



Invited commentary

Innate immunity as the orchestrator of allergic airway inflammation and resolution in asthma

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ABSTRACT

The respiratory system is constantly in direct contact with the environment and, has therefore, developed strong innate and adaptive immune responses to combat pathogens. Unlike adaptive immunity which is mounted later in the course of the immune response and is naive at the outset, innate immunity provides the first line of defense against microbial agents, while also promoting resolution of inflammation. In the airways, innate immune effector cells mainly consist of eosinophils, neutrophils, mast cells, basophils, macrophages/monocytes, dendritic cells and innate lymphoid cells, which attack pathogens directly or indirectly through the release of inflammatory cytokines and antimicrobial peptides, and coordinate T and B cell-mediated adaptive immunity. Airway epithelial cells are also critically involved in shaping both the innate and adaptive arms of the immune response. Chronic allergic airway inflammation and linked asthmatic disease is often considered a result of aberrant activation of type 2 T helper cells (Th2) towards innocuous environmental allergens; however, innate immune cells are increasingly recognized as key players responsible for the initiation and the perpetuation of allergic responses. Moreover, innate cells participate in immune response regulation through the release of anti-inflammatory mediators, and guide tissue repair and the maintenance of airway homeostasis. The scope of this review is to outline existing knowledge on innate immune responses involved in allergic airway inflammation, highlight current gaps in our understanding of the underlying molecular and cellular mechanisms and discuss the potential use of innate effector cells in new therapeutic avenues.

1. Introduction

Allergic asthma is a heterogeneous disease of the conducting airways characterized by variable airflow obstruction coupled with airway hyperresponsiveness (AHR) that occurs following exposure to allergic stimuli in genetically susceptible individuals. Asthma-related symptoms include wheezing, dyspnea, cough and sputum production [1,2]. Central to the pathophysiology of asthma is the initiation and perpetuation of allergen-driven airway inflammation which is triggered through activation of the innate and adaptive arms of the immune

system. Apart from immune cells, lung-resident structural cells, and in particular airway epithelial cells play also a central role in the pathogenesis of allergic responses and the ensuing asthmatic phenotype.

The prevalence of asthma and allergic diseases, in general, has markedly increased over the last decades in Western countries [3]. In an effort to explain this phenomenon, the “hygiene” or the more recent “biodiversity” hypothesis was formulated, which argues that declining biodiversity, urbanization and associated changes to diet and lifestyle have led to a higher prevalence of atopic diseases [4,5]. These

Abbreviations: AEC, airway epithelial cell; AHR, airway hyperresponsiveness; AM, alveolar macrophage; APC, antigen presenting cell; ASM, airway smooth muscle; BAL, bronchoalveolar lavage; CCR, C-C chemokine receptor; CCL, C-C motif ligand; DAMP, damage-associated molecular pattern; DC, dendritic cell; ECP, eosinophil cationic protein; EDN, eosinophil-derived neurotoxin; EGFR, epithelial growth factor receptor; EMT, epithelial-to-mesenchymal transition; EPO, eosinophil peroxidase; FGF, fibroblast growth factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HDM, house dust mite; IL, interleukin; ILC, innate lymphoid cell; IM, interstitial macrophage; INF- γ , interferon- γ ; iNKT, invariant natural killer T cell; JAM, junctional adhesion molecules; MBP, major basic protein; MDSC, myeloid-derived suppressor cell; MHC, major histocompatibility complex; MMP, matrix metalloproteinase; NF- κ B, necrosis factor κ B; NLR, NOD-like receptor; PAF, platelet activating factor; PAMP, pathogen-associated molecular pattern; PLZF, promyelocytic leukemia zinc finger; PRR, pattern recognition receptor; RLR, RIG-I-like receptor; ROS, reactive oxygen species; SCF, stem cell factor; TAM, tumor-associated macrophages; TCR, T cell receptor; TGF- β , transforming growth factor- β ; TJ, tight junction; TLR, toll-like receptor; TNF- α , tumor necrosis factor; TSLP, thymic stromal lymphopoietin; VEGF, vascular endothelial growth factor

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hypotheses are grounded on the immunological basis that asthma and allergic diseases are strongly associated with a T helper (Th)2 cell-mediated response to environmental allergens that guides the influx of eosinophils, mast cells and other leukocytes in the airways, along with excessive IgE production. The “hygiene” hypothesis postulates that exposure to components of microbes early in life, skews the immune response of the offspring from a Th2 type at birth, to a Th1 type in childhood and, thus, protects from the development of Th2-cell associated allergic response. Still, this view leaves a lot of questions unanswered, especially those pertinent to the mechanisms responsible for driving the initial phase of Th2 cell differentiation, the type of allergens required and the pathways that control dysregulated Th2 immunity. Moreover, it does not explain why Th1 cell-associated respiratory viral infections, although deemed protective, often aggravate allergic airway inflammation and lead to asthma exacerbations.

This is where the role of the innate immune system may be of the outmost importance, since innate cells are considered as the early responders that direct the subsequent Th cell-mediated allergic response in the respiratory tract [6]. It has been shown for some time that damage to the respiratory epithelium by allergens, pathogens and/or irritants is the initiating event leading to the activation of antigen presenting cells, such as, macrophages and dendritic cells in the inflamed lung [7]. More recently, the idea that mast cells and/or basophils may also be an initial source of IL-4, which is obligatory for Th2 cell polarization, has gained ground [8]. In addition, the recently-identified innate lymphoid cells which respond to epithelial cell-derived innate cytokines and produce copious amounts of Th2 cytokines are considered as key drivers of the initiation and maintenance of the allergic response. Hence, the innate immune system not only plays a critical role in determining the type of T cell differentiation, but also directs the outcome and chronicity of the allergic response. Importantly, innate cells along with airway epithelial cells control the resolution phase of airway inflammation and the maintenance of lung homeostasis. This review focuses on how innate immunity regulates acquired immune responses in the context of allergic inflammation and asthma. It also describes recent advances in our understanding of the mechanisms underlying innate effector responses and discusses how these cells can be exploited for the design of more effective therapeutic approaches for allergic diseases.

2. The role of airway epithelial cells in allergic airway inflammation

Airway epithelial cells (AEC) lie at the interface between the host and the environment and represent the first line of defense against noxious stimuli. The airway epithelium extends from the trachea to bronchioles and is pseudostratified columnar consisting mainly of ciliated cells. Other, non-ciliated, cell types are the secretory cells, which include goblet, serous, club (Clara) and neuroendocrine cells. Basal cells locate in proximity to the basal membrane and regenerate the epithelium after damage, serving as progenitor AECs. Each cell type has specialized functions in the orchestration of innate immune defense and together mediated the formation of a rather impermeable physical barrier, enhanced by effective mucociliary clearance. This barrier consists of the airway surface liquids, and mucous and apical junctional complexes between neighboring cells.

AEC become activated either through direct enzymatic activity of the encountered allergens or through activation of pattern recognition receptors (PRRs), including Toll-like receptors (TLRs), RIG-I-like receptors (RLRs), NOD-like receptors (NLRs) and C-type lectins. PRRs rapidly detect and respond to pathogen-associated molecular patterns (PAMPs), such as viruses and microbial contaminants of allergens, and to damage-associated molecular patterns (DAMPs) released by tissue structural cells after tissue damage, cellular stress or death [9]. Some allergens also induce production of reactive oxygen species (ROS), such as, superoxide anion, hydrogen peroxide, hydroxyl radicals and perox-

ynitrate, which activate DCs or AECs through NF- κ B signalling. Upon allergen exposure, AECs release chemoattractants and recruit DCs, innate lymphoid cells (ILCs), basophils, eosinophils, Tregs and Th2 cells, amplifying the allergic response. C-C motif ligand (CCL)17 and CCL22 act on C-C chemokine receptor (CCR)4 receptors and attract ILC2s, basophils, Tregs and Th2, while the eotaxins CCL11, CCL24 and CCL26 act on CCR3 receptors and recruit eosinophils and Th2 cells [10,11]. AECs produce CC chemokine ligand 2 (CCL2) and CCL20 in response to HDM inhalation, which attracts monocytes and immature DCs to the lung [12,13]. Prostaglandin D2 produced by AECs attracts basophils, ILC2s and Th2 cells through binding to the CRTH2 receptor [14].

Allergen-induced PRR activation results in the production of the triad of innate epithelial cell-derived cytokines, IL-33, IL-25 and TSLP, that act as endogenous danger signals orchestrating innate and adaptive immune responses [15]. These prototypical pro-Th2 cytokines share the propensity to activate DCs that prime Th2 responses by inhibiting the production of the Th1-polarizing cytokine IL-12, to induce chemokines that attract Th2 cells and/or to enhance the expression of surface molecules, such as OX40L, that instruct Th2 cell differentiation. IL-33 is a member of the IL-1 cytokine superfamily detected in several tissue resident and immune cells [16,17]. Full length IL-33 is secreted as a biologically active alarmin which gains full bioactivity when processed by inflammatory proteases, such as, neutrophil elastase and cathepsin G, whereas processing by caspases inactivates IL-33 [18]. Murine models identify IL-33 as a key initial trigger of the Th2 priming cascade [19]. Th2 cell differentiation and eosinophilic infiltration are decreased in IL-33 deficient mice during intranasal allergen administration [20,21]. The IL-33 receptor T1/ST2 is expressed primarily by Th2 cells, but IL-33-dependent responses from murine ILC2s, DCs, and human eosinophils have been also described [22,23]. A human IL-33/IL-25 responsive ILC has been also defined [24]. IL-13 activates DCs through binding to ST2 receptors and this in turn, induces Th2 cell priming to allergens [25–27]. IL-33 acts as a strong activator of both mouse and human mast cells and basophils inducing bronchoconstriction [28,29]. IL-33 not only accounts for mast cell activation but also induces the expression of preformed mediators in vivo [30]. IL-33 promotes eosinophilic infiltration in murine models of asthma [31] and enhances the survival of eosinophils and eosinophil degranulation in humans [23]. ST2 knockout results in abolishment of allergic inflammation [32], while anti-ST2 or anti-IL-33 antibodies induce a significant inhibition of Th2-cell associated airway inflammation. Genome wide association studies have linked IL-33 and ST2/IL1RL1 gene polymorphisms with asthma [33,34]. However, there is little and conflicting evidence concerning human epithelial IL-33 expression and release [17,32].

IL-25 (IL-17E) is a member of the IL-17 cytokine family that initiates allergic airway inflammation [35]. IL-25 is expressed constitutively by AECs and is released quickly after allergen challenge [36]. IL-25 promotes Jagged1 expression on DCs and subsequent Th2 cell priming in the airways [37]. IL-25 participates in angiogenesis and fibrosis, cardinal features of airway remodelling [38,39]. Both murine and human studies of viral challenge demonstrate that IL-25 contributes to virus-induced allergic inflammation and disease exacerbations [40].

TSLP is a cytokine belonging to the IL-2 family that signals through a heterodimeric receptor comprising from the IL-7 receptor α -chain and a specific TSLP receptor β -chain. The TSLPR is expressed on DCs, CD4⁺ and CD8⁺ T cells, B cells, mast cells and on AECs. The TSLPR is also expressed by human eosinophils and modulates their survival and activation [41]. TSLP secreted from AECs upon challenge with proteolytic allergens, diesel exhaust particles and cigarette smoke, activates DCs [42,43], which polarize and recruit Th2 cells in the airway [44]. TSLP overexpression in mice results in spontaneous allergic sensitization to the OVA model antigen [45]. TSLP has also been implicated in airway remodelling, particularly in smooth muscle proliferation and fibrosis [46]. Allergen-primed T cells amplify TSLP production in a

feed-forward loop [47]. In asthmatics, TSLP expression is increased in BAL, bronchial biopsies and sputum [48,49].

AECs have the ability to enhance allergic airway inflammation through the production of other intrinsic DAMPs, released by non-apoptotic cell death and tissue damage or by active secretion. Granulocyte-macrophage colony-stimulating factor (GM-CSF) is released by AECs upon HDM exposure and stimulates DCs to promote Th2 immunity [50]. Allergens like HDM, papain and *Alternaria alternata* trigger the production of the endogenous alarmins ATP and/or uric acid, which enhance the production of Th2 cytokines. Moreover, HDM induces the release of High Mobility Group Box 1 (HMGB1) and IL-1 α , whose blockage impedes the production of pro-Th2 cytokines [51–53].

There is evidence that TLR4 mediates the recognition of inhaled allergens, and therefore promotes Th2 reactions. It has been demonstrated that Der-p2 and Der-p7 from HDM, feline Fel-D1 and fibrinogen cleavage products (FCPs) mimic TLR4 ligands and activate TLR4 [54,55]. Cigarette smoke and viruses upregulate TLR4 expression [56,57], which may, at least partly, explain why cigarette exposure or viral infections, early in life, predispose to allergic sensitization. Several other subsets of PRRs are activated upon viral infections, which are triggers of AHR [58,59]. Seminal studies comparing AECs from asthmatic and healthy subjects have provided evidence that the IFN response is defective following viral infection in asthmatics [60,61]. A defective IFN receptor expression on AECs, as well as gene polymorphisms, may confer susceptibility to airway disease [62].

Epithelial structural abnormalities are a hallmark of asthma as evidenced by marked areas of denudation in bronchial biopsy specimens and shedding of epithelial cells in the BAL. Patchy and discontinuous tight junctions are seen in biopsies of asthmatic subjects [63]. Barrier damage and dysfunction in allergic airway disease models is provoked either directly by allergens with protease activity (i.e., pollens, house dust mite-HDM) disrupting tight junctions [64,65], or indirectly by the production of cytokines, such as interleukin (IL)-4, IL-13, interferon (IFN)- γ , tumor necrosis factor (TNF)- α [66] and other inflammatory mediators, such as, histamine [67]. E-cadherin is the most well-studied adhesion molecule disrupted in asthma. Defective E-cadherin expression is demonstrated in lung biopsies and in ex vivo cultures [63]. The epithelial growth factor receptor (EGFR) mediates junctional breakdown after HDM exposure [68]. Defective E-cadherin expression accounts for the increased release of thymic stromal lymphopoietin (TSLP) [69], while sustained loss of E-cadherin results in epithelial-to-mesenchymal transition (EMT), a key feature of airway remodelling in asthma [68,70]. The increased epithelial permeability generates a feed-forward loop of even greater penetration of inhaled allergens facilitating antigen uptake from intraepithelial dendritic cells (DCs) and perpetuating the allergic response [71]. Moreover, a defective barrier renders the epithelium more susceptible to viral and bacterial infections [72].

3. Innate effector cells in the initiation and perpetuation of the allergic response

3.1. Pulmonary macrophages

Macrophages represent the most abundant immune cell of the respiratory tract and consist of alveolar (AM) and interstitial (IM) macrophages. Pulmonary macrophages exert several functions, such as, maintenance of respiratory tract sterility, clearance of cellular debris and immune surveillance [73]. Interstitial macrophages exert predominantly immunoregulatory functions in asthma, preventing allergic airway inflammation and actively suppressing Th2 responses through IL-10 and TGF- β release [74,75]. AMs originate either from circulating blood monocytes or from IMs [76,77]. According to their activation pattern, AM are divided in at least two functionally distinct subsets; M1 and M2 macrophages. M1 (classically activated) macrophages are pro-inflammatory; upon induction by IFN- γ and LPS, they produce high

levels of nitric oxide, release inflammatory cytokines, such as, TNF- β , IL-1 β , IL-6 and IL-12 and exhibit protective functions towards intracellular pathogens. M2 (alternatively activated) macrophages are induced by the Th2 cytokines, IL-4 and IL-13, produce the anti-inflammatory cytokines IL-10 and TGF- β and control the elimination of extracellular pathogens and apoptotic cells [78]. M2 are further divided into M2a (parasite encapsulation and destruction), M2b (immunoregulation) and M2c (tissue remodelling) subsets [79].

Macrophages are being increasingly implicated in the pathogenesis of allergy and asthma. Their function remains controversial with some studies suggesting that macrophages promote allergic inflammation while others show a suppressive role for these cells. Although the M2 subset is expected to contribute to the development and progression of asthma, growing evidence implicates both subsets. It is not yet clear which one is most involved due to the plasticity and overlapping of phenotypes. Growing evidence supports that M1 macrophages may have a pro-asthmatic role through the release of IL-1 β and IL-6, which aggravate Th2 cell-mediated inflammation and promote the activation of fibroblasts [80]. In an animal model of acute asthma exacerbation, increased expression of IL-1 β , IL-6 and TNF- α by M1 triggers CD4⁺ T cells to produce Th2 cytokines [81]. In severe asthmatics, especially in patients resistant to glucocorticoids, macrophages are skewed towards M1, produce copious amounts of TNF- α , IL-1 β and nitric oxide (NO), exacerbate lung injury and accelerate airway remodelling [82]. It has been also proposed that during allergic Th2 responses, macrophages may retain their M1 phenotype despite their presence in a high Th2 cytokine milieu. Both IL-4 and IL-33 have been shown to retain [83], if not, amplify the M1 pool [84].

Whereas in non-allergic allergic asthma, M1 macrophages predominate in the lungs, in allergic inflammation, M2 macrophages are more prevalent [85]. It is widely accepted that M2 macrophages, although responsible for tissue repairing and restoration of homeostasis, take a leading role in the pathogenesis of asthma. Excessive macrophage skewing towards M2 may increase Th2 cell recruitment and mucus secretion resulting in AHR and remodelling [86]. The transfer of M2-skewed macrophages into the lungs of fungus-exposed mice enhanced collagen deposition [87]. Moreover, depletion of AMs during allergic disease delayed the resolution of inflammation and there was a decrease in the production of the immune regulatory cytokine IL-27 [88]. Overall, M1 subtype seems to be involved in the acute exacerbation of asthma whereas M2 macrophages may account for over-repairing of damaged lung and remodelling. Due to space limitations, we will not review the extensive literature on other antigen presenting cells in the respiratory tract, such as DCs, the function of which has been extensively reviewed elsewhere.

3.2. Eosinophils

Eosinophils are considered as the main cytotoxic effector cells during the late and chronic phases of asthma. They constitute the most abundant cellular airway infiltrate in asthma, although they are not encountered in the lungs of healthy individuals [89]. Increased eosinophil numbers are observed in the airways and blood of most asthma phenotypes and correlate with disease severity [90]. Eosinophils stem from a CD34⁺/IL-5Ra⁺ bone marrow progenitor [91] upon IL-5 stimulation, with contributions from IL-3 and GM-CSF [92]. Once mature, eosinophils circulate in the peripheral blood in relatively low numbers and, during inflammation, transmigrate to tissues following IL-5 and eotaxin stimulation. IL-5 is the most widely acknowledged eosinophilopoietin [93] and is released by activated Th2 lymphocytes and to a lesser extent by ILC2, invariant natural killer T cells (iNKTs), mast cells and eosinophils themselves. IL-5 controls eosinophil differentiation, maturation, recruitment and activation at sites of inflammation [94,95], while eotaxins promote eosinophil chemotaxis, migration and activation [96]. IL-33, IL-25 and TSLP also promote eosinophilia by inducing IL-5 production [89,94].

Activated eosinophils release an array of destructive molecules that contribute to airway damage and remodelling. Eosinophilic granules contain major basic protein 1 and 2 (MBP1 and MBP2), eosinophil peroxidase (EPO), eosinophil cationic protein (ECP) and eosinophil-derived neurotoxin (EDN) [97], which are released upon degranulation and account for bronchoconstriction, mucus over-secretion and AEC cytotoxicity [98]. Moreover, eosinophils produce lipid mediators including leukotrienes, which enhance vascular permeability and smooth muscle contraction [99]. Upon activation, eosinophils produce ROS that enhance airway damage and various cytokines, such as, IL-13 IL-4, IFN- γ , osteopontin, activin-A, TGF- β , vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) [99] and matrix metallo-proteases (MMPs) all involved in airway remodelling [99–103]. A substantial difference in cytokine production between eosinophils and Th2 cells, which generate much larger quantities of cytokines, is that eosinophils store them intracellularly as preformed mediators and release them immediately [104].

Mouse models of airway inflammation deciphering the role of eosinophils have elicited controversial results. Acute allergen sensitization models do not develop eosinophil degranulation. There are currently two eosinophil-deficient mouse strains. The first one was constructed with transgenic expression of the diphtheria toxin-A chain under control of eosinophil peroxidase promoter (PHIL) and researchers concluded that eosinophils are necessary for both AHR and remodelling [105]. In the second one, eosinophils were depleted by deleting the GATA-1-binding site on the palindromic GATA-1 promoter; the Δ dbl-GATA-1 mice did not develop collagen deposition or increased smooth muscle mass and eosinophils proved critical for airway remodelling, but not for AHR [106]. These discrepancies have been explained by differences in the distinct mouse strains [107]. IL-5 gene KO results in reduced airway eosinophilia, mucus production and fibrosis [108]. In contrast, mice overexpressing IL-5 and eotaxin 2 manifest prominent airway eosinophilia and degranulation resulting in airway remodelling and AHR, features abrogated when the transgenic mice are crossed with PHIL mice [109].

Eosinophils propagate a chronic Th2 cell-mediated inflammation through several mechanisms, including the recruitment of Th2 cells through the release of CCL17 and CCL22 and also through eosinophil-DC interactions [110]. Eosinophils reside in close proximity with mast cells and exert bi-directional signalling [111]. Eosinophils can also promote the resolution of airway inflammation as they produce several pro-resolving agents, leading in direct suppression of allergic inflammation and tissue repair [112,113], while a defective synthesis accounts for a more severe asthma phenotype in mouse models and humans [114,115].

3.3. Mast cells and IgE

Mast cells (MCs) were described over a century ago by Paul Ehrlich as “well fed cells”, due to their unique staining characteristics and large granules [116]. They are derived from bone marrow mast cell progenitors, enter the circulation as poorly defined, undifferentiated mononuclear cells and migrate into target tissues, wherein they differentiate [117]. MCs are not, therefore, a homogeneous population, as they differ depending upon the tissue where they reside and the local cytokine milieu. Human lung MCs can be discriminated from those residing in other tissues based on the mediators they release and the pattern of chemokine receptor expression.

MCs play a central role in allergic reactions. They store and secrete a vast arsenal of biological substances, including histamine, proteases, chemotactic factors, cytokines and metabolites of arachidonic acid that act on the vasculature, smooth muscle, connective tissue, mucous glands and inflammatory cells in the airway [118]. Upon repeated allergen challenge, the effects of these mediators are deleterious to the host and drive several aspects of airway inflammation and remodelling [118]. MCs regulate adaptive immune responses, upon exposure to

allergens that crosslink immunoglobulin E (IgE) bound to the Fc ϵ RI [119]. IgE production requires allergen uptake by APCs and presentation to naive T cells in the context of major histocompatibility complex (MHC) class II [120]. The latter differentiate into a Th2 cell phenotype with enhanced IL-4 and IL-13 production, which induce B cells to undergo isotype switching. There are two types of IgE receptors; the high affinity Fc ϵ RI and the low affinity receptor Fc ϵ RII (CD23). Fc ϵ RI is expressed on MCs and basophils in the form of tetramers ($\alpha\beta\gamma_2$) and on APCs in the form of trimers ($\alpha\gamma_2$) at much lower levels [121]. The expression of Fc ϵ RI on MCs is upregulated by circulating IgE, as IgE binding stabilizes Fc ϵ RI at the cell surface, while unoccupied Fc ϵ RI has a short half-life [121]. CD23 expressed on AECs mediates the transfer of IgE and allergen-IgE complexes through the epithelium by transcytosis, facilitating the binding of IgE on Fc ϵ RI of MCs, basophils and APCs.

Activation of the Fc ϵ RI increases intracellular Ca⁺⁺, which results in the reorganization of the cytoskeleton and the release of preformed and newly generated mediators. MCs synthesize and release a vast array of pro-inflammatory chemokines and cytokines and recruit other immune cells, such as, eosinophils, activated macrophages and lymphocytes [118]. Therefore, MCs are involved in both the early and the late phase of allergic responses in sensitized individuals. A growing amount of evidence suggests that in asthma MCs are in constantly activated state resulting in enhanced mediator release and the establishment of chronic airway inflammation. Moreover, MCs reside close to key structures of the bronchial wall, such as, airway smooth muscle (ASM) [122], contributing to ASM hypertrophy and other remodelling features [122–124].

MCs also act as sentinels of infection, as they are capable of sensing microbes through a variety of PRRs [125] and release IL-1 β , TNF, IL-6 and IFN- γ [126]. This is particularly important in patients with asthma wherein respiratory infections are the commonest trigger of disease exacerbations. MCs may also exhibit immunoregulatory functions, as they have the ability to down-regulate inflammation through the production of IL-10 [127]. Given their diverse functions, it is reasonable to consider MCs as key innate immune modulators that regulate allergic inflammation in asthma.

3.4. Basophils

Basophils are the smallest population of circulating granulocytes, accounting for less than 1% of leukocytes in the blood and spleen. Their name is due to the fact that their cytoplasmic granules stain with basophilic dyes. Basophils were discovered by Paul Ehrlich just a year after he described MCs [128]. Their relative small numbers and their resemblance to MCs have taken basophils out of the spotlight for some time, therefore our knowledge on their role in the initiation and establishment of allergic responses is rather limited. However, recent work with novel mouse models has provided evidence that basophils exert essential effector functions in Th2-mediated allergic responses [129,130].

Basophils arise from a granulocyte precursor in the bone marrow which is common for eosinophils and MCs; however, unlike the latter, basophils exit to the periphery with a fully mature phenotype [131]. Basophilic granules contain effector molecules, such as histamine, cysteinyl-leukotrienes and antimicrobial peptides. Upon activation, basophils produce numerous Th2 associated cytokines, such as IL-4, IL-6, IL-13, and various chemokines [132]. In addition, basophils express Fc ϵ RI receptors [132]. These features allow basophils to contribute to the symptoms of type-I hypersensitivity reactions, during both early and late phase responses.

Basophil presence has been demonstrated in the airways of asthmatics, in the skin of atopic dermatitis patients and in the nose in the context of allergic rhinitis [133]. However, it is the ability of basophils to be a prime early source of IL-4 and IL-13 that has raised the question of whether they can also act as immunomodulators during allergen sensitization and the priming of Th2 cell responses. The generation of

new mouse strains to study the role of basophils in asthma models has provided us with valuable, but sometimes conflicting information [129]. Basophils may indeed promote the inflammatory response in the skin especially during chronic allergic reactions, as basophils were experimentally shown to be required for IgE-mediated chronic skin allergic inflammation [134–136]. Furthermore, basophil depletion resulted in a loss of antibody-mediated resistance against ticks, revealing a non-redundant role of basophils in acquired immunity [137]. It has also been shown that inflammatory monocytes recruited to allergic skin acquired an M2-like phenotype in response to basophil-derived IL-4 and exerted an anti-inflammatory function, highlighting an anti-inflammatory function for basophils [138].

The data concerning the role of basophils in allergic airway inflammation are less clear. Basophil depletion in an acute model of OVA-induced allergic airway inflammation revealed normal recruitment of eosinophils and Th2 cells in the airways [136]. Moreover, in a HDM model of allergic sensitization, basophils were found to play only a minor role in Th2 cell polarization [139]. On the other hand, *Aspergillus fumigatus* stimulation upregulated BAFF expression on the basophils of severe asthmatics and bronchopulmonary aspergillosis patients, suggesting that basophils may contribute to the polyclonal production of IgE commonly observed in these patients [140]. More studies are needed to determine whether basophils are implicated in the regulation of chronic allergic inflammation of the lung.

4. Innate lymphoid cells

4.1. Invariant natural killer T cells (iNKTs)

Natural killer T cells constitute a small population of total lymphocytes that express markers of both NK (NK1.1) and T cells, such as the T cell receptor (TCR) and the promyelocytic leukemia zinc finger (PLZF) transcription factor [141] and combine properties of both innate and adaptive immune cells. Type I or invariant natural killer T cells (iNKT) express a restricted repertoire of TCR α chains (V α 14-J α 18 in mice or V α 24-J α 18 in humans), associated with a highly skewed set of V β chains (V β 8, V β 7 and V β 2 in mice and V β 11 in humans). iNKTs use their TCRs to recognize exogenous and endogenous lipid antigens (ceramide-based glycolipids and glycerol-based lipids), the prototypical antigen being α GalCer [142].

Airway DCs and macrophages capture the α GalCer antigen and present it to iNKTs. Based on several phenotypic characteristics, iNKTs can be further divided in three major subsets; Th1-like, Th2-like and Th17-like iNKTs [143]. The Th2-like iNKT subset is of prime importance in the context of asthma [144]. These cells are abundant in the airways and, upon IL-25 triggering, produce IL-4, IL-9, IL-10 and IL-13, which enhance allergic inflammation [145–147]. HDM, aspergillus and plant pollens contain glycolipids that activate iNKTs and initiate allergic inflammation [148,149]. Th2-like iNKTs contribute to prolonged AHR through IL-13-induced M2 polarization in a post-viral airway inflammation model [150]. Th17-like iNKTs are also implicated in the development of AHR; they produce IL-17 in response to IL-23 and contribute to neutrophilic airway inflammation [151]. Ozone exposure results in the expansion of Th17-like iNKTs, which contribute to AHR [152].

Early-life viral exposure can also affect the later development of allergen-induced AHR by altering the functional phenotype of the iNKT cell compartment. Influenza infection in lactating mice is reported to be associated with iNKT cell-dependent inhibition of airway hyperreactivity, possibly through the induction of Tregs [153]. Quite recently, a new regulatory iNKT subset was identified that lacks expression of the transcription factor PLZF and has the ability to control the homeostasis of Tregs [154]. Therefore, although the activation of different iNKT subsets results in different outcomes, these cells play a critical role as innate responders and modulators of adaptive immunity of the airway.

Human studies do not suggest a clear role for iNKT cells in AHR

[155,156]. Although initial studies have demonstrated increased numbers of iNKTs in the lungs of asthmatics indicative of iNKT contribution [155,157], several subsequent studies have contradicted these findings [156,158]. The precise role of iNKT cells in asthma remains uncertain, although there seems to be a correlation between increased iNKT frequency and the most severe forms of allergic asthma [159].

4.2. Type II innate lymphoid cells

Recent studies have identified a population of innate immune cells called innate lymphoid cells (ILCs) [160]. ILCs are derived from a bone marrow common lymphoid progenitor, exhibit lymphoid cell morphology and lack rearranged antigen receptors and classic cell-surface lineage markers (Lin⁻). They are considered to have evolved to mount a rapid immune response to environmental challenges and are classified into three groups, according to their cytokine expression and transcription factors required for their development: group 1 ILCs (ILC1s and NKs), group 2 ILCs (ILC2s) and group 3 ILCs (ILC3s and LTi) [161]. This review will focus mainly on ILC2s, which are predominantly involved in type 2 immune responses and may also participate in lung repair and remodelling [162,163].

ILC2 were first described in 2001 in Rag-deficient mice, as non-B/non-T cells that produce IL-5 and IL-13, but not IL-4, in response to IL-25 [164]. Shortly thereafter, IL-5 was found to be produced by non-B, non-T cells after intranasal administration of IL-25 and infection of mice with *Nippostrongylus brasiliensis* [165]. A comprehensive and detailed characterization of ILC2s took place in 2010 by three independent research groups, which named them natural helper cells [166], innate type 2 helper cells [167] and nuocytes [168]. Mouse ILC2s are negative for classical cell surface markers for T cells, B cells, NK cells, myeloid cells and DCs. On the other hand, they express the IL-33 receptor (ST2), CD127 (IL-7R α -chain), ICOS, CD117 (c-kit), Thy1, IL-17RB (IL-25 receptor), CD44 and CD25 (IL-2R α -chain) [169]. ILC2 are considered to be the innate counterpart of Th2 CD4⁺ T cells and therefore a critical innate source of type 2 cytokines. They require for their development the transcription factor inhibitor of DNA-binding 2 (Id2), the retinoic acid receptor-related orphan receptor- α (ROR α) [170], GATA-binding protein 3 (GATA3) [171] and Bcl11b [172]. Notch signalling, a master regulator of T-cell lineage commitment, is also of particular importance in ILC2 development [173].

Lung ILC2s represent only 0.25–1% of total live cells and are located in collagen-rich regions of medium-sized airways [174]. Allergen-induced ILC2s infiltrating the mouse lung, are a major source of IL-13 and induce AHR after IL-25 inhalation [175]. Murine ILC2 is involved in AHR triggered by respiratory viral infections, such as influenza [176], as well as in airway repair [177]. Following the discovery of ILC2 in mice, the search for their human counterparts began. Human ILC2s were first described in 2011 [24,177], although these two studies showed opposing roles (inflammatory vs protective) of ILC2s in respiratory immunity.

ILC2s expand and exert their effector functions in response to various myeloid and epithelial cell-derived cytokines and alarmins produced after allergen or viral disruption of the airway epithelium [175,178]. IL-33 is more potent than IL-25 in inducing ILC2 propagation [25]. Lung ILC2s are also regulated by lipid mediators produced during allergic inflammation, such as leukotriene D4 (LTD4) [179] and prostaglandin D2 (PGD2) [180]. In contrast, lipoxin A4 and PGI2 inhibit ILC2s [181]. In response to these stress signals, lung ILC2 undergoes proliferation and produces robust amounts of Th2 cytokines, notably IL-5 and IL-13, possibly at levels greater or, at least, equivalent to those produced by Th2 cells [178]. They also produce IL-6, IL-9 in response to protease allergens [182], and IL-2, presumably in an autocrine and/or paracrine manner [177].

ILC2s can provoke allergic airway inflammation in the absence of CD4⁺ T cells [175,183], following intranasal administration of IL-33 or IL-25 [164,184]. Papain also induces allergic airway inflammation in

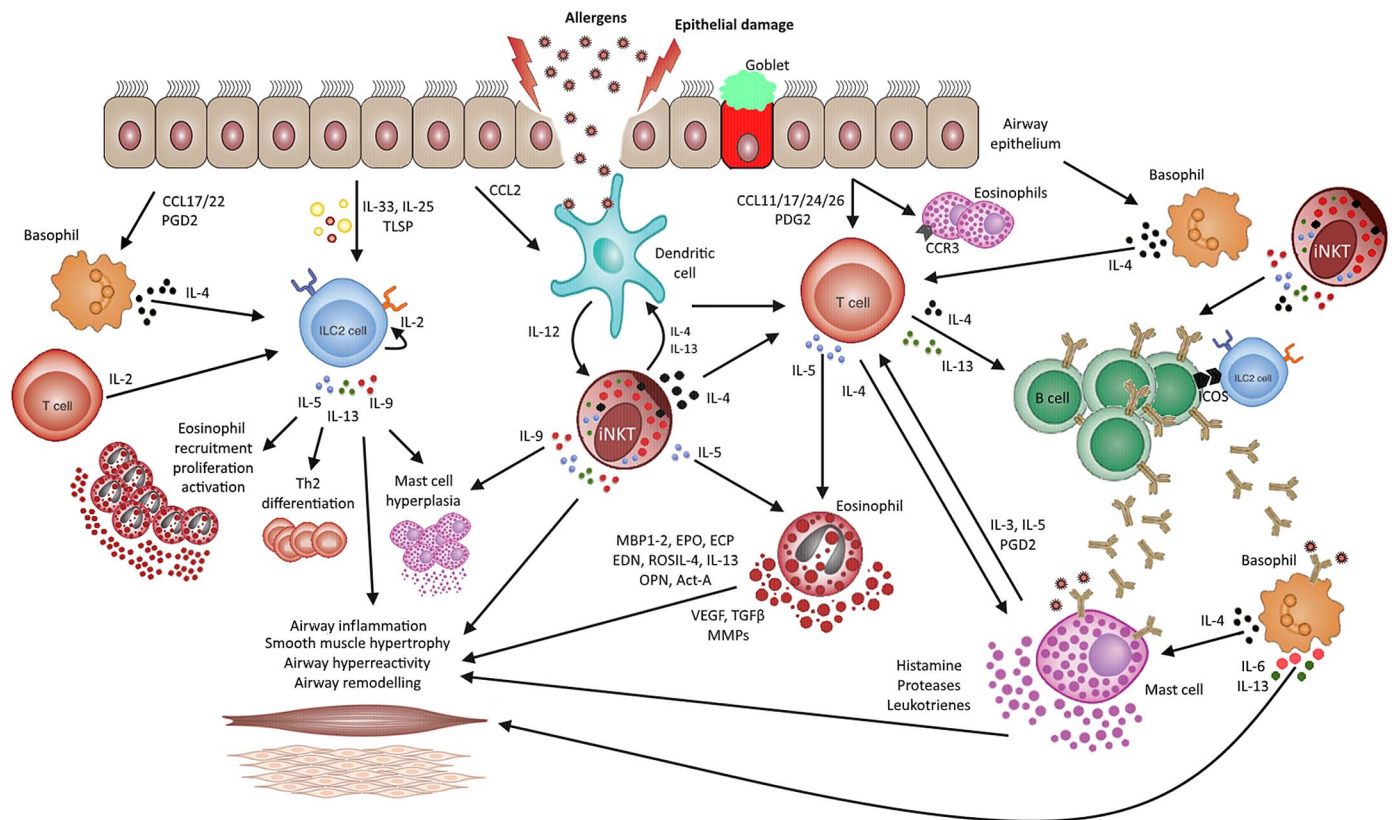


Fig. 1. Complex interactions between innate and adaptive immunity in allergic airway inflammation. Schematic representation of the functional crosstalk between innate and adaptive immune cells, highlighting the central role of innate lymphoid cells in initiating and perpetuating allergic airway inflammation and remodelling.

RAG-deficient mice [185]. ILC2s are the main source of IL-5 and IL-13 in RAG-deficient mice, and ILC2 transfer in T-cell depleted mice is sufficient to restore lung inflammation [186].

The extent to which ILC2s contribute to type 2 immunity depends on their interactions with the adaptive immune system. A subset of ILC2s is shown to express MHC class II molecules and could potentially activate CD4⁺ T cells [182,187]. ILC2-derived IL-13 is critical for the initiation of Th2-cell-mediated responses [20]. ILC2s may also interact with B cells through cytokine production and promote both B1 and B2 cell expansion and antibody production in vitro. Moreover, ILC2s display high expression of the inducible costimulatory ICOS, a member of CD28 superfamily, which may bind to ICOS-ligand on B cells and shape germinal center responses [188]. IL-2 secreted by T cells may account for the co-activation and further proliferation of ILC2s in a tri-cellular crosstalk model where Tregs diminish the IL-2 dependent proliferation of ILC2s [189].

Although most studies suggest a pro-allergic role of lung ILC2s, they may also be implicated in beneficial tissue repair after acute epithelial damage. Lung ILC2s participate in airway repair by producing amphiregulin, a member of the EGF family, in response to IL-33 stimulation after influenza-induced AEC damage [177]. The ability of ILC2s to contribute to tissue repair is in accordance with the hypothesis that type 2 responses have evolved to repair wounded tissues [190]. ILC2s initiate low type 2 innate immune responses and may act as a first line defense to airway insults. Repeated allergen challenges may lead to sustained activation of ILC2s and subsequent activation of antigen-specific Th2 cell immunity. Nevertheless, little is known on how ILC2s are involved in the chronic phase of the immune response.

4.3. Type I and III Innate lymphoid cells

ILC1s have been identified mainly in the gut epithelium of mice and humans with colitis as IL-12- and IL-15-responsive cells secreting IFN- γ

[191,192], but have not been extensively studied in the context of asthma. ILC3 cells are characterized by the expression of the transcription factors ROR γ t and GATA3 [193]. They are divided in three different subtypes according to their cytokine profile and role: a) LTi cells which produce IL-17 and IL-22 and are necessary for lymphoid organogenesis [194], b) IL-17 producing ILC3s, located mainly in the intestine [195] but also in the lungs of patients with obesity-associated asthma [196], and c) IL-22 producing ILC3s encountered in lungs, skin and intestine [197,198]. Obesity is usually associated with a Th2-independent form of asthma which is often steroid-resistant [199]. Mice made obese by high fat diet spontaneously develop AHR, which correlates with a remarkable increase of IL-17-producing ILC3s [196]. The NLRP3 inflammasome is required for the development of IL-17-producing ILC3s, via the release of IL-1 β from M1 macrophages [196]. The putative role of ILC3s in human obesity-related asthma is further corroborated by the recent finding that ILC3s are present in the BAL fluid of asthmatic patients, particularly in those with more severe asthma [196]. IL-23 and IL-1 β from airway epithelial cells rapidly induce IL-22 production from ILC3s, which protects from AHR in allergic asthma.

5. Concluding remarks and future prospects

Innate immune cells contribute to the initiation, effector phase and resolution of allergic responses and, as such, are essential for asthma pathophysiology (Fig. 1). Innate immune cells are recruited in the inflamed airways through the dynamic interaction between a variety of cytokines and chemokines and their corresponding receptors in both innate immune and structural cells (Table 1). The development of targeted biological therapies, such as anti-IL-5, anti-IL-13, omalizumab and anti-CD123 seems to be critical for the suppression of the pathological functions of innate effectors and the control of the asthmatic response. Still, the role of these cells in immune response

Table 1
Cytokine and chemokine ligands and their corresponding receptors involve in the recruitment of innate immune cells in the inflamed airways.

Innate immune cell type	Cytokine receptor	Chemokine receptor	Cytokine ligand	Chemokine ligand	Reference
Macrophages	GM-CSFR, TGF- β R, IL-10R, TNFR, IFN- γ R, IL-1 β R	CCR2, CCR1, CCR3, CCR5, CXCR3	GM-CSF, TGF- β , IL-10, TNF α , IFN- γ , IL-1 β	CCL2, CCL5, CCL7, CCL13, CXCL9, CXCL10, CXCL11	[10,77]
Dendritic cells	IL-33R, TSLPR, IL-25R, GM-CSFR, IL-1R, TNFR	CCR6, CCR10, CCR7	IL-33, TSLP, IL-25, GM-CSF, IL-1 β , TNF- α	CCL20, CCL27, CCL19	[9,11]
Eosinophils	IL-5R, GM-CSFR, IL-3R, IL-17R	CCR3, CCR1, CCR5	IL-5, GM-CSF, IL-3, IL-17A	CCL11, CCL24, CCL26, CCL5, CCL7, CCL13, CCL3	[9,11,10]
Mast cells	IL-4R, IL-9R, IL-13R	CCR3, CXCR2, BLT1, CVSLT1	IL-4, IL-9, IL-13	CCL11, CCL24, CCL1, CXCL1, CXCL2, LTB4, LTD4	[9,11,10]
Basophils	GM-CSFR, IL-9R	CCR3, CCR2, CCR1	GM-CSF, IL-9	CCL11, CCL24, CCL5, CCL7, CCL13, CCL17, CCL22, PDG2	[9,11,10]
Invariant natural killer T cells	IL-25R	CCR2, CXCR3, CXCR6, CCR5, CCR6, CCR4	IL-25	CCL2, CXCL16, CCL17, CXCL9, CXCL13, CCL20	[11,144,147]
Type II innate lymphoid cells	IL-25R, IL-33R, TSLPR, IL-4R	CCR9, CXCR4, CXCR6	IL-25, IL-33, TSLP, IL-4	CCL2, CX3CL1	[11,160,163]
Type I and III innate lymphoid cells	IL-12R	CXCR6, CXCR1, CXCR2, CXCR3, CXCR4, CX3CR1, CXCR5, CCR6	IL-12	CCL2, CX3CL1	[11,160,163]

regulation and tissue repair should not be ignored and careful evaluation of these therapeutics is needed to avoid potential adverse effects. Advances in our knowledge on the biology and functions of iNKT cells and the recently-identified ILCs have also greatly facilitated the understanding of innate pathways regarding asthma immunopathology. However, future research should focus on dissecting the role of these cells in tissue repair and remodelling, processes strongly associated with asthma severity. Finally, the airway epithelium should clearly not be considered as an innocent bystander in allergic inflammation, as it exhibits critical innate immune functions that become dysregulated in asthma. Considering that steroids, the main-stay asthma treatment, do not effectively restore airway epithelial cell function or restrain innate immune cell responses, the application of advanced in vitro culture systems and novel state-of-the-art molecular biology and bioinformatic approaches will shed new light on the mechanisms underlying dysregulated immunity in asthma and facilitate the identification of novel targets for drug discovery.

Conflict of interest

The authors report no conflict of interest or any financial contribution for the work being reported.

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