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Orchestration of epithelial-derived cytokines and innate immune cells in allergic airway inflammation

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ABSTRACT

Allergic asthma, a chronic respiratory disease, is a leading worldwide health problem, which inflames and constricts the airways, leading to breathing difficulty. Many studies have focused on the pathogenesis contributed by the adaptive immune system, including $CD4^+$ T lymphocytes in delayed type hypersensitivity and B cell-produced IgE in anaphylaxis. More recently, a focus on the airway mucosal barrier and the innate immune system has highlighted, in coordination with T and B cells, to initiate and establish disease. This review highlights the impacts of epithelial-derived cytokines and innate immune cells on allergic airway reactions.

1. Introduction

Pathogenic organisms elicit three major cell-mediated immune responses categorized as type 1, 2 and 3 immunity [1,2]. For instance, intracellular microbes prompt a Type 1 immune response which is characterized by a potent IFN-γ and cytotoxic response by $CD4^+$ T helper 1 (TH1) and cytotoxic $CD8^+$ T cells, innate cells (such as group 1 innate lymphoid cells (ILC1s) and natural killer (NK) cells), and classically activated (M1) macrophages. Type 1 immune response also involve immunoglobulin G (IgG) antibody production. Type 2 immunity confers protection to helminthes and foreign environmental stimuli such as toxins and venom at both cutaneous and mucosal surfaces by various cells producing interleukin-4 (IL-4), IL-5 and IL-13. These cells include TH2 cells, ILC2s, alternatively activated (M2) macrophages, basophils, eosinophils, mast cells. Type 2 immune response promotes IgE production. Extracellular bacteria and fungi initiate type 3 immune response characterized by IL-17 and IL-22 producing TH17 cells and ILC3s and by neutrophil activation. Given their protective nature, dysregulation of these responses can lead to autoimmune (type 1 and 3 inflammation) or allergic (type 2 inflammation) diseases. Over the last 50 years, the incidence for autoimmune and allergic diseases has increased in developed countries [3]. Allergic diseases, asthma and helminth infection continue to rise at an epidemic proportion with billions of individuals worldwide suffering and even succumbing to chronic type 2 inflammation. In developing countries, people are in constant exposure to parasitic worms as well as bites and stings from insects and animals that can lead to type 2 inflammation. In developed countries, these exposures are lower but still present; however, industrialization introduces an environmental aspect. This public health problem calls for global action and a deeper understanding of the biological mechanisms regulating type 2 inflammation.

1.1. Allergic airway inflammation

Asthma is a chronic lung disease that inflames and constricts the airways, leading to breathing difficulty. Asthma nowadays affects 300 million people worldwide and more than 25 million people (7%) including 7 million children in US (Ref. [4]; CDC data, 2015). Allergic asthma is the most common type of asthma (60% of all cases), which is triggered by inhaled allergens such as pollen, dust mite, pet dander, and mold. From an immunological standpoint, allergic airway inflammation describes the sensitization of the epithelium and underlying immune cells to antigenic allergen and subsequent immune response (at the effector phase) as well as tissue repair due to the allergen- and immune-induced damage. Often categorized as a T cell–mediated disease, allergic asthma is associated with TH2 cells and TH2 type cytokines including IL-4, IL-5 and IL-13, which can act on innate immune cells and the mucosal barrier. Among these, IL-5 recruits and activates eosinophils leading to eosinophilia [5]. IL-13 acts directly on airway epithelial cells to induce airway hyper-responsiveness and mucus production [6]. Interestingly, IL-4 induces and maintains TH2 cells, and contributes to IgE class switching in B cells as well as population expansion [7].

Abbreviations: TSLP, thymic stromal lymphopoietin; TSLPR, TSLP receptor; iNKT, invariant natural killer T cell; TH, $CD4^+$ T helper cell; ILC2, group 2 innate lymphoid cell; Ig, immunoglobulin; IFN, interferon; IL, interleukin; HMGB1, high-mobility group box 1 protein; PRR, pattern recognition receptors; PAMP, pathogen-associated molecular pattern; DAMP, damage-associated molecular pattern; HDM, house dust mite; LPS, lipopolysaccharides; EC, epithelial cell

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Because of the importance of IL-4 in the TH2 responses, one may ask, how is type 2 immunity in allergic airway inflammation initiated? Which type of cells provides the early source of IL-4 or other cytokines (such as IL-13) to drive TH2 differentiation? Are there other upstream mediators that promote and maintain type 2 immune responses in airway inflammation? The next few sections will discuss and highlight recent work describing the various cells and effectors promoting type 2 immune responses.

1.2. Initiation of an allergic microenvironment: allergens, alarmins and PAMPs

Lung epithelial cells (ECs) express a plethora of pattern recognition receptors (PRRs) and act as the first line of defense against pathogens and inhaled allergens. Lung ECs can recognize environmental allergens that drive chronic allergic diseases like asthma [8]. This recognition is through the detection of pathogen-associated molecular patterns (PAMPs). Allergens such as house dust mite (HDM) and HDM fecal pellets contain lipopolysaccharides (LPS) from Gram-negative bacteria that activate toll-like receptors (i.e. TLR4). Several reports have illustrated the amount of LPS (in coordination with an allergen) determines the type of immune response in airway inflammation. Low dose of LPS will allow type 2 immune response to drive airway inflammation while type 1 and 3 occurs with a high dose of LPS [9–11]. Type 2 immune response can occur in the absence of LPS as seen in mice challenged with chitin, a major component of helminthes and insects [12], which is likely through induction of chitinase and activation of protease-activated receptor 2 (PAR2)[13,14].

Allergens can also cause direct damage to the lung epithelium. Allergens with protease activity, such as papain and HDM proteases (e.g. Der p1, Der p3, Der p6), disrupt epithelial integrity via tight junction interactions and activate the PAR-2 pathway [15,16]. Direct cellular damage causes the release of damage-associated molecular patterns (DAMPs). DAMPs, also referred to as alarmins, are host cell-derived molecules released to signal damage/danger to neighboring cells. Alarmins include uric acid, IL-1α and high-mobility group box 1 protein (HMGB1) recognized by PRRs, cytokine receptors and various other transmembrane receptors.

HDM can cause the release of ATP, uric acid, IL-1α and HMGB1 by lung ECs [8]. Asthmatic patients have higher levels of HMGB1 compared to healthy patient controls [17]. Various mouse models of allergen-induced airway inflammation have also shown an increase in IL-1α and HMGB1 and blocking either alarmin ameliorates allergic asthma [18,19]. Therefore, antigenic molecular pattern recognition or a direct insult to ECs results in the production of various alarmins, cytokines, and chemokines.

The major immune mediators released due to allergen exposure by epithelial cells are IL-25, IL-33 and thymic stromal lymphopoietin (TSLP) [20–23]. Interestingly, lung ECs also produces IL-25, IL-33 and TSLP upon exposure to IL-1α, HMGB1 and uric acid [18,19,24]. These alarmins and cytokines are major drivers of type 2 inflammation. These various effector molecules recruit and activate the appropriate immune cells to control and eliminate the allergen/pathogen and initiate epithelial repair. Thus, barrier epithelial cells of the lung sit at the apex of type 2 immunity.

1.3. Epithelial cytokines: the early composer of allergic airway inflammation

As described above, lung epithelium can produce type 2 polarizing cytokines IL-25, IL-33 and TSLP [25–27]. These epithelial derived cytokines initiate type 2 responses and can activate and trigger the production of IL-4, IL-5, IL-9 and IL-13 by innate cells (lymphoid and granulocytes) and TH2 cells (discussed below). Concerning allergic asthma, numerous environmental allergens can trigger the release of IL-25, IL-33 and TSLP. The discovery and inquiry of these epithelial-derived cytokines in response to allergens has brought forth a clearer understanding of the initiation of allergic airway inflammation [8]. Nevertheless, the induction of airway inflammation is a complex process that involves multiple cell types and cytokines. Herein, we discuss the role these epithelial-derived cytokines play in allergic airway inflammation.

1.3.1. IL-25

IL-25, a member of the IL-17 cytokine family, is expressed by a variety of cells besides epithelial cells including T cells, basophils, eosinophils, and mast cells [8]. Nonetheless, bronchial epithelium from asthmatic patients produce high levels of IL-25 and these patients have high plasma levels of IL-25 [28]. Interestingly, IL-25R is highly expressed on eosinophils and basophils in asthmatic patients [29,30]. IL-25 is critical for airway eosinophilia and can activate and expand ILC2s and TH2 cells [31,32]. Activation of these cells leads to IL-4, IL-5 and IL-13 cytokine expression. IL-25 also regulates basophil apoptosis, and cytokine expression (IL-4 and IL-13) as well as degranulation [33]. Besides the production of type 2 cytokines by both innate and adaptive immune cells, it also promotes IL-7, IL-33 and TSLP production by stromal cells which further drive airway remodeling and angiogenesis [34].

1.3.2. IL-33

IL-33, one of the newest additions to the IL-1 cytokine family, has been found in numerous inflammatory conditions. Recent genome wide association studies have implicated IL-33 and its receptor ST2/IL1RL1 in various allergic diseases [35,36]. Allergens papain, HDM, and chitin induce IL-33 [20–23]. IL-33 is mainly expressed in lung epithelial and endothelial cells with a few reports describing hematopoietic cells such natural killer T (NKT) cells, mast cells and macrophages producing IL-33 [37–39]. IL-33 exerts its effects on multiple cells including basophils, eosinophils, mast cells, ILC2s and T cells. Like IL-25, the levels of IL-33 and its receptor ST2 in asthmatic patients are higher than controls and are enhanced upon acute stimulation with an allergen [28], which correlate with asthma severity. In humans, IL-33 expression is elevated in severe allergic disease [40,41]. Multiple mouse models of allergic diseases have highlighted the role of IL-33 in increased airway hypersensitivity by enhancing IgE production, goblet cell hyperplasia and eosinophilia [42–44]. Blockade of the IL-33/ST2 signals ameliorates murine allergic airway inflammation [45,46]. IL-33 has also been found to be a potent activator of IL-5 and IL-13 production by ILC2s and IL-4, IL-5 and IL-13 production by basophils [47–49]. IL-33 also enhances the survival and migration of human eosinophils [50].

1.3.3. TSLP

TSLP is an IL-2 cytokine family member utilizing receptor TSLPR and sharing the IL-7 receptor IL-7Rα [51,52]. Similar to IL-25 and IL-33, epithelial cells (lung and skin) are the primary producers of TSLP but it is also produced by basophils, mast cells, macrophages and dendritic cells (DCs) [51,52]. Numerous cells can respond to TSLP from both innate (basophils, DCs, eosinophils, ILC2s, mast cells and monocytes) and adaptive (T and B cells) arms of the immune system in addition to airway smooth muscle and epithelial cells [51,52]. In concert with IL-33, TSLP can induce the production of IL-5 and IL-13 from ILC2s and the differentiation of TH2 cells and the production of cytokines [53,54]. Additionally, TSLP in coordination with IL-4 can differentiate monocytes into M2 macrophages and alone can lead to basophil activation, expansion and survival [55–57]. Furthermore, stimulation of eosinophils with TSLP results in the degranulation [58]. TSLP also promotes basophil development and activation [56,59]. Like IL-33, asthmatic patients display genetic polymorphisms in the promoter region of TSLP [60]. TSLP levels are higher in asthmatic patients as well as in animal models of allergic airway inflammation [61,62]. The blockade of TSLPR in animal models reduces the allergic response demonstrating a potential target for allergic airway inflammation [63,64].