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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 metalloprotease; NF-κB, necrosis factor κB; 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 peroxynitrate, which activate DCs or AECs through NF-κB 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