



The Emerging Role of Innate Immunity in Respiratory Allergy

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Abstract - The author's overview recent findings on the pathogenesis of respiratory Allergies with special emphasis on the emerging role of innate immunity

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Introduction

Allergic rhinitis and asthma are the two main clinical manifestations of respiratory allergy and their prevalence and incidence is continuously increasing worldwide. According to recent epidemiological studies up to 20% of population in Western countries have allergic rhinitis whereas up to 10% have bronchial asthma [1]. The classical paradigm of pathogenesis of respiratory allergy is based on an abnormal immune response to non pathogenic antigens (allergens) that induce an IgE-mediated inflammatory response leading to the activation of effector cells, such as mast cells, basophils and eosinophils, that are ultimately responsible of secretion of proinflammatory mediators.

Adaptive responses in rhinitis and asthma are primarily driven by Th2 cells that produce a unique cytokine profile including IL-3, IL-4, IL-5 and IL-13 [2]. These cytokines induce switching of B cells towards IgE-producing cells, increase mast cell, basophil and eosinophil activation and promote changes in the target tissues (upper and lower airways) that facilitate persistent inflammation and remodeling [3].

During the last decades it has become increasingly evident that not all patients with respiratory allergy had clinical features consistent with the Th2-type of immune response. A large number of clinical studies confirmed that both rhinitis and asthma have multiple clinical phenotypes distinct by age of onset, clinical presentation, comorbidities and response to treatment [4]. While the majority of patients with asthma have an early onset of the disease and a clearly evident IgE-mediated response to aeroallergens, between 20 and 30 percent of asthmatics have a delayed onset of clinical symptoms and they do not show any sensitization to allergens, i.e., they have consistently negative skin prick test and no measurable allergen-specific serum IgE. Similarly, 10 to 20 % of patients with rhinitis have



all clinical features of an allergic form but no definite sensitization to aeroallergens can be demonstrated.

These forms of “non allergic” rhinitis and asthma cannot be explained by classical mechanisms of an adaptive Th2 response and led to hypothesize alternative pathways to induce persistent chronic inflammation of the airways.

Recently, innate immunity has been increasingly hypothesized as a fundamental mechanism to explain the clinical phenotypes on “non allergic” asthma and rhinitis. Innate immunity has been the focus of extensive studies in the last decades that led to the discovery of new effector cells and pathways potentially able to promote airway inflammation. It has long been known that cells of innate immunity are particularly abundant in upper and lower human airways which are a major interface area with the external environment [5]. Moreover, environmental stimuli such as viral and bacterial infections, air pollutants and irritants, which are known activators of innate immunity, strongly influence the development of inflammation in patients with rhinitis or asthma [6]. Finally, allergens, beside being recognized by adaptive immunity, contain also molecules, e.g., proteases, other enzymes and biologically active glycolipids, that may play a crucial role in activating cells of innate immunity [7]. This review will briefly summarize the most recent findings on the potential role of innate immunity in the development of respiratory allergy.

Activation of Innate Immunity in Human Airways

The mucosal surface of airways plays a fundamental role in the defense against infections and provides protection from chemical and toxic damage from external environment. Innate immunity is a first line mechanism to regulate early responses to potentially harmful agents. Human airways are richly endowed with cells that work together to orchestrate a fast innate immunity response that functions not only to limit tissue damage but also to shape the subsequent adaptive immune response if required. In the following chapter, a review of the major mechanisms of activation of some cells of innate immunity, namely epithelial cells, mast cells and eosinophils, as they relate to the development of allergic sensitization and inflammation.

Airway Epithelial Cells

Epithelial cells, once thought to be just a mechanical barrier, are now increasingly recognized as cells fully capable to detect virus, bacteria and other toxic agents and to respond to this stimuli by activating other cells in the subepithelial layers. Airway epithelial cells are equipped with many receptors, including Toll-like receptors, protease-activated receptors (PAR) and other Pathogen-Associated Molecular Patterns (PAMP) and Damage-Associated Molecular Patterns (DAMP) receptors [8]. Engagement of these receptors induces the production of several cytokines and chemokines including IL-25, IL-33 and Thymic Stromal Lymphopoietin (TSLP). These molecules play a fundamental role in promoting maturation of immature



dendritic cells that are resident in the subepithelial mucosa [8]. Mature dendritic cells become then fully capable of recognizing, capture and processing allergens and of inducing a Th2 response. Thus, messages sent by epithelial cells exposed to environmental agents are crucial to initiate the early phases of sensitization to aeroallergens. In addition, epithelial cells produce a large set of chemokines, including CCL5, CCL17, CCL22 and CX3CL1 when stimulated by toxins and infectious agents [9]. These chemokines potently favor Th2 cell differentiation and their migration into the airway mucosa, thus providing support for long term memory of allergic sensitization and for persistent inflammation.

Mast cells

Human airways are a major site where mast cells, originating as precursors from the bone marrow, reach their final maturation and become fully competent cells. The role of mast cells in innate responses against bacterial, viral and parasitic infections has been clearly established. However, mast cells are key effector cells in the development of symptoms and clinical features of rhinitis and asthma [10]. They are activated by crosslinking of the IgE bound to the high affinity IgE receptor and release a variety of proinflammatory mediators including histamine, cysteinyl leukotrienes and Platelet Activating Factor. In addition, human mast cells produce a wide array of proinflammatory and immunomodulating cytokines and chemokine that are important for dendritic cell maturation and

differentiation toward a Th2-inducing antigen-presenting cells. In vitro studies demonstrated that human mast cells are an important source of IL-4 and IL-13 that can contribute to Th2 responses and to sustain local IgE production in the airway mucosa, Secretion of these cytokines from mast cells can be induced by IgE-independent mechanisms primarily because mast cells are endowed with a unique profile of Toll-like receptors [11]. Therefore, mast cells can be activated by PAMPs and DAMPs to generate cytokines and chemokines that, on one side, can contribute to modulate adaptive immune responses toward the Th2 and, on the other, may directly promote airway inflammation independently from specific IgE sensitization. The latter mechanism may be particularly relevant to explain rhinitis and asthma exacerbations induced by bacterial and viral infections.

Eosinophils

Eosinophils constitute a first-line defense against infections by parasites and helminthes. These cells play also a prominent role in respiratory allergy being the predominant cells infiltrating the nasal and bronchial mucosa of patients with rhinitis and asthma [12]. Eosinophils recruitment and activation is classically driven by Th2 cytokines and chemokines such as IL-3, IL-5 and eotaxin 1-3. While accumulation of eosinophils in the airway mucosa has always been considered a hallmark of “allergic” asthma, recent studies have challenged this dogma by showing that certain phenotypes of “non allergic” asthma are



associated with marked tissue and peripheral blood eosinophilia [13]. Asthmatic patients with eosinophilic asthma without clearly demonstrable allergen sensitization are usually adults (late-onset asthma), mostly females, that often have important comorbidities such as chronic rhinosinusitis and intolerance to aspirin. It is still unknown how a Th2 response can be triggered in these patients that have apparently no “atopy” and no evidence of type I hypersensitivity. In the last few years the discovery of new subsets of cells of innate immunity has open new perspectives on the pathogenesis of these form of non-atopic eosinophilic asthma. Innate lymphoid cells (ILCs) represent an emerging family of non-T, non-B cells that retained effector cell functions and play an important role in tissue homeostasis and remodeling and in innate immunity to pathogenic and nonpathogenic microorganisms [13]. Unlike adaptive immune cells, ILCs lack antigen-specific receptors (antigen nonspecific) but react promptly to a wide range of innate signals. In particular, the ILC2 subtype of cells are able to produce large amounts of IL-5 and IL-13 in response to IL-25 and IL-33 produced by activated epithelial cells [14]. ILC2 are particularly abundant in the mucosa of patients with eosinophilic asthma and currently represent a major target to modulate chronic airway inflammation.

Conclusions and Future Perspectives

Rhinitis and asthma, the two most diffuse allergic disorders, although efficiently controlled by currently

available treatments, are still far from being preventable and curable diseases. This is mostly because our understanding of the pathogenetic mechanisms of these heterogeneous diseases is still incomplete. Major advances in this field have been achieved in the last few years by demonstrating the role of cells of innate immunity in the basic mechanisms by which persistent airway inflammation is initiated and maintained. Cells once thought to enter the scene only at late stages, e.g., mast cells, eosinophils and epithelial cells, are probably involved in the early phases of antigen presentation, modulation of dendritic cells and Th2 cell development. Further studies are required to define better the role of ILC in rhinitis and asthma, including their helper and suppressor activities and how they are recruited in human airways. Interfering with cells and mediators of innate immunity may provide novel strategies to reach a better prevention and control of respiratory allergy.

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