative effects through CysLT(2)R. Mice deficient in CysLT(2)R developed a considerably stronger Th2 immune response to HDM, and adoptive transfer of DCs lacking CysLT(2)R had a similar effect. One of the main HDM

allergens, Der p 2, is a functional homolog of MD-2, the LPS-binding component of the TLR4 signaling complex, and so it amplifies TLR4 signaling and DC activation (66).

It is not quite clear how activated DCs, after migrating to the draining nodes, prime for Th2 immune responses because IL-4, which drives Th2 differentiation, is not produced by DCs. The situation is different for cytokines involved in Th1 and Th17 differentiation, namely transforming growth factor- β , IL-6, IL-12, and IL-23. It is possible that Th2 differentiation is the default pathway unless DCs produce Th1 or Th17 polarizing cytokines. Otherwise, ligands interacting with Notch receptors on Th cells might provide a direct polarizing signal for induction of Th2 immune responses (67, 68). Also, the B7 family costimulatory molecule PDL2 was identified as a marker of Th2-inducing DCs, although it remains to be shown if signaling via PD1 on T cells boosts Th2 immunity (9). It is believed that after migrating to the draining lymph nodes, DCs move to the T cell zone, where they activate T cells. But based on experiments in a model of *Heligmosomoides polygyrus* infection, León and colleagues (69) recently challenged the applicability of this proposition to Th2 immunity. They showed that B cells in the draining lymph nodes of infected mice secreted CXCL13 and recruited CXCR5-expressing DCs and T cells, resulting in DC-T interactions outside the T cell zone. Mice lacking CXCR5 on T cells or on DCs had impaired Th2 immunity against *H. polygyrus* infection, indicating that these interactions are required for optimal Th2 development (69). It is not known if this model is valid for all Th2-dependent immune responses. Polarizing pro-Th2 cytokines might also be delivered in trans from innate immune cells like basophils, mast cells, or ILC2s (as for IL-13 in the papain response).

Lung DCs Activated Indirectly by Epithelial Cells

Although DCs express pattern recognition receptors that can directly sense the environment, recent studies have shown that the epithelium is as important for activation of DCs after exposure to allergens (Figure 1) (70). This is certainly true for environmental adjuvants such as diesel particles, fine dust particles, and toxic gases like NO₂, all of which can promote Th2/

Th17 sensitization by DCs. Epithelial cells provide more than a physical barrier, because they express TLRs, C-type lectin, and protease-activated receptors (71). We and others have recently shown that DC activation requires TLR4 triggering on epithelial cells. In radiation-chimera mice lacking TLR4 on radiosensitive hematopoietic cells or radioresistant epithelial cells, the activation and migration of DCs depended on signals emanating from the radioresistant cells after HDM administration. On the other hand, HDM-driven allergic asthma could not be induced in epithelial cells lacking TLR4 (16, 68). Similar effects have been described for other TLR ligands like flagellin acting on TLR5 (72). The effects of triggering TLR4 seem to depend on the dose, because a high dose of endotoxin can also suppress the development of an allergic response to HDM (73). Airway epithelial cells produce the cytokines TSLP, IL-33, IL-25, and GM-CSF in a TLR4-dependent manner. These cytokines are essential for DC activation and allergic Th2 sensitization. The relative importance of these cytokines is related to the type of allergen or respiratory adjuvant, which has caused some confusion in the field (74, 75). TSLP is made not only by epithelial cells but also directly by DCs, and it acts on DCs and T cells to promote Th2 immunity (76). In mice lacking STAT5 (a crucial intermediary of TSLP signaling) only in DCs, Th2 immune response induction is severely defective. This phenotype resembles that of TSLPR-deficient mice, indicating that TSLP acts mainly through its effects on DCs that require STAT5 to respond to it (77). IL-33 too affects mainly the activation DCs and ILC2. Production of IL-33 by lung epithelial cells is strictly regulated; in homeostatic conditions it is suppressed by the recognition and clearance of apoptotic cells (78). When epithelial cells are exposed to allergen, they also produce trefoil factor 2 (TFF-2), which further increases the production of IL-33 in DCs and epithelial cells (79). Necrotic cells too can release IL-33, but there is not much in the literature about substantial necrotic cell death in asthma. Moreover, lung macrophages and DCs can also produce IL-33, and allergen-specific IgG1 immune complexes triggering the Fc γ RIII receptor greatly enhance this process (57).

Besides the well-known role of innate pro-Th2 cytokines, we and others recently

demonstrated a central role for IL-1 α in the crosstalk between epithelial cells and DCs in HDM allergy. In a manner that was dependent on the NLRP3 inflammasome and caspase-1, HDM triggered epithelial cells to produce IL-1 α and in an autocrine fashion led to the release of IL-33, TSLP, and GM-CSF. Cytokines downstream of IL-1 α (e.g., GM-CSF and IL-33) also played a role in DC activation. Consequently, mice deficient in IL-1R were resistant to the asthma caused by HDM (80). In contrast to this predominant IL-1 α role in DC activation, others reported that IL-1 β and caspase-1 mediated the adjuvant effects on DC activation and Th2 development in a model of NO₂-enhanced airway inflammation (81).

There are many studies on how the innate pro-Th2 cytokines are produced in response to various allergens. Epithelial cells (ECs) do produce cytokines, but they may also activate DCs by producing damage-associated molecular patterns in response to allergens. For example, ECs can induce DC activation by producing uric acid (UA), which is released in response to inhaled HDM in both mice and humans and plays a role in increasing cytokine production (82). UA crystals are classic activators of the NLRP3 inflammasome, but mice deficient in *Nlrp3* or *Asc* had normal HDM and UA-induced Th2 responses in the lung. Another inflammasome believed to negatively regulate other inflammasomes is NLRP10. This inflammasome was found to have a function in the induction of Th2 immune responses by regulating the ability of DCs to migrate to the draining nodes (83).

If epithelial cells are so decisive in controlling the activation of DCs, one can speculate that the threshold for recognition of allergens by epithelial cells is an important checkpoint in the development of Th2 sensitization to inhaled allergens. Many of the receptors expressed by the epithelial cells are TLRs and IL-1R family members, whose signaling cascades are also controlled by negative feedback mechanisms. One such mechanism involves the deubiquitinating molecule TNFAIP3, also known as A20. This enzyme turns off activating lysine-63 (K63) ubiquitin tags from key signaling intermediates in the TLR and IL-1R signaling pathway. Overexpression of A20 and of its binding partner ABIN1 (TNIP1)

in the lungs of mice was sufficient to suppress all the salient features of asthma (84, 85). Recently, a genetic polymorphism in TNIP1 was found to be associated with development of asthma (86). It will be interesting to see how this molecule is regulated and how it affects epithelial-DC biology.

The Role of Inflammatory DCs in Human Allergy

Monocyte-derived DCs have been grown *in vitro* for decades but have been hard to trace in human samples. Nevertheless, a recent study identified and characterized inflammatory (infl)DCs in general terms. Besides expressing CD11c and HLA-DR, (infl)DCs expressed CD206, CD11b, Sirp α , CD14, CD1a, and Fc ϵ R1. Analysis by microarray showed that the inflDCs were enriched for an *in vitro* moDC gene signature. This indicates that these inflDCs were derived from monocytes and that they were the *in vivo* counterparts of moDCs. The inflDCs produced Th17-polarizing

cytokines and preferentially induced Th17 cells. Whether the nature of the pathologic condition affects inflDCs T helper lymphocyte polarization is not yet known (43).

Inflammatory Fc ϵ R1⁺ DCs are present not only in allergic lungs but also in the skin of patients with atopic dermatitis, in which case they are named inflammatory dendritic epidermal cells (IDECs) (87). A phenotypically similar cell type has also been observed in the lungs of humans undergoing lung surgery, but we do not know if larger numbers of these moDCs exist in patients with asthma (88). But it is known that circulating and tissue-resident DCs of patients with asthma or allergy have higher levels of Fc γ RI armed with IgE (89, 90).

Conclusions

Much insight has been gained over recent years into how lung DCs initiate and maintain Th2 immunity to allergens and how lung epithelial cells influence

this function. This knowledge is crucial for interpreting ongoing genome-wide association studies and gene-by-environment interactions, which are being done on large groups of children. Studies on mice have led to much progress, but translational studies on human subjects with asthma are lacking. We need to understand better if the various subsets of DCs are also present in the human (asthmatic) lung, and we need to understand how we can selectively target the function of one subset, while leaving the other subsets unaffected. It will also be a big challenge to find strategies that target DCs without causing (local) immunodeficiency. Finally, we need to understand how the epithelial-DC crosstalk is influenced by ongoing disease and current and prior infection history. Unraveling these aspects will be complex, but holds the key for finding new therapies for asthma. ■

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