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Pathogenesis of airway inflammation in bronchial asthma

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Abstract

Bronchial asthma is a chronic disorder characterized by airway inflammation, reversible airway obstruction, and airway hyperresponsiveness. Eosinophils are believed to play important roles in the pathogenesis of asthma through the release of inflammatory mediators. In refractory eosinophilic asthma, anti-IL-5 mAb reduces exacerbations and steroid dose, indicating roles of eosinophils and IL-5 in the development of severe eosinophilic asthma. Even in the absence of IL-5, it is likely that the ''Th2 network'', including a cascade of vascular cell adhesion molecule-1/CC chemokines/GM-CSF, can sufficiently maintain eosinophilic infiltration and degranulation. Cysteinyl leukotrienes can also directly provoke eosinophilic infiltration and activation in the airways of asthma. Therefore, various mechanisms would be involved in the eosinophilic airway inflammation of asthma.

In the pathogenesis of severe asthma, not only eosinophils but also mast cells or neutrophils play important roles. Mast cells are much infiltrated to smooth muscle in severe asthma and induce airway remodeling by release of inflammatory mediators such as amphiregulin. Treatment with anti-IgE Ab, which neutralizes circulating IgE and suppresses mast cell functions, reduces asthma exacerbations in severe asthmatic patients. Furthermore, infiltration of neutrophils in the airway is also increased in severe asthma. IL-8 plays an important role in the accumulation of neutrophils and is indeed upregulated in severe asthma. In the absence of chemoattractant for eosinophils, neutrophils stimulated by IL-8 augment the trans-basement membrane migration of eosinophils, suggesting that IL-8-stimulated neutrophils could lead eosinophils to accumulate in the airways of asthma. In view of these mechanisms, an effective strategy for controlling asthma, especially severe asthma, should be considered.

Keywords: Bronchial asthma; Eosinophils; IL-5; Cysteinyl leukotrienes; Mast cells; Neutrophils

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1. Introduction

Bronchial asthma is a chronic disorder characterized by airway inflammation, reversible airway obstruction, mucus hypersecretion, and airway hyperresponsiveness (AHR) [1]. In the process of airway inflammation of asthma, a variety of cells, such as eosinophils, T lymphocytes, mast cells, neutrophils, and dendritic cells (DCs), are involved. In this review, recent advances in the pathogenesis of airway inflammation in asthma are discussed.

2. Eosinophilic airway inflammation in bronchial asthma

Eosinophils preferentially accumulate at sites of allergic inflammation and are believed to play important roles in the pathophysiology of asthma through the release of a variety of inflammatory mediators, including major basic protein (MBP), cysteinyl leukotrienes (CysLTs), radical oxygen species, and cytokines [2,3]. However, earlier studies involving anti-IL-5 mAb treatment of asthmatic patients raised the possibility that eosinophils may play only a limited role in asthma [4–6]. For example, Leckie et al. reported that anti-IL-5 treatment significantly reduced eosinophils in sputum or serum, but the Ab did not modify AHR to histamine or the magnitude of the late asthmatic response observed with allergen provocation [4], suggesting that eosinophils have no role in the development of AHR or airflow limitation in response to specific allergens.

A follow-up study with anti-IL-5 mAb revealed that the treatment only partly eliminated tissue eosinophilia and did not modify the deposition of MBP in the airways of asthmatic patients [7]. Although the interpretation of this study remains controversial, these findings suggest that IL-5 has a limited role in the development of eosinophilic infiltration and is not responsible for the release of specific granule proteins from eosinophils in mild asthma.

On the other hand, in asthmatic patients with persistent sputum eosinophilia, treatment with anti-IL-5 mAb reduced asthma exacerbations and the requirement for systemic corticosteroids, and improved asthma-related quality of life (QOL) [8,9]. These results strongly suggest essential role of eosinophils in the development of asthma exacerbation. Furthermore, antagonizing IL-5 could be an effective strategy for controlling refractory eosinophilic asthma, as well as controlling hypereosinophilic syndrome (HES) [10–12].

Accumulating evidence established that eosinophils largely contribute to the development of airway remodeling of asthma [13–15]. For example, Flood-Page et al. reported that anti-IL-5 mAb significantly reduced eosinophils expressing mRNA for transforming growth factor (TGF)-β and the concentration of TGF-β protein in bronchoalveolar lavage (BAL) fluid [13]. In their study, they also demonstrated that anti-IL-5 treatment reduced the deposi-

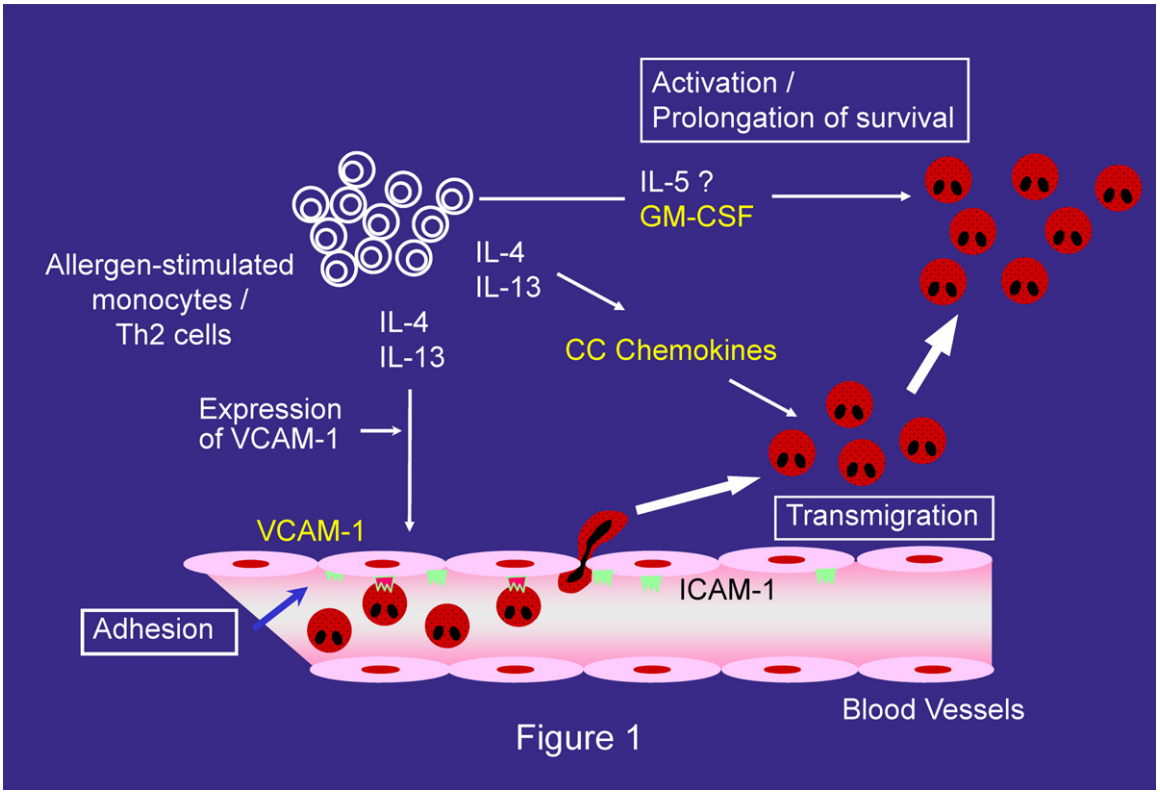

Fig. 1. Mechanisms of eosinophilic airway inflammation in bronchial asthma.