

T Cells in Allergic Asthma: Key Players Beyond the Th2 Pathway

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Abstract Asthma is a common chronic lung disease that affects 300 million people worldwide. It causes the airways of the lungs to swell and narrow due to inflammation (swelling and excess mucus build-up in the airways) and airway constriction (tightening of the muscles surrounding the airways). Atopic asthma is the most common form of asthma, and is triggered by inhaled allergens that ultimately promote the activation of the Th2-like T cells and the development of Th2-mediated chronic inflammation. Different subsets of T cells, including T follicular helper cells, tissue-resident T cells and Th2 effector cells, play different functions during allergic immune response. Dendritic cells (DCs) are known to play a central role in initiating allergic Th2-type immune responses and in the development of the T cell phenotype. However, this function depends on the complex interaction with other cells of the immune system and determines whether the response to environmental allergens will be one of tolerance or allergic inflammation. This review discusses cell interactions leading to the initiation and maintenance of allergic Th2-type immune responses, particularly those associated with allergic asthma.

Keywords Th2-driven allergic asthma · T follicular helper cells · Tissue-resident T cells · Dendritic cells · B cells · Epithelial cells

Introduction

Asthma is a chronic lung disease characterized by recurrent bronchospasms (smooth muscle spasm narrowing airways), airway inflammation, and mucus hypersecretion that ultimately lead to airway obstruction and breathing problems [1]. Allergy-induced asthma is the most common type of asthma [2]. Asthma symptoms begin when the body reacts to “innocuous” environmental antigens (allergens) such as house dust mites (HDM), animal dander, fungal spores, plant, or tree pollen. Inhaled allergens trigger a complex immune response that begins with the activation and differentiation of allergen-specific T helper type 2 (Th2) cells [3, 4] that, later on, control immunoglobulin E (IgE) production against allergens, IgE-dependent mast cell activation, eosinophil recruitment into the lung, and finally, persistent airway inflammation and asthma symptoms [3, 4]. Th2 cells mediate these functions by producing various cytokines such as IL-4, IL-5, and IL-13 [4]. Therefore, Th2 cells and their cytokine products are regarded as important targets for the treatment of allergic asthma.

Recent advances reveal that the induction of pathogenic allergen-reactive Th2 cells requires a two-step process that includes initial priming or “sensitization” and a posterior reactivation [1, 5]. Induction of allergen-reactive T cells expressing type 2 cytokine profile is a complex process that requires the coordinated interactions occurring between multiple cell types, both in the lungs, and lung-draining lymph nodes. Airway dendritic cells (DCs), the most potent antigen-presenting cells in the lung, are endowed with the capacity to integrate signals derived from the exposure to allergens and translate it to direct allergen-specific T cell responses [6, 7]. Therefore, the modulation of DC activation is crucial for the induction of Th2 cell-mediated immune responses against harmless allergens. Activation of DCs can be triggered by

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direct interaction with the allergen; however, it is now well accepted that the functional activation of DCs is critically influenced by interactions with other cells of the innate immune system [6, 7]. In this review, we will discuss the recent findings regarding how DCs and other cells types, including bronchial epithelial cells, type 2 innate lymphoid cells (ILC2), and B cells, work together to initially prime or “sensitize” allergen-specific T cell responses and later to reactivate/differentiate pathogenic Th2 responses to aeroallergens.

Priming of Allergen-Specific T Cells: T Follicular Helper Cells and Tissue-Resident Memory Cells

The development of an allergic reaction to an environmental allergen requires an initial exposure to the allergen or “sensitization” that induces a primary response, but does not cause pathology or symptoms. Second and subsequent exposures, however, result in the symptoms we associate with allergies [1]. Early studies indicate that allergen-specific T cells are primed after the first contact with the allergen, during the sensitization phase [1]. Upon subsequent exposure to the same allergen, these allergen-specific T cells migrate to sites of allergen exposure and produce Th2 cytokines [1, 5]. This has also been confirmed by adoptive transfer studies using CD4 T cells from naïve mice or from mice sensitized to HDM allergen. Specifically, we have shown IL-4 producing Th2 cells with high levels of IL-13 production can be generated from donor HDM-primed CD4 T cells but not from naïve CD4 T cells [8•]. Therefore, the development of cytokine producing allergen-specific Th2 cells in the site of allergen exposure requires a two-step process. The first step begins with the priming of allergen-specific T cells. The second step involves the re-exposure to the same allergen and the local infiltration of effector Th2 cells.

Using a mouse model of HDM exposure, we have shown that the initial intranasal sensitization with HDM induced the differentiation and expansion of IL-4-producing T cells in the draining lymph nodes. These IL-4-producing T cells also unregulated expression of the B cell homing chemokine receptor CXCR5 and B cell lymphoma 6 (Bcl6) transcription factor [8•], which define the T follicular helper (Tfh) cell lineage [9–12]. Tfh cells are a particular CD4⁺ T cell subset distinguished by their ability to deliver helper signals to the B cells and to promote B cell memory and long-lived plasma cell differentiation [9]. But, in addition to this function, recent studies suggest that Tfh cell are not lineage committed and, depending on the nature of the secondary stimulus, they retain the capacity to differentiate into effector cells [13•]. Specific pre-primed Tfh cells have been shown to be required for the induction of Th2 responses to HDM, since depletion of pre-existing IL-4-committed Tfh [8•] or the absence of Tfh cell-derived signals [14•] prevent effector Th2 cell responses after

HDM challenge. Therefore, Th2 responses are impaired in the absence of Tfh cells. In fact, IL-4-producing Tfh cells induced after HDM sensitization have been shown to differentiate into effector Th2 cells when recalled [8•]. These data indicate that Tfh cells are precursors of effector Th2 cells and are largely responsible for the production of a supply of new effectors after encounter with allergen. Several recent studies have provided evidence into the capacity of Tfh cells to persist following primary immunization and therefore to progress and become memory cells [15–20], retaining their flexibility/plasticity following reactivation with antigen [8•, 13•, 21, 22•]. These data argue in favor of the suggestion that Tfh cells might in fact serve as reservoirs of allergen-specific memory CD4 T cells in the secondary lymphoid organs.

Conversely, other studies have shown the generation of allergen-specific CD4⁺ lung resident T cells after the first intranasal contact with the allergen [23•]. Tissue-resident memory cells are memory T cells that are retained in the tissues and may be uniquely suited to provide immediate responses following exposure to the same antigen [24]. In a different acute HDM allergen challenge model, in which mice were exposed to a higher dose of the HDM allergen, HDM-specific lung resident memory T cells were generated after initial sensitization with HDM [23•]. Although HDM sensitization also induced memory cells in the draining lymph node, lung resident memory T cells were able to induce airway hyper-responsiveness. Local immunity by HDM-specific lung resident memory T cells is dependent on signals that antagonize Tfh cell differentiation, including the cytokine IL-2 [25•], and inhibited by pro-Tfh signals including the transcription factor BCL-6 [12] and B cell help [26]. These data suggest that allergen-specific CD4⁺ undergoing differentiation after priming can follow antagonistic pathways that generate either lymph node resident Tfh cells or tissue-resident memory T cells (Fig. 1). However, further work is needed to fully understand the factors that control this decision-making. HDM allergen Der p 1 cleaves CD25 on activated CD4⁺ T cells and therefore prevents IL-2 signaling [27], hence favoring the Tfh cell pathway. Therefore, the dose and composition of the HDM allergens and the levels of IL-2 released in response to the allergens must be critical to turn the differentiation of the CD4 T cells in one direction or another. Likewise, the outcome of this decision-making will then determine whether secondary responses to allergen require a continued demand for new waves of effector cells generated in the draining lymph nodes from lymph node resident Tfh cells or on the contrary require local activation of lung resident memory T cells. In this regard, recent data suggest that the amount of inhaled allergen is the cue [28•]. Although these data will be discussed later (see role of B cells in the priming of allergen-specific T cells), the new data suggest that lung resident memory T cells are strategically positioned to respond immediately and predominantly contribute to the induction of

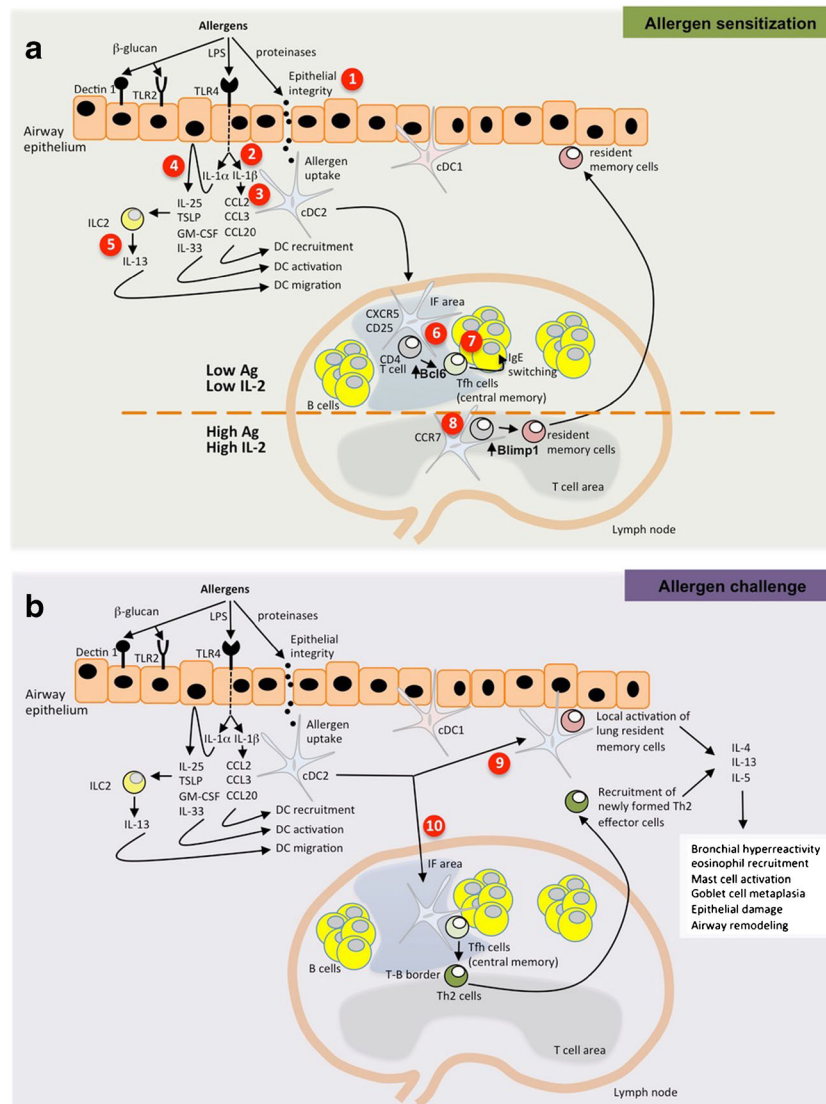


Fig. 1 Development of Th2 responses to allergens. **a** 1 Allergen interactions with the epithelium cause increased epithelial permeability, which facilitates allergen entry and uptake by cDC2s. 2 In response to allergens, lung epithelial cells produce IL-1 α and IL-1 β . 3 IL-1 β stimulates the production of chemokines by interstitial lung fibroblasts that induce cDC2s recruitment. 4 IL-1 α acts in an autocrine fashion to induce the production of instructing cytokines (e.g., TSLP, GM-CSF, IL-33) that favor cDC2s activation. 5 At the same time, ILC2s produce IL-13 in response to epithelium-derived cytokines, which supports cDC2s migration to the draining lymph nodes. 6 In the lymph node and under low-dose allergen exposure, cDC2s induce the initial priming of HDM-specific IL-4 committed Tfh cells in the interfollicular areas. 7 Later, allergen-specific IL-4-committed Tfh cells receive help from B cells for

their full differentiation program. IL-4-committed Tfh cells are retained in the lymph nodes, contribute to IgE production, and behave as central memory precursors that serve as a source of effector Th2 cells upon secondary and subsequent exposure to the same allergen. 8 On the contrary, under high-dose allergen exposure, cDC2s migrate to the T cell areas of the lymph node and prime allergen-specific lung resident memory cells in an IL-2-dependent manner. These memory cells rapidly migrate to the lung and mediate local and rapid local recall responses. **b** During allergen challenge, 9 DCs could locally restimulate effector functions in lung resident memory cells or 10 can migrate to the draining lymph node and induce the differentiation of lymph node resident Tfh cells into effector Th2 cells that migrate to the lung and locally produce Th2 cytokines

asthma features when they respond locally to high allergen doses [28••]. On the contrary, the allergen-specific lymph node resident CD4 T cells with characteristics of Tfh cells [8••, 22••] are reservoirs of antigen-specific memory CD4 T cells in the secondary lymphoid organs that significantly contribute to the secondary response and the allergen-induced features of asthma when the dose of inhaled antigen is limiting [28••]. Importantly, lymph node resident Tfh cells are able to

fuel effector immune responses in particular locations when these are re-exposed to the same allergen; however, they may also represent reservoirs of antigen-specific memory CD4 T cells that can uniquely contribute to systemic memory and to the activation, differentiation, and migration of effector cells to new locations that are first exposed to the allergen. In addition, Tfh cells are also responsible for IgE responses to HDM-derived allergens after allergic sensitization [29].

Therefore, Tfh cells not only represent a central memory precursor population of effector Th2 cells but also a source of help for the switching of B cells to production of allergen-specific IgE.

Priming of Allergen-Specific T Cells: The Role of Dendritic Cells

Dendritic cells (DCs) are professional antigen-presenting cell (APC) that are specialized to take up antigens and convert them into major histocompatibility complex (MHC)-peptide complexes that can be recognized by T cells [30]. Multiple subsets of DCs have been described and classified based on their localization, ontogeny, function, or the expression of cell surface markers [31, 32]. DCs can be subdivided into three main types with different origins, namely conventional DCs (cDCs), plasmacytoid DCs (pDCs), and monocyte-derived DCs (moDCs) (Fig. 2). cDCs and pDCs develop under steady-state conditions, whereas monocyte-derived DCs derive from monocytes under inflammatory conditions [32, 33]. pDCs are specialized in the production of type I interferons (IFNs) that respond to most viruses [31]. cDCs are the ones that are often involved in T cell priming, including the priming of allergen-specific CD4 T cell responses and hence will be the focus of this section. In mice, lymph node cDCs can be divided into resident and tissue-derived cDCs (also called migratory cDCs). Resident cDCs are also present in other secondary lymphoid organs like the spleen and are also called blood-derived DCs since they differentiate from blood-borne precursors once they enter lymphoid organs [31]. Tissue-derived cDCs, on the contrary, differentiate from circulating precursors that exit into peripheral tissues [31]. There, tissue-derived cDCs sample antigens and migrate constantly through afferent lymphatics to the draining lymph node, where they encounter and activate naïve T cells. Both resident cDCs and tissue-derived cDCs contain two major subsets: IRF8/CD103-expressing cDCs (recently called cDC1s) and IRF4/CD11b-expressing cDCs (recently called cDC2s) [32] (Fig. 2).

Tissue-derived IRF4/CD11b-expressing cDCs or cDC2s have been shown to induce Th2 responses to common allergens, such as HDM [34•, 35, 36•, 37] and the proteinase papain [38, 39], both in the lung [34•, 35, 36•] and skin [37–40] draining lymph nodes.

Expression of the transcription factor IRF4 plays an important role in the biology of tissue-derived IRF4/CD11b-expressing cDC2s, and conditional deletion of IRF4 in DCs selectively impairs the development of allergen-specific effector Th2 responses. DC-specific *Irf4*-deficient mice generated in one particular CD11c-Cre system have been described to lack certain populations of tissue-derived cDC2s in several publications [38, 41, 42], suggesting that expression of IRF4 is required for development of these DCs. However, other publications [36•]

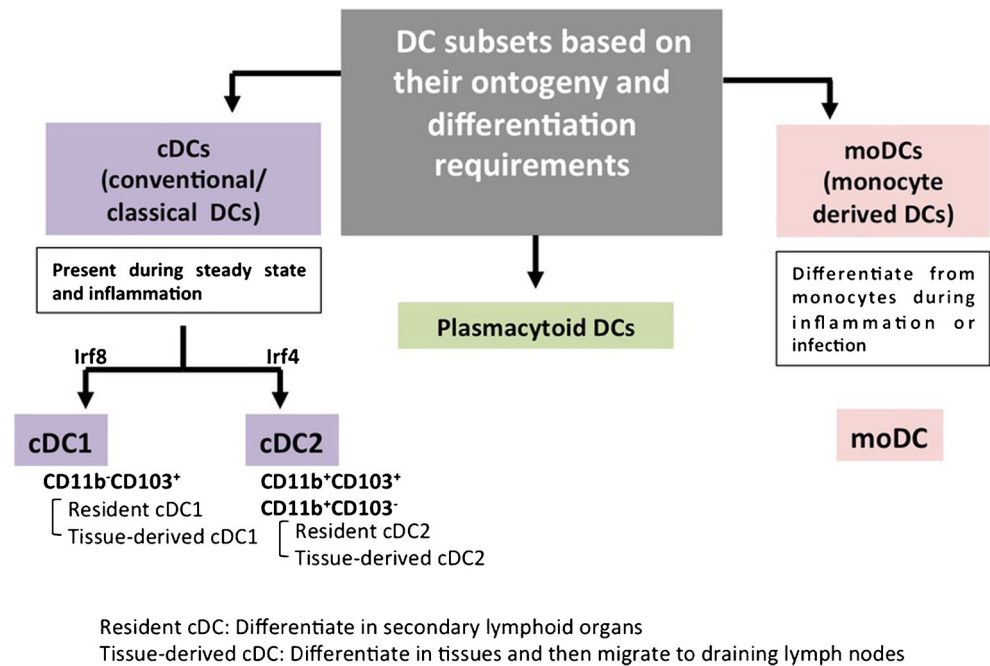
(including our unpublished observations) did not find defects in the development of DC subpopulations using a different CD11c-Cre system, containing a shorter inserted expressed sequence (5 kb) of the 5' *Cd11c* promoter region. Since, IRF4 is required in the CD11c + cDC precursors (pre-cDCs) for differentiation of cDC2s, it might be suggested that those CD11c-Cre systems that are expressed at the pre-cDC stage would result in the lack of cDC2 subpopulations, whereas the use of CD11c-Cre systems that results in the deletion of the *Irf4* gene after the pre-DC stage of development will otherwise have normal differentiation of cDC2s. If that were true, IRF4 would not be required for homeostasis of already differentiated cDC2s. However, additional work is still required in others to clarify the differences between these two CD11c-Cre systems and how they drive deletion of IRF4 at different stages of DC development. In addition to controlling the differentiation of cDC2, IRF4 has been shown to exert selective effects on cDC2 activation and Th2 cell function. IRF4 regulates the migratory function of cDC2 in the skin [43], the MHC class II antigen presentation capacity of cDC2 [44], and their capacity to respond to TLRs and upregulate Blimp1 [45], IL-10, and IL-33 [36•]. Whether the lack of these functions by cDC2 can selectively affect the induction of Th2 responses is a matter for further investigation.

Although, IRF4/CD11b-expressing cDC2s have been identified in several publications as important players in the induction of Th2 responses to common allergens such as HDM or papain, others have also found that IRF8/CD103-expressing cDC1s can prime Th2 responses to inhaled OVA [46]. Papain is a cysteine protease and group 1 HDM allergen has papain-like cysteine protease activity. Therefore, it is possible that protease activity of allergens controls allergic sensitization via IRF4/CD11b-expressing cDC2s, whereas proteolytically inactive antigens induce T cell responses via IRF8/CD103-expressing cDC1s. This scenario implies that DCs subsets are not pre-designed to induce a specific T cell response. Instead, DCs subsets are endowed with functional plasticity that allows them to induce different immune responses according to the microenvironment. For example, lung-derived IRF8/CD103-expressing cDC1s are located in close contact with the epithelial cells and therefore are more exposed to the allergens, whereas IRF4/CD11b-expressing cDC2s accumulate deeper in the lung parenchyma [47]. Therefore, the function of these DCs may depend on the accessibility of the antigen and the antigen-promoting microenvironment inflammation. Hence, the capacity to induce Th2 responses may not be linked to one specific DC subpopulation, but rather, may be dependent on the nature of the antigen.

Role of Epithelial Cells in Th2-Skewing Function of DCs

The function of the airway DCs is closely controlled by their intimate association with airway epithelial cells. Disruption of

Fig. 2 Classification of DCs. On the basis of their ontogeny, DCs can be classified into monocyte-derived DCs, plasmacytoid DCs, and conventional DCs (cDCs). cDCs can be further subdivided by their function and phenotype into type 1 (cDC1s) and type 2 (cDC2s). On the basis of their localization and migratory behavior, cDC1s and cDC2s can be additionally subdivided into resident and tissue-derived DCs



the integrity of the epithelial barrier by intrinsic proteolytic activity of allergen [48] may facilitate the penetration of allergens deeply into the tissues but additionally can affect the activation of the airway epithelial cells and the release of mediators [49], which provide a pro-inflammatory environment that promote DC activation.

Although DCs may be directly stimulated by allergens, recent studies have demonstrated that the allergen interaction with epithelium is essential for the functional activation of DCs after exposure to allergens *in vivo* [4]. Both DCs and epithelial cells express pattern recognition receptors that recognize conserved structures expressed by various pathogens but absent from host cells [50]. Allergens also express conserved structural patterns not present in the host. Specifically, allergens are glycosylated and can be recognized by various receptors in DCs, including DC-SIGN [51, 52] and mannose receptor [53, 54]. In addition, DCs can recognize allergens such as HDM through toll-like receptor 4 (TLR4) [55]. Epithelial cells also recognize glycosylated motifs in allergens through Dectin-1 [56] and TLR2 [57], or via lipopolysaccharide (LPS)-driven TLR4 signaling [58•]. *In vitro* studies have shown that allergen glycosylation is important for allergen recognition and internalization by DCs [53, 54, 59]. It is still unclear, however, whether this is also relevant *in vivo*. In epithelial cells, conversely, recognition of allergen-derived β -glucan motifs or activation of TLR2, TLR4, or protease activated receptor 2 (PAR2) induce the release of cytokines and chemokines implicated in the migration and activation of DCs, such as CCL-2, CCL-20, interleukin 1 α (IL-1 α), IL-1 β , IL-18, IL-33, IL-25, thymic stromal lymphopoietin (TSLP), and granulocyte-macrophage colony-stimulating factor (GM-

CSF) [49]. Therefore, although the allergen-specific pattern recognition by DCs may trigger antigen internalization for processing and antigen presentation, the allergen recognition by epithelial cells has been demonstrated to be essential for the functional activation of DCs, which in turn is needed to induce effective T helper cell responses.

Among the pathogen-associated conserved patterns present in allergens, LPS is likely the most studied in the context of Th2 sensitization. The dose of LPS is a determining factor in the development of allergic inflammation. Whereas low doses of LPS are necessary to cause Th2 sensitization to inhaled allergens, high doses of LPS attenuate the development of allergen-induced allergic inflammation [58•, 60, 61]. HDM allergens contain low levels of LPS [58•] and additionally HDM allergens contain the protein Derp2 that facilitate TLR4 signaling by functional mimicry of TLR complex protein [62]. In mice, the development of Th2-biased allergic inflammation to inhaled HDM or model antigens depends on TLR4 expression on epithelial cells [58•, 63, 64]. TLR4 triggering on radioresistant cells, most likely epithelial cells, upon HDM administration caused the production of CCL20, CCL2, and CCL3 and the recruitment of DCs to the lung [58•, 63]. CCL2 and CCL20 are mainly produced by interstitial lung fibroblasts in response to IL-1 β released by activated epithelial cells [65]. In addition, TLR4-mediated epithelial cell activation induced the production IL-1 α , which then acted in an autocrine manner to trigger the release of TSLP, GM-CSF, and IL-33 [58•, 66]. The release of these mediators was associated with (1) functional activation of DCs, including the upregulation of the costimulatory molecules CD40, CD86, and OX40L, which are required for full activation of

naïve T cells; (2) the increased DC migration to lymph nodes, where they encounter T cells and the increased capacity to stimulate there antigen-driven T cell proliferation and differentiation into Th2 cells that secrete Th2-type cytokines; and (3) the induction of the salient features of asthma, such as eosinophilic inflammation, goblet cell hyperplasia, and airway hyper-responsiveness [58••] (Fig. 1). Inversely, lung epithelial cells can also have an anti-inflammatory role during immune responses to airway allergens such as HDM by producing IL-10 and restricting IL-33 production via small GTPase Rac1-dependent engulfment of apoptotic epithelial cells [67].

As mentioned before, epithelial cells are known to express multiple receptors involved in allergen recognition, including different TLRs, C-type lectin receptors, and PARs; therefore, many of the effects described here for HDM and TLR4 would also be true for other allergens signaling through other receptors.

Priming of Allergen-Specific T Cells: The Role of B Cells

We and others have demonstrated that Th2 cell responses following sensitization and challenge with common allergens such as HDM are dependent on DCs [8••, 34•]. Our studies revealed two critical ways in which DCs are important, first for carrying allergen from the lung to the regional lymph node and second for priming allergen-specific CD4⁺ T cell via presentation of MHC class II-allergen peptide complexes to CD4⁺ T cells [8••]. However, antigen presentation by DCs alone is not sufficient for the development of Th2 cell responses to HDM, but also requires additional cognate interactions with antigen-presenting B cells [8••]. As mentioned before, sensitization with HDM elicits allergen-specific IL-4-committed Tfh cells that rapidly differentiate into secondary effector Th2 cells that infiltrate lung tissue after challenge. DCs found near the B cell follicles initially prime Tfh cell responses [8••, 68]. However, continuous Ag-presentation by B cells is necessary to complete the Tfh cell differentiation program [8••, 26] (Fig. 1). Therefore, DCs and B cells synergize to expand specific IL-4-committed Tfh precursors of effector Th2 cells during the HDM sensitization phase.

However, data from a recent study suggest that this synergy seems to be much more important at low-dose antigen exposure, under which B cells are necessary for the optimal priming and expansion of IL-4-committed central memory CD4⁺ T cells that serve as precursors of effector Th2 cells, and for the development of the characteristic features of asthma, such as eosinophilia and hyper-reactivity in murine airways [28••]. Tfh cells and central memory cells CD4⁺ T cells are intimately bound [22••, 69, 70] and therefore the IL-4-committed central memory CD4⁺ T cells described in this study most likely resemble IL-4-committed Tfh precursors. However, more

investigations are needed to establish the precise developmental relationship between these cells. High-dose antigen exposure, on the contrary, can elicit features of asthma in the absence of B cells [28••]. Tfh cell responses are associated with prolonged antigen presentation by B cells after initial DC-mediated priming [26]. However, late B cell-mediated antigen presentation is not required when antigen is in excess. Indeed, DCs can substitute for B cells to present antigen and support prolonged Tfh cell responses when mice receive high-dose repeated antigen exposure [71]. Therefore, it is a possibility that under high-dose allergen exposure, IL-4-committed Tfh precursors can still be generated and maintained in the absence of B cells. These data may suggest that the antigen dose/availability determine whether Tfh cell priming and later maintenance is dominated by DCs themselves or requires synergistic antigen presentation transition from DCs to B cells. Alternatively, high dose of antigen can elicit the differentiation of CD4⁺ lung resident T cells that mediate asthma features on local allergen encounter. These cells are inhibited by B cells and depend on signals that antagonize Tfh cells differentiation, including the cytokine IL-2 [23••, 25••]. Thus, under conditions of strong antigen stimulation, dendritic cells may acquire the activation necessary to induce IL-2 production in responding T cells and therefore promoting their differentiation into CD4⁺ resident T cells that migrate into the lungs and at the same time inhibiting the differentiation of IL-4-committed Tfh memory precursors in the lymph node (Fig. 1). Besides the dose, allergens displaying with different enzymatic activities may impact T cell responses differently. For example, HDM selectively cleaves CD25 from T cells and as a result T cells lose their capacity to respond to IL-2 [27]. Therefore not only the dose but also the catalytic activity of HDM may determine the requirement for B cells and the differentiation of IL-4-committed memory precursors, including resident vs. Tfh cells.

The exact mechanism by which DC prime Th2 responses to inhaled antigens is still not clear. Various molecular pathways have been implicated including TSLP [72], OX40-OX40L [72–75], Notch ligands [76], and suboptimal TCR triggering [77–80]. However, none of these pathways are exclusively involved in Th2 differentiation. Importantly, priming of effector Th2 responses seems to occur within the T-B cell border or the interfollicular zone of the lymph node. Recently, we found that following nematode infection, intestine-derived IRF4/CD11b-expressing cDC2s upregulate CXCR5, downregulate CCR7, and home to the T-B cell border and the interfollicular regions of the draining lymph nodes in response to CXCL13, where they prime effector Th2 cell responses [81••]. Expression of CXCL13 is dependent on B cells and in their absence, DCs fail to localize in the T-B borders and interfollicular regions of the lymph node and the development of Th2 responses is impaired [81••]. Importantly, the initiation of the Tfh cell responses also seems to occur

within the interfollicular area of the LN, where responding CD4⁺ T cell start to express BCL-6 and CXCR5 [82]. Therefore, the localization of DCs in the interfollicular zone of the secondary lymphoid organs is likely to be instrumental for their ability to prime Tfh and Th2 cell responses, not only to pathogens but also to allergens. In agreement, we found that lung-derived, HDM-bearing cDC2s preferentially localize within the interfollicular area of the lymph nodes early after HDM sensitization, where they hand off Ag to B cells [8•]. In this scenario, B cells control another checkpoint in the regulation of IL-4-producing Tfh cells and Th2 cells, not only by presenting antigen but also by controlling the positioning of the DC in the interfollicular zone of the secondary lymphoid organs. Interestingly, Tfh cell differentiation seems to occur near the B cell follicle, which is an environment poor in IL-2 [83]; as such, T cells at these regions have an advantage in maintaining Bcl6 expression (essential for the formation and maintenance of Tfh cells and central memory T cells). In this regard, CD11b-expressing cDC2s that localize at the interface of the follicle and T zone could actively control the availability of IL-2 and the differentiation of Tfh cells. Concerning this, a recent study shows that DC-derived CD25, the IL-2 receptor α -chain, is able to quench IL-2 and direct IL-2 sensitive T cell differentiation, including Tfh cell differentiation [84]. On the contrary, the T cell area is an IL-2 rich environment and therefore T cells in the T cell area receive strong IL-2 signals, which results in high levels of Blimp1 expression in these cells and their differentiation into terminal differentiated short-lived effector CD4⁺ T cells and tissue-resident memory cells [85]. Therefore, the spatial localization of the T cell–APC interactions within the secondary lymphoid organs determines the exposure to environmental triggers and therefore is also an important factor in their subsequent differentiation (Fig. 1).

Priming of Allergen-Specific T Cells: The Role of Lung Innate Lymphoid Cells (ILCs)

Group 2 innate lymphoid cells (ILC2) are a subset of innate lymphoid cells that are characterized by their capacity to produce type 2 cytokines, including IL-5 and IL-13 [86]. These ILC2 are activated by epithelial cell-derived cytokines such as IL-25, IL-33, and TSLP [86]. After activation, ILC2-derived cytokines are responsible for the initiation of acute innate allergic inflammation, including early eosinophil infiltration, mucus hyper-production, and airway hyper-reactivity [86, 87]. Besides the role in the early innate immune response to allergens, ILC2 have recently shown to contribute to both the initiation of the adaptive response to allergens [88•] and the reactivation of the memory T cell response [89]. ILC2 are required to promote Th2 responses in response to local sensitization to aeroallergens in the lung but not systemic sensitization [90]. The recent data show that the IL-13 produced by

ILC2 in response to airway allergen sensitization is critical to promote the migration of the activated DC to the lymph node and hence to promote efficient Th2 priming [88•] (Fig. 1). ILC2 also have a crucial role in memory Th2 cell responses. In particular, after antigen re-encounter, ILC2-derived IL-13 within the lung licenses IRF4/CD11b-expressing cDC2s to efficiently recruit memory Th2 cells to the inflamed lung tissue [89]. ILC2 have also been shown to express MHC class II and costimulatory molecules, suggesting that they may also have the capacity to present antigen and modulate CD4 T cell activation [91]. However, whether ILC2 are antigen-presenting cells relevant to asthma remain to be addressed. Together, although DC are the principal inducers of T cell response to allergens, their function and T cell stimulatory ability is critically fine-tuned by their interaction with epithelial cells, B cells, and ILC2s.

Conclusion

Asthma is a complex human disease and it is difficult to build an animal model that perfectly reproduces this disease. It is also difficult to translate into an experimental mouse model the heterogeneity and complexity of clinical asthma. However, experimental models of asthma, particularly murine models, have helped researchers to better understand the mechanisms of the complex type 2 endotype in allergy and asthma. We now know that there is modulatory crosstalk between the airway epithelium and cells of the immune system (including DCs, B cells, and ILC2s) in the initiation and maintenance of the disease. Moreover, the dose and nature of the allergen can differently modulate the crosstalk between these cells and ultimately influence Th2 cell differentiation. Clinical data reflect the heterogeneity of this disease. Thus, the identification of the basis of the underlying immunological processes can help to develop personalized therapies for asthma.

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Compliance with Ethical Standards

Conflict of Interest The author declares no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance
- Of major importance

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