

New insights into the generation of Th2 immunity and potential therapeutic targets for the treatment of asthma

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Purpose of review

Asthma is a heterogeneous disease with unknown cause; however, allergic asthma is driven largely by Th2-type immune responses. The pathways that interact to induce Th1 and Th17-type immune responses are well understood; however, until recently the innate immune pathways involved in the induction of Th2-type immunity were unknown. In this review we sought to outline many of the recent advances in uncovering the cell and molecular mechanisms that generate Th2 responses.

Recent findings

It is clear that the Th2 pathway can no longer be considered a 'default pathway' of the lung immune system as multiple cells and cytokines have now been identified that work to actively instruct Th2 differentiation. Basophils and dendritic cells have been investigated for their critical role in Th2 induction, and newly identified cell subsets have also been shown to play an important function in Th2 responses. The identification of the Th2-inducing cytokines IL-25, IL-33 and thymic stromal lymphopoietin has also accelerated studies examining the development of Th2 responses in asthma.

Summary

Studies of the role played by the innate immune system in the induction of Th2 responses have begun to unravel the cellular and molecular mechanisms potentially underlying the pathogenesis of allergic asthma. Further study in this area may lead to the discovery of new therapeutics for the treatment of allergic disease.

Keywords

allergens, asthma, basophil, IL-25, IL-33, nuocyte, Th2, Th9, TSLP, virus

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Introduction

Asthma is the most common chronic lung disease worldwide; however, it remains without prevention or cure. Although asthma is now recognized as a heterogeneous disorder the cause and pathogenesis of asthma are still incompletely understood. Thus, significant progress in the development of new treatments has not been made since the introduction of inhaled glucocorticosteroids over 25 years ago. In the main allergic asthma has long been considered to be a disease driven by CD4⁺ T helper (Th) 2 lymphocyte responses; however, the fundamental mechanisms inducing Th2 responses remain to be fully elucidated.

Over the last decade there has been a resurgence in understanding the cellular and molecular processes regulating innate host defence responses and inflammatory diseases. Although the innate immune mechanisms underlying the generation of Th1, Th17, and regulatory T cell (Treg) responses are now well understood, until recently those responsible for the initiation of a Th2 immune response remained largely unknown. Recent discoveries

have identified various innate immune pathways responsible for the generation of a pro-allergic Th2 response and these will form the focus of this review. In particular, we will describe the emerging role of the critical cells and cytokines responsible for generating a Th2 response (see Fig. 1 for an overview of these processes).

Innate Th2-inducing cytokines in asthma: IL-25, IL-33, and thymic stromal lymphopoietin

The innate immune cytokines IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) were discovered several years ago for their potent Th2-inducing capacity. Protease allergens or parasitic antigens stimulate the epithelium to induce the release of these Th2-priming cytokines. The fundamental role of these cytokines in priming the immune system for Th2 responses has generated great interest in their role in the pathogenesis of asthma and allergic inflammatory disorders.

IL-25

IL-25 has been previously demonstrated by multiple groups to play a potent role in the induction of

pro-allergic Th2 responses to protease allergens, ovalbumin (OVA)-induced models of asthma, and parasitic infestation [1–4]. More recent experimental work on IL-25 has shown its capacity to induce allergic airways inflammation in OVA and protease allergen models is dependent on CIKS/Act signalling. OVA-induced allergic airways inflammation can be suppressed by treatment with a monoclonal antibody raised against IL-25 [2,5]. Multiple groups have also shown that at least part of the action of IL-25 during the induction of airways hyper-responsiveness (AHR) in mouse models of asthma is due to its effect on natural killer (NK) T cells, which express the IL-25 receptor (IL-17RB) [6,7]. Work from our own laboratory has demonstrated a mechanism to explain how respiratory viruses can interact with the innate immune system in order to generate a Th2 immune response [8]. Respiratory syncytial virus (RSV) infection in a host with a deficiency in the innate immune response was able to induce epithelial-derived IL-25. This led to IL-25-dependent allergic airways inflammation, consisting of

Key points

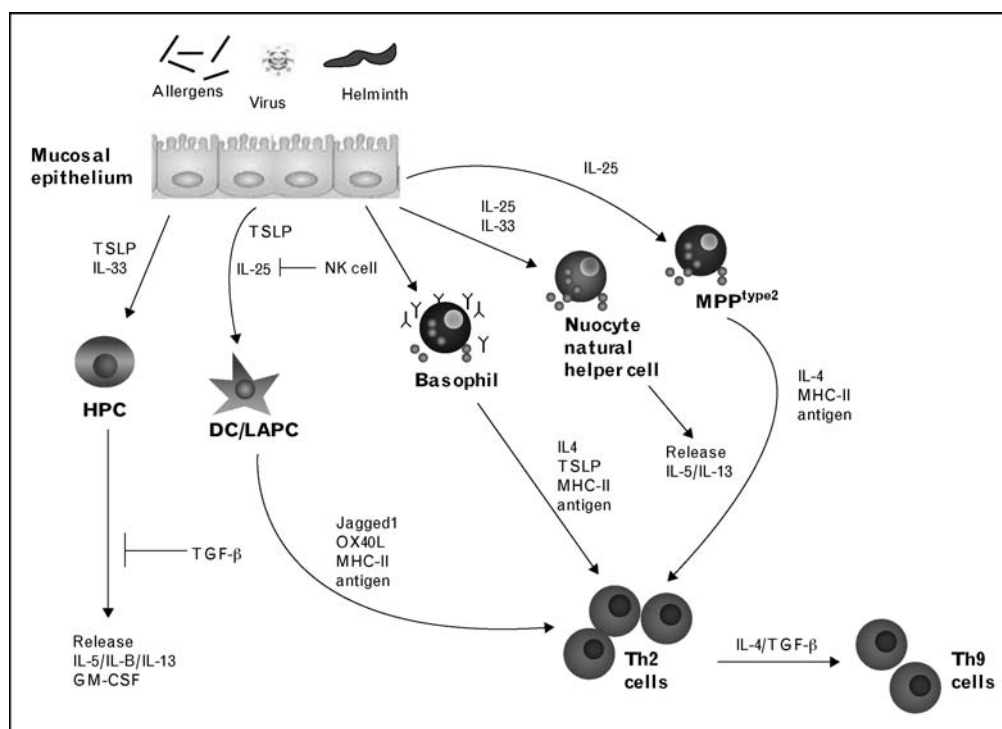
- IL-25, IL-33, and TSLP have been discovered as key epithelial-derived molecules responsible for the initiation of Th2 differentiation in animal models of asthma.
- Basophils and dendritic cells play important functions in the induction of allergic Th2 responses.
- Innate lymphoid-like cells ('nuocytes') and haematopoietic progenitor cells are key effector cells in Th2 immunity.

increased airway eosinophilia, mucous hypersecretion, IgE, Th2-related chemokines, and enhanced differentiation of Th2 cells that developed into long-term memory cells.

IL-33

IL-25 and TSLP have for some time been known to induce the hallmark features of asthma in mouse models

Figure 1 The innate immune pathways involved in the induction of Th2 cells



Protease allergens, Helminth parasites, and certain viral infections such as RSV and influenza, induce Th2 immune responses via interaction with the mucosal epithelium, leading to secretion of the cytokines IL-25, IL-33, and TSLP. These cytokines have an array of effects on various innate immune cells. TSLP and IL-33 can activate haematopoietic progenitor cells (HPCs) to secrete IL-5, IL-6, IL-13 and GM-CSF, which can be inhibited by the action of TGF-β. TSLP can induce DCs to up-regulate OX40 ligand and present antigen via MHC class II, whereas IL-25 can increase the expression of Jagged1 on DCs to induce Th2 cells in the lymph nodes. The latter can be inhibited by natural killer (NK) cells. LAPCs also have a role to play in Th2 induction but their cell-contact dependent mechanism is as yet unknown. Basophils can secrete IL-4, TSLP and present antigen via MHC class II in order to initiate Th2 differentiation. Nuocytes and natural helper cells in the gut are activated in response to IL-25 and IL-33 to release large amounts of IL-5 and IL-13; however, their capacity to initiate Th2 differentiation as a pose to effector function is as yet unclear. MPP^{type2} cells are stimulated by IL-25 to produce IL-4, and have the capacity to differentiate into multiple types of innate cells, some of which can present antigen via MHC class II to induce Th2 cells. TGF-β alone can act on differentiated Th2 cells, or on naïve cells in concert with IL-4, to generate the Th9 cell lineage. DC, dendritic cell; LAPC, late-activator antigen-presenting cell; RSV, respiratory syncytial virus; TSLP, thymic stromal lymphopoietin.

of disease. Recently, IL-33 has also been shown to have a similar function. IL-33 induces allergic airway inflammation (AHR, mucous hypersecretion, eosinophilia, IgE, and Th2 cytokines) in both the presence and absence of the adaptive immune system. IL-33-induced responses were dependent on the myeloid differentiation primary response protein 88 (MyD88) adaptor signalling but independent of IL-4 [9,10]. One might postulate that this effect may be achieved through several mechanisms as IL-33; enhances the eosinophil-mediated differentiation of alternatively activated macrophages in the airways [11]; activates both IgE-dependent and independent pathways in basophils and mast cells to induce the release of type 2 cytokines; and IL-33 can also trigger the release of type 2 cytokines from eosinophils and T cells [9–11]. Conversely, the absence or blockade of the IL-33 subunit receptor (T1/ST2) has been demonstrated to attenuate allergic airways inflammation [10,12[•]]. Importantly, the IL-33 pathway may have potential therapeutic value as bronchial biopsies from asthmatics have increased protein levels of IL-33 (found in both airway smooth muscle and epithelial cells) compared with healthy controls. These elevated levels of IL-33 were positively correlated with asthma severity [13[•],14[•]].

Thymic stromal lymphopoietin

Although TSLP has been recognized to induce Th2 responses in mouse models of asthma and is elevated in the airways of asthmatics its mechanism of action and induction has been less well defined. To attempt to address this Shi *et al.* [15] demonstrated that blockade of the TSLP receptor could reduce allergic airways inflammation via a reduction in the migration of airway dendritic cells resulting in diminished CD4 T cell priming. Kouzaki *et al.* [16[•]] have also demonstrated that TSLP production by epithelial cells is initiated at the level of the protease receptor. Common airborne fungal and protease allergens have been shown to act through the protease-activated receptor-2 (PAR-2) G-protein-coupled receptor, whose signalling could be enhanced by IL-4 and diminished by IFN- γ . This suggests TSLP might have a function in early activation of the innate host defence response at the initial site of exposure in the epithelium leading to a Th2 polarization. Interestingly, the transgenic overproduction of TSLP specifically in mouse skin keratinocytes, which acts as a trigger for atopic dermatitis in the skin, can also simultaneously lead to a worsening of pre-existing allergic airways inflammation. This suggests a possible link between TSLP and the 'atopic march' with one allergic condition leading to a worsening of another [17]. Two key human studies have provided strong evidence that TSLP is involved in the pathogenesis of allergic asthma. Firstly, recombinant TSLP was shown to inhibit Treg function (the 'break' on Th2 responses) *in vitro*, and this inhibition could also be demonstrated utilizing the bronchoalveolar lavage

fluid from allergic asthmatics (known to contain higher TSLP than controls) in culture with Tregs [18[•]]. Secondly, single-nucleotide polymorphisms enhancing expression of the TSLP gene have been positively associated with an increased susceptibility to asthma [19[•]].

The role of dendritic cells in Th2 differentiation

Recently, the specific types of innate immune cells that initiate Th2 differentiation in the lymph nodes have received a great deal of attention. Although dendritic cells have a well defined role in secreting specific cytokines and expressing co-stimulatory molecules in order to induce either a Th1, Th17, or Treg response, it is incompletely understood how these cells may induce a Th2 response. For many years it was considered that because dendritic cells were unable to secrete IL-4, they played a minimal role in directing Th2 differentiation aside from providing the necessary cognate antigen to initiate a specific T cell response as antigen-presenting cells (APCs). There is also no strong evidence that dendritic cells can respond to IL-25, IL-33, or TSLP with the production of the prototypical Th2 cytokines. Despite this, however, studies have shown that TSLP can directly activate dendritic cells to up-regulate co-stimulatory molecules, such as OX40 ligand, and induce Th2 responses in animal models of asthma [20,21]. Furthermore, dendritic cells expressing high levels of Jagged1 and low levels of delta-like ligand 4 are capable of inducing Th2 cells in a STAT6/IL-4-independent fashion [22]. More recently, our group has shown that respiratory epithelial-derived IL-25 produced as a consequence of viral infection induced a strong Th2 immune response and allergic lesions in the lungs, at least in part by up-regulating Jagged1 on dendritic cells [8]. *Schistosoma mansoni* eggs have been discovered to contain a glycoprotein, omega-1, that is responsible for driving dendritic cells to induce Th2 polarization. Omega-1 exerted its effects by conditioning dendritic cells for reduced synapse formation with CD4⁺ T cells thereby suppressing the strength of the antigen-derived TCR activation signal and inhibiting the effects of Th1-inducing factors (such as IL-12) on dendritic cells [23[•],24[•]]. Interestingly, this mechanism occurred independently of IL-4; however, *S. mansoni* eggs unlike the purified omega-1 protein do induce IL-4-secreting basophils *in vivo*, suggesting possible immunological redundancy of *S. mansoni*-induced responses. Dendritic cells have again moved into the spotlight recently with the identification of a new dendritic cell subset by morphological, phenotypic, and genetic analysis. These cells designated as late-activator APCs (LAPCs) were initially identified in the lymph nodes of naïve and influenza-infected mice [25^{••}]. LAPCs enter the lymph nodes with delayed

kinetics compared with conventional dendritic cells and express lower levels of most co-stimulatory molecules and MHC class II. Despite these differences influenza-activated LAPCs were capable of stimulating the same degree of T cell activation as for conventional dendritic cells but with a strong bias towards Th2 rather than Th1 cell differentiation. The LAPCs initiated Th2 polarization via a cell-to-cell contact-dependent process, but whether this interaction relies on Jagged1 or OX40 ligand remains to be determined. Although this is an elegant study, influenza infection induces only a very weak Th2 response, and thus the role of LAPCs in more robust models of Th2-mediated responses remains to be determined.

Basophils as inducers of the Th2 response

The lack of a soluble Th2-inducing factor produced by dendritic cells suggested the existence of an alternate haematopoietic non-CD4 T cell source of IL-4 to initiate STAT6-dependent Th2 differentiation. As basophils have the ability to rapidly release IL-4, IL-9, IL-25, and TSLP upon activation they were considered a possible candidate contributing to Th2 cell polarization. These circulating granulocytes, despite their low abundance in peripheral blood (1% leukocytes), have long been appreciated as key Th2 responder/effector cells [26]. A seminal study by Sokol *et al.* [27] transformed this paradigm by demonstrating that subcutaneous immunization with the protease allergen papain induced basophils to migrate to lymph nodes in which they directly promoted Th2 differentiation. This was dependent on basophil secretion of IL-4 and TSLP, and was diminished by the depletion of basophils by targeting of the high-affinity IgE receptor FcεRI [27]. This observation has since been replicated by other groups to show that basophils are an important source of early non-CD4 T cell-derived IL-4 in various Th2 immune models. More recently the role of basophils in Th2 polarization has been attributed even greater significance due to the demonstration of the potent antigen-presenting capacity of these cells [28•,29••,30•]. These studies neatly demonstrated that induction of a Th2 response to papain is dependent not only on basophil-derived IL-4 but also on basophil expression of MHC class II and antigen presentation by these cells. The authors suggested that dendritic cells were neither necessary for Th2 differentiation when basophils were present nor capable of inducing a Th2 differentiation program by themselves in this immunological context. Although these findings were demonstrated in various models of Th2 priming including protease allergens, soluble antigen (OVA), complexes of antigen/IgE, and helminthic parasite infestation (*Trichuris muris* and *S. mansoni*) they remain controversial for several reasons. Firstly, they contradict numerous studies that directly indicated dendritic cells have an important

role to play as APCs in the generation of Th2 responses [31–36]. Secondly, in these basophil studies when parasite antigen presentation was restricted to dendritic cells either by use of transgenic MHC class II expression or in-vitro culture with dendritic cells alone (neutral conditions) a Th2 response would not develop; however, when dendritic cells were exposed to a biased cytokine milieu (exogenous IL-4) naïve CD4 T cells did in fact differentiate into Th2 cells [30•]. Thirdly, during Helminth parasite *Nippostrongylus brasiliensis* infestation migrating basophils (removed by direct depletion or employment of IL-3–/– mice) were dispensable for the generation of Th2 immunity [37]. Similarly, basophils can secrete IL-4 in response to RSV infection *in vivo* both in the lung and lymph nodes; however, Th2 induction was not dependent on these cells [8,38]. A very elegant study by Tang *et al.* [39••] appears to provide evidence for an integrative model involving cross-talk between basophils and dendritic cells. This study suggests an alternative to the mutual exclusivity of the two cell types and suggests a cooperative relationship exists between IL-4-secreting basophils and dendritic cells [39••]. Administration of papain activated reactive oxygen species (ROS) [39••] derived from the epithelium. These ROS induced oxidized lipids, which signalled through TLR4 in the epithelium to initiate the release of TSLP. ROS also induced dendritic cell-derived CCL7, which mediated the recruitment of TSLP activated IL-4-secreting basophils that then acted in concert with dendritic cells to induce terminal Th2 differentiation. How to interpret the incongruous results of these various studies is not yet clear but significant caution should be taken with broad interpretations of the role of one cell over another as paradoxical conclusions may arise in different models. Perhaps the relative role of the basophil and dendritic cell in Th2 induction is specific for particular stimuli, in particular whether or not the allergenic preparation contains solely protease activity or also dendritic cell-activating pathogen recognition receptor (PRR) ligands. Under physiological conditions multiple redundant mechanisms may exist for the development of Th2 immunity in asthma.

Newly discovered innate immune cells are key to Th2 immunity

A trilogy of papers recently published in *Nature* have independently identified three new types of immune cells derived from the mucosal gut-associated lymphoid tissue of mice and humans. These cells uniquely respond to the innate Th2-type-inducing cytokines IL-33 and/or IL-25 (boosted in the presence of IL-2) by releasing a burst of IL-4, or IL-5 and IL-13. The discovery of these cells is a potential landmark in the field of Th2 immunity as they identify a link between epithelial-derived innate cytokines and the initiation of a Th2 response

in peripheral mucosal tissues. The three new cell types termed 'nuocytes' (Lineage⁻c-kit⁺CD45⁺ICOS⁺IL-7R α ⁺IL-17RB⁺T1/ST2⁺) [40[•]], 'natural helper cells' (Lineage⁻c-kit⁺CD45⁺Sca-1⁺CD27⁺IL-7R α ⁺IL-17RB⁺T1/ST2⁺) [41[•]], and 'multipotent progenitor (MPP)^{type2} cells' (Lineage⁻c-kit⁺Sca-1⁺IL-7R α ⁺IL-17RB⁺T1/ST2⁺) [42^{••}] were shown in mice to be critical for protection against Helminth parasites and mucosal Th2 inflammation induced by IL-25 and IL-33. It is plausible that at least two of these cell types 'nuocytes' and 'natural helper cells' identified separately may actually be the same cell population as both share similar phenotypes. Both cells are the predominant source of early IL-5 and IL-13 in response to *N. brasiliensis*, both were dependent on IL-33 and IL-25 for expansion *in vivo*, and were essential for mucous production, eosinophilia, and worm expulsion. The other cell type, MPP^{type2} cells, identified as the IL-25-responsive non-B non-T cell (discovered but not completely identified by Fallon *et al.* [3] several years earlier), appear distinct from the other Th2-inducing cells as they were expanded and activated solely in response to recombinant IL-25 or IL-25 derived from Helminth infestation. MPP^{type2} cells secrete IL-4 and induce differentiation of Th2 cells. Moreover, these cells are heterogeneous for IL-4 production and this heterogeneity dictates the multipotent progenitor capacity of the cell. The IL-4 producers inherently differentiate into mast cells *in vitro*, whereas the non-IL-4 producers differentiate into a range of cells *in vitro* including mast cells, basophils, macrophages, and a population of CD11b⁺MHC-II⁺ APCs. One potential caveat of these findings is that they fail to convincingly exclude the possibility that MPP^{type2} cells are simply circulating haematopoietic progenitor cells (see below). It also remains to be seen whether these three innate Th2-cytokine producing cells are important in the Th2 inflammation underlying allergy, especially in asthma.

Haematopoietic cells in asthma

Circulating haematopoietic progenitors released from the bone marrow play a crucial role in asthma through their capacity to migrate to sites of allergic inflammation and differentiate into effector cells including mast cells, basophils, and eosinophils [43,44]. Of particular interest is a recent publication from Allakhverdi *et al.* [45[•]], demonstrating that human haematopoietic progenitors can also function as inflammatory effector cells during the asthmatic response without having to first undergo differentiation. The haematopoietic progenitors expressed receptors for the innate cytokines TSLP and IL-33 and when stimulated with these molecules were able to produce an array of Th2 (but not Th1 or Th17) cytokines including IL-5, IL-6, IL-13, and GM-CSF. These responses were enhanced by exposure to other cytokines commonly found at the site of allergic inflam-

mation, including IL-4, TNF- α , IFN- γ , prostaglandins and leukotrienes, but inhibited by the effects of TGF- β . Furthermore, when these progenitor cells were cultured with the supernatants from airway epithelial cells or nasal explants from rhinosinusitis patients they secreted IL-5 in a TSLP-dependent and IL-33-independent manner. Finally, it was demonstrated that these IL-5 and IL-13-producing haematopoietic progenitors exist in the sputum of patients with allergic asthma unlike healthy controls and that their numbers were rapidly increased after allergen challenge.

Discovery of Th9 cells as a new subset in asthma

IL-9 was originally described as a part of the Th2 family of cytokines promoting T cell growth and mastocytosis; however, more recently IL-9-producing T cells have been identified as being a distinct subset from Th2. These Th9 cells produce IL-9 and IL-10 but few or none of the other Th2 cytokines. They are differentiated in response to IL-4 and TGF- β and can be found in both humans and mice [46[•],47]. TGF- β re-programs Th2 cells to Th9 and also enforces responsiveness to IL-25 [48]. Adoptively transferred Th9 cells are capable of generating allergic airways inflammation in mouse models of asthma, which was ameliorated by neutralization of IL-9 [46[•]]. Given the nature of the role of TGF- β in Th9 cell development, perhaps this cell type plays an integral part in the remodelling processes of asthma. Clearly, IL-9 has shared overlap with the Th2 pathways as it may be secreted by both Th2 and Th9 cells during a stage of transition between the two T cell subsets. Therefore, this has blurred the line of lineage commitment to Th9 cells and their precise role in asthma. Interestingly, however, because of its previously recognized role as a Th2 cytokine family member, a humanized monoclonal antibody for blockade of IL-9 (MEDI-528) is already undergoing phase I clinical trials for the potential treatment of moderate to severe asthma [49].

Conclusion

Major progress has been made in the discovery of the innate pathways that lead to Th2 immune responses and potentially allergic asthma; however, there still remain several unanswered questions. What are the innate immune receptors employed by the epithelium, or even perhaps the basophil and dendritic cells directly, for the recognition of allergens? It appears that there are alternative pathways than just the conventional protease-activated receptors. Are different pathways involved for different Th2 stimuli? The precise dissection of Th2 pathways involving coordinate action by multiple cell types will also be important to resolve. Targeting LAPCs, basophils, nuocytes, and haematopoietic progenitors

along with the innate cytokines (IL-25, IL-33, and TSLP) may lead to improved treatment of allergic asthma and potentially the suppression of the disease earlier during its course of progression.

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- of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 66–67).

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