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Biologics and the lung: TSLP and other epithelial cell-derived cytokines in asthma

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ABSTRACT

Asthma is a chronic airway inflammatory disorder with characteristic symptoms of dyspnea, wheeze, chest tightness and cough, and physiological abnormalities of variable airway obstruction, airway hyperresponsiveness, and in some patients with chronic long standing disease reduced lung function. The physiological abnormalities are due to chronic airway inflammation and underlying structural changes to the airway wall. The interaction between the airway epithelium and the environment is crucial to the pathobiology of asthma. Several recent discoveries have highlighted a crucial role of airway epithelial derived cytokines such as interleukin (IL)-25, IL-33 and thymic stromal lymphopoietin (TSLP). These cytokines are collectively known as epithelial "alarmins", which act solely or in concert to activate and potentiate the innate and humoral arms of the immune system in the presence of actual or perceive damage. Understanding the role of alarmins and how they are activated and released may allow the development of novel new therapeutics to treat asthma. This review describes the interactions between inhaled air, the pulmonary microbiome, airway epithelial cell layer and the alarmins, IL-25, IL-33 and TSLP. There is already compelling evidence for a role of TSLP in the airway responses to environmental allergens in allergic asthmatics, as well as in maintaining airway eosinophilic inflammation in these subjects. Further work is required to develop human monoclonal antibodies (hMabs) directed against IL-25 and IL-33 or their receptors, to help understand their role in the initiation and/or persistence of asthma.

Contents

Abbreviations: AHR, airway hyperresponsiveness; ASMCs, airway smooth muscle cells; DCs, dendritic cells; GM-CSF, granulocyte macrophage-colony stimulating factor; HDM, house dust mite; ICAM-1, intercellular adhesion molecule-1; IgE, immunoglobulin E; IL, interleukin; ILC2, innate lymphoid cell type 2; LPS, lipopolysaccharide; mAb, monoclonal antibody; MAPK, mitogen activated protein kinases; mDCs, myeloid dendritic cells; PAMPs, pathogen-derived molecular patterns; PRRs, pattern recognition receptors; SNP, single nucleotide polymorphism; Th-2, T-helper 2 cells; TLRs, Toll-like-receptors; TNF-α, tumor necrosis factor- alpha; Tregs, regulatory T cells; TSLP, thymic stromal lymphopoietin.

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1. Introduction

Asthma is a common chronic airway disease, which has been defined in the most recent iteration of the Global Initiative for Asthma as "a heterogeneous disease, usually characterized by chronic airway inflammation (Reddel et al., 2015). It is defined by the history of respiratory symptoms, such as wheeze, shortness of breath, chest tightness and cough that vary over time and intensity, together with variable expiratory airflow limitation". The physiological hallmarks of asthma are variable airflow limitation and the presence of airway hyperresponsiveness (AHR) to a wide variety of bronchoconstrictor stimuli.

Airway inflammatory responses in asthmatics vary in patients, and from time to time. The most characteristic inflammatory response is manifest by the presence of airway eosinophils (Kirby et al., 1987), T-helper 2 (Th-2) cells (Robinson et al., 1992), mast cells (Sont et al., 1996) and basophils (Gauvreau et al., 2000). In some patients, however, an airway neutrophilia is prominent (Gibson et al., 2001), while in a small minority there is no evidence of an increase in airway inflammatory cells (Simpson et al., 2006). The heterogeneity of the inflammatory response in asthma likely reflects the heterogeneity in the initiating stimuli and in the genetic background that sets the stage for the responses to these stimuli. Some of the stimuli that initiate asthma have been identified and these include environmental allergens (Gauvreau et al., 2015) and occupational sensitizers, some of which are conventional allergens and some (small molecular weight chemicals) are not (Tarlo & Lemiere, 2014). Also, exacerbations of asthma are known to be mainly initiated by the airway's responses to respiratory viruses, mainly human rhinovirus (HRV) (Johnston, 1995). The mechanism by which these environmental stimuli and viruses initiate asthma or cause worsening of the disease is an area of intense research.

2. Function of the airway epithelium

Apart from skin, the only other major organ that is in continuous contact with the external environment is the lung. Between 8×10^3 and 16×10^3 l of air is inspired daily by the average human lungs. This ensures that the airways are exposed to a huge array of allergens, microbes and particulate matter. Once thought of as a sterile environment in health, the distal airway and lung have been shown to host a wide variety of microbes, now referred to as lung microbiome (Baughman et al., 1987; Charlson et al., 2011; Erb-Downward et al., 2011). This has been elucidated through advanced molecular techniques such as real time-polymerase chain reaction. The gene for 16S ribosomal RNA (rRNA) is highly conserved across bacteria archaea. A study of respiratory samples, including those obtained via bronchoscopy, has evaluated the presence of 16S rRNA and other bacterial RNA signatures in both health controls and asthmatic subjects. Compared with healthy control subjects, asthmatic subjects had significantly more pathogenic Proteobacteria, such as Haemophilus species, but fewer Bacteroidetes, especially Prevotella species (Hilty et al., 2010).

The airway epithelium forms a continuous, highly regulated palisade covering the airway lumen. Intercellular epithelial junctions form the structural adhesive forces that maintain the integrity of the airway epithelial barrier. They are composed of tight junctions, adherence junctions and desmosomes. Tight junctions are the primary regulators of intercellular permeability and control the movement of ions and solutes between cells. Transmembrane proteins such as junction-adhesion-molecules, occludins and claudins, anchor the cell cytoskeleton to zonular occludin and cingulin that forms these tight junctions. Adherence junctions mechanically connect the adjacent cells and initiate proliferation and differentiation through homotypic transmembrane E-cadherin adhesions. These adhesions are anchored to the actin cytoskeleton and microtubule network by p120 catenin, β-catenin and α-catenin. E-cadherin provides the architectural support or scaffolding required to form other junctional complexes. Delocalization of the tight junction proteins ZO-1, occludin and claudins occurs following distorted adherence junction architecture (Carayol et al., 2002; Jiang et al., 2007; Heijink et al., 2010). Desmosomes consist of atypical cadherins that form adhesive links between the filamentous cytoskeleton of epithelial cells and the lamina propria. E-cadherin is also a ligand for the cognate receptor CD103 (αEβ7 integrin) expressed on innate and adaptive immune cells such as CD8 + ve T cells, effector CD4 + ve T cells and regulatory T cells (Tregs), which have been well characterized in the pathogenesis of asthma (Bernatchez et al., 2015). CD103 also identifies a subset of dendritic cells (DCs) that express E-cadherin and Langerin that are involved in tolerogenesis following inhaled allergen. They are also essential for the clearance of several respiratory viral infections (Beauchamp et al., 2010; Edelson et al., 2010). Thus, alteration of the airway microbiome environment may enhance or attenuate airway epithelial cells responses to microbes and allergens.

The interaction of the airway epithelium with inhaled allergens or pathogens results in the activation of immune responses by influencing tissue-resident or circulating antigen-presenting cells, such as dendritic cells (DCs) (Holt et al., 1990). The immune system usually maintains an equilibrium between protective responses towards pathogens and the ability to maintains homeostasis in response to innocuous foreign antigens (Mattila et al., 2011). Tolerance to self-antigens and harmless environmental antigens is critical to immunological functioning. This tolerance is achieved through the engagement of multiple cells such as Tregs and DCs (Probst et al., 2014). After sensing pathogen-derived molecular patterns (PAMPs) or other signals of inflammation and cellular distress, DCs differentiate into potent activators of naïve CD4 + ve and CD8 + ve T cells. DCs stand out as one of the master regulators of adaptive immunity owing to their indispensable role for both naıve T-cell priming and peripheral immune tolerance induction.

Epithelial derived cytokines such as interleukin (IL)-25, IL-33 and thymic stromal lymphopoietin (TSLP) prime and stimulate DC maturation and enhance the recruitment of Th2 effector cells (Papazian et al., 2014). Airway epithelial cells express a multitude of receptors such as protease activated receptors (PARs), scavenger receptors (SRs), and pattern recognition receptors (PRRs) of which the Toll-like-receptors (TLRs) are best known (Davies, 2014). These receptors allow the epithelium to interact and respond to contact with specific components of allergens and microbes with the release of pro or anti-inflammatory cytokines and chemokines.

Epithelial cytokine production and release as a response to these allergens and microbes may be drivers of asthma pathophysiology (Lloyd & Saglani, 2015). Most allergens, such as house dust mite (HDM), cockroach, and environmental fungi, are not intrinsically pathogenic to the host. However, some proteins or lipids from these organisms, or bacterial contaminants attached to allergens (e.g. lipopolysaccharide (LPS)) can trigger PRRs. HDM, for example, is known to contain at least 22 allergens that can activate immunoglobulin E (IgE) responses in human subjects (Hammad et al., 2009), as well as LPS, or their own microbiota in fecal pellets from HDM, that can act as the agonist for TLRs. Loss of epithelial integrity and subsequent breach of barrier function may also be due to proteolytic properties of the allergens themselves and this abnormality may be relevant in asthma (Xiao et al., 2011).

Allergen-induced release of chemokines and cytokines from the airway epithelium recruits neutrophils, eosinophils, mast cells, DCs and lymphocytes into the airways, as well as modulates their responses (Davies, 2014). Airway epithelial cells from asthmatic patients react differently after allergen stimulation compared with those from healthy individuals, by producing increased levels of IL-1, GM-CSF, and TNF-α (Mattoli et al., 1992). Several studies have shown that the airway epithelium influences DCs and subsequent T cell responses through mechanisms requiring direct contact between epithelial cells and DCs, as well as through secreted cytokines (Davies, 2014).

IL-25, IL-33 and TSLP are the airway epithelial alarmins that drive allergic Th2 reactions. Alarmins are defined as a group of immune-modulating molecules that are released from damaged and/or stressed