Cytokines in Induced Sputum: A Role for the Ratio of IL-6/IL-13 in the Differentiation of Asthma and Chronic Obstructive Pulmonary Disease?

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Asthma and chronic obstructive pulmonary disease (COPD) are both defined by the presence of airflow obstruction, airway remodeling, and airway inflammation, but the two conditions are clinically and pathophysiologically distinct [1, 2]. Therefore, it is quite common to observe patients with asthma showing COPD-like phenotypes, and vice versa, making it a priority to search for optimal prevention, treatment, and management strategies for each case. Studies on the underlying inflammation demonstrate differences in the preponderance of inflammatory cells and mediators in each disease [3]. The main characteristic of obstructive diseases of the lung is airway inflammation, which appears differently but with significant overlaps between asthma and COPD [4].

In the last years, airway inflammation has been revealed to be a very complex process in lung disease. In the last 3 decades, the number and role of humoral mediators has become increasingly known. In this field, cytokines (more exactly, cytokine balance) represent messengers for communication in the tissues. Particularly, secreted proteins that bind to their specific receptors and play a role in communication among leukocytes are named interleukins (ILs). Since the discovery of IL-1 in 1977, approximately 200,000 published articles have referred to ILs. In a recent review, ILs 1–37 were examined [5]. The

source of ILs is mainly the T helper lymphocyte (T_H). On the basis of IL profiles, CD41-naïve T cells can differentiate into T_H1 , T_H2 , T_H9 , T_H17 , T_H22 , and T-follicular effector cells, and these T-cell subsets can promote different types of inflammatory responses. For example, both T_H2 and T_H17 cytokines are thought to contribute to the pathogenesis of bronchial asthma. Evaluation of the relationship between different ILs provides a better measure of airway inflammation than measurement of each IL.

In this issue of *Respiration*, in the study of Grubek-Jaworska [6], IL-6 and IL-13 were chosen to evaluate the difference between asthma and COPD based on their balance. In fact, IL-6 and IL-13 are known to be involved in respiratory diseases.

IL-13 is secreted predominantly by T_H2 cells. It shares receptor components and many biological properties with IL-4. IL-13 receptors are expressed on mast cells, leukocyte subsets (eosinophils, monocytes, B cells), and structural cells (epithelial cells, fibroblasts, smooth muscle), all of which are considered relevant in asthma. The action of IL-13 on these cells is to stimulate processes that promote AHR, inflammation, and underlying airway structural changes including fibrosis and mucus hypersecretion, which are cardinal features of asthma [7]. IL-13 mRNA and protein levels are elevated in bronchial biop-

sies, sputum, and bronchoalveolar lavage (BAL) fluid from asthmatics compared to control subjects [8, 9] and they are further increased in BAL samples from allergen-challenged asthmatics [10]. IL-13 protein expression in the lung is also correlated with both asthma severity and control. Mild steroid-naïve asthmatics have upregulated IL-13 in the sputum compared to normals, as do severe asthmatics who have poor control despite the standard of care up to, and including, oral corticosteroids; moderate asthmatics controlled by inhaled corticosteroids do not have upregulated IL-13 expression [11]. Genetic polymorphisms in the IL-13 pathway are also associated with both atopy and asthma [12]; IL-13 Q130R has been associated with asthma, atopy, and raised serum IgE [13], activating the signalling IL-13 receptor (R α 1) and downstream functions more efficiently, while binding to the decoy receptor (R α 2) less efficiently, than wild-type IL-13 [14]. Given the range of cells involved in asthma on which IL-13 is known to act, and the pathogenic functions ascribed to this IL, a significant role for IL-13 in asthma can be expected. Neutralization of IL-13 is a credible approach for the treatment of asthma and allergy. An anti-IL-13 Ab showed specific action in the nasal allergen challenge model, causing profound inhibition of nasal lining fluid IL-13 responses [15]. Moreover, IL-13 neutralizing IgG4 mAb CAT-354 [16] in an animal model and IgG1 Ab neutralizing IL-13 bioactivity in a human model [17] are advancing toward clinical development, also demonstrating controversial results.

IL-6 is a pro-inflammatory cytokine that is secreted by the stimuli on T cells, being able to induce development of the inflammation by means of T_H17 and T_H22 cells by amplification of IL-6 production. This inflam-

matory mechanism provokes the neutrophilic reaction to fight, firstly, extracellular pathogens [5]. IL-6 is responsible for modulation of the synthesis of acute phase proteins such as C-reactive protein (CRP) [5] and plasma fibrinogen [18] in many models of inflammation in many tissues of the entire body. On this basis, IL-6 could be considered as a useful biomarker of COPD, a disease with systemic inflammation as marked by increased CRP. IL-6 is not exclusive to a single lung disease. In patients with asthma, similarly to IL-8, sputum IL-6 levels have an inverse relationship with FEV₁ [19]. In a prospective cross-sectional study in patients with mild asthma it was reported that sputum IL-6 levels correlated inversely with post-bronchodilator FEV₁ [20]. Other reports demonstrated a negative correlation between FEV₁ and sputum IL-6 and IL-8 levels and a weak correlation with asthma control [19]. Moreover, IL-6 proteins were found to be significantly increased in subjects with chronic rhinosinusitis with nasal polyps [21].

IL-13 and IL-6 are not specific for a single disease, but they show different relationships with asthma and COPD. A strong link between IL-13 and airway inflammation has been demonstrated in allergy and mainly in asthma, but no link has been found between IL-13 and pulmonary function levels. IL-6 is associated with systemic and local inflammation in COPD but is mainly related to pulmonary function. The balance between these two ILs increases the sensibility and specificity of the measures of airway inflammation. This contributes to the phenotypic characterization of obstructive pulmonary diseases which represents, presently and in the future, an important target in the management and treatment of respiratory diseases.

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