Tumor Necrosis Factor Alpha-Mediated Asthma?

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According to established knowledge, the mechanisms of allergic asthma are as follows: when an inhaled allergen penetrates the airway epithelium, it is detected by dendritic cells, which migrate to the lymph node and present the processed antigen to T cells, and B cells start to produce antigen-specific immunoglobulin E (IgE). IgE binds to Fcε receptors on a variety of cell types including mast cells and basophils. When an allergic individual is subsequently exposed to the specific allergen, the allergen binds to the specific IgE on the cells, causing activation of mast cells and basophils to release chemical mediators, such as histamine, arachidonic acid metabolites and proteases into the airway tissue. These mediators cause an early asthmatic response, which is an airway obstruction induced within 30 min after allergen exposure. There is also a specific population of asthmatic subjects which exhibits a late asthmatic response, i.e. an airway obstruction triggered several hours after allergen challenge and persisting for a relatively long time.

The late asthmatic response has been thought to be based on airway inflammation orchestrated by Th2 cells and eosinophils [1]. In addition to the early and late asthmatic responses, Th2-biased airway inflammation leads to airway hyperresponsiveness (AHR) to nonspecific stimuli and structural remodeling of airway tissues. Various experimental models reproduce these phenotypes of asthma.

Thus the pathophysiology of allergic asthma is traditionally explained by mast cell- and/or Th2 cell-mediated airway inflammation, which is a manifestation of the acquired immune response. On the other hand, recent studies have identified various other important molecules associated with phenotypes of asthma, including tumor necrosis factor (TNF-α) [2, 3], thymic stromal lymphoprotein [4, 5], interleukin (IL)-33 [6, 7] and IL-25 [8, 9]. TNF-α is produced mainly in macrophages and mast cells, and thymic stromal lymphoprotein, IL-33 and IL-25 are mainly from epithelial cells and various leukocytes. Those molecules are considered to play roles in the innate immune response. In order to understand novel pathophysiological mechanisms of asthma, a recent trend has been toward the generation of novel animal models, including asthma associated with both acquired and innate immunity, severe asthma such as steroid-resistant phenotypes [10–12], neutrophilic asthma [13, 14] and the viral exacerbation of allergic inflammation [15, 16]. It is believed that these new asthma models will lead to the development of new strategies for asthma.

In this issue of International Archives of Allergy and Immunology, Kim et al. [17] present a well-conducted murine asthma model of AHR, where part of the mechanism reported was TNF-α-mediated airway inflammation. They observed detailed time-course changes in the occurrence of AHR after antigen (ovalbumin) challenge in...
sensitized C57BL/6 mice, and found that a late AHR consists of 2 phases, with first and second phases peaking at 10 and 24 h, respectively. It was interesting that the first phase of late AHR was a TNF-α-dependent response because anti-TNF-α antibody and TNF-α knockout animals impaired the response. The second phase of late AHR, however, was not mediated by TNF-α. TNF-α was transiently produced in the airway 1.5–2 h after the antigen challenge, whereas only a single exogenous administration of TNF-α could reproduce the induction of AHR 10 h but not 24 h after administration. They suggested that the cellular source early after antigen challenge could be not only mast cells but also other inflammatory cells, such as macrophages, dendritic cells, eosinophils and platelets (which possess Fcγ receptors on their cell surface), because intratracheal instillation of the immune complex of IgG and antigen markedly developed AHR at 12 h in a TNF-α-dependent manner. In addition, they suggested that TNF-α-induced AHR was mediated by leukotriene B_4, which was produced by the activation of cytosolic phospholipase A_2 and 5-lipoxygenase. Finally, the second phase of late AHR was suggested to be induced by Th2 cell activation because its response (but not the first-phase response) was prevented by CpG-oligonucleotide, a well-established Th1 inducer. Collectively, first-phase response (but not the second phase of late AHR) was prevented by CpG-oligonucleotide, a well-established Th1 inducer. It is expected that the TNF-α-induced AHR model reported by Kim et al. [17] will be utilized to elucidate novel mechanisms underlying the pathogenesis of asthma and to develop new strategies against the disease.

References


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