

Th1/Th2 lymphocyte polarization in asthma

Asthma is a complex inflammatory disease of the lung characterized by variable airflow obstruction, bronchial hyperresponsiveness, and airway inflammation. Inflammation in asthma consists of airway infiltration by mast cells, lymphocytes, and eosinophils. There is accumulating evidence that CD4⁺ lymphocytes with a Th2-cytokine pattern play a pivotal role in the pathogenesis of asthma. These cells orchestrate the recruitment and activation of the primary effector cells of the allergic response (mast cells and eosinophils), through the release of cytokines such as IL-4, IL-5, and IL-13. Allergic inflammation is also implicated in airway epithelium changes, although the mechanisms by which inflammatory cells and, in particular, T cells interact with the epithelium are not completely clarified. This paper explores the role of T cells in the allergic inflammation of asthma.

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Asthma is a chronic disease characterized by three main events occurring in the airways: a partially reversible obstruction of the lower respiratory tract, increased bronchial responsiveness to several stimuli, and inflammation. While bronchial responsiveness has been considered the clinical hallmark of asthma, airway inflammation represents the key marker of this disease. Indeed, the severity of asthma reflects the degree of inflammation even in the mildest or asymptomatic forms of the disease that require little or no treatment (1, 2). Although asthma has a multifactorial origin, the common histopathologic findings consist of bronchial infiltration by eosinophils, mast cells, and lymphocytes.

Mast cells and eosinophils are considered to be the prominent effector cells in asthma. Upon different stimuli, these cells are able to secrete a large array of preformed and newly generated mediators that lead to tissue inflammation. Several other cell types such as lymphocytes, macrophages, and epithelial cells are involved in a complex network consisting of soluble factors mediating the cell–cell signaling critical in asthma inflammation (3, 4). Recently, a large body of data have indicated that CD4⁺ T helper (Th) cells producing a Th2-like pattern of cytokines play a critical role in determining the disease (5). This paper will focus on Th cells and their pivotal role in modulating

interactions between different cell types which concur in establishing airway inflammation in asthma.

Th1/Th2-cell subsets in asthma

As we have already mentioned, mast cells and eosinophils are commonly considered to be the principal effector cells of allergic airway response, but growing evidence suggests the pivotal importance of T cells in the induction and persistence of airway inflammation in asthma (5). T cells play a central role in controlling immune responses, as they are the cells that determine the specificity of the response (12). T cells are able to kill target cells directly, to provide help for such killing, to help B cells mount an antibody response, and to down-modulate the activities of various immune system cells as well as to activate them. Most of these T-cell functions derive from the production of cytokines, chemokines, and other mediators. Studies performed on murine CD4⁺ T-cell clones have divided Th cells into at least two distinct subsets depending on their profiles of cytokine secretion: Th1, which produces interleukin-2 (IL-2), IL-12, interferon (IFN)- γ , and tumor necrosis factor (TNF)- β ; and Th2, which secretes IL-4, IL-5, IL-6, IL-10, and IL-13 but no or very low levels of IL-2 and IFN- γ . Both types of Th cells synthesize IL-3, granulocyte-macrophage colony-stimulating factor

(GM-CSF), and TNF- α (6). Most human T-cell clones do not fit strictly into the murine Th1 and Th2 categories, although representatives of these two subsets do exist (7, 8). It is not clear whether, and to what extent, the nature of the antigen may influence the quality of the response producing an imbalance of the Th1 or Th2 phenotype. Th1 cells induce delayed hypersensitivity responses and promote the activation of specific cytotoxic lymphocytes (CD8+ T cells and natural killer [NK] cells) by secretion of IL-2 and IFN- γ (9).

Recent evidence has shown that CD8+ T cells can also function as helper cells and produce cytokines (10, 11).

Th2 cells are needed for the differentiation and proliferation of B cells. Their production of IL-4, IL-5, IL-10, and IL-13 induces B-cell differentiation to plasma cells, and the production of IL-4 mainly promotes the IgG-IgE switch (12, 13). The cross-talk between T and B cells is mediated by two main signals:

- 1) soluble T-cell-derived factors (cytokines)
- 2) T/B cell-to-cell physical contact through the CD40/CD40L system (14).

Th1 cells may control Th2 cells and vice versa. The production of IL-4 and IL-10 by Th2 cells blocks the production of cytokines by Th1 and NK cells. Th1 cells, by secreting IFN- γ , inhibit the proliferation and differentiation of basophils, mastocytes, and eosinophils, whose activities are controlled by the Th2 synthesis of IL-3, IL-4, IL-5, and IL-10 (14–18). The interplay of Th1/Th2 with the other cells controls the release of mediators accounting for the inflammatory response (5). IFN- γ is the main macrophage-activating factor; in combination with TNF- β , it increases the bactericidal and tumoricidal activity of the mononuclear phagocytes (14). While IFN- γ produced by Th1 cells enhances IL-1 and TNF- β secretion by macrophages, IL-4 or IL-10 secreted by Th2 cells may strongly inhibit the synthesis of these proinflammatory molecules (17, 18).

A consistent number of T cells, mainly those CD4+, have been found in bronchoalveolar lavage (BAL) fluid and bronchial biopsies from asthmatics (1–3, 19). Several authors have shown that the depletion of CD4+ T cells abrogates recruitment of eosinophils during allergic inflammation *in vivo* (20).

There is considerable evidence of the role of Th2 cells in the pathogenesis of asthma, but very little is known about the mechanisms determining the aberrant expansion of Th2 cells within asthmatic airways. The number of cells expressing Th2 cytokine mRNA are increased during allergic inflammation (21, 22). In some cases, CD4+ T cells from atopic patients display an aberrant *in vitro* production of IL-4 and IL-5 even in response to antigens that usually elicit Th1 responses (23, 24).

Allergen-induced asthma and bronchial hyperresponsiveness are abolished in IL-5 knockout mice, and also in animals treated with anti-IL-5 antibodies, while reconstitution of IL-5 deficiency in IL-5 knockout mice can restore the bronchial hyperreactivity (20). In contrast to the asthma-promoting effects of the Th2 cytokines, treatment of animals with the Th1 cytokine IFN- γ decreases eosinophil recruitment during allergic inflammation (5, 20). Thus, molecules capable of decreasing IgE levels, of Th2 cytokine production, and of increasing Th1 cytokine production can inhibit allergic reactions. On the basis of this idea, several studies have tested the capacity of IL-12 to decrease Th2 cytokine synthesis *in vitro* and *in vivo* (25, 26). In all the experiments performed, it has been demonstrated that IL-12 influences allergic inflammation and bronchial hyperresponsiveness. Recently several papers have reported that IL-12 treatment decreases IgE production *in vivo* and *in vitro* and has strong immunomodulatory effects on allergic lung inflammation, depending on the timing of IL-12 administration relative to allergic sensitization and allergen challenge (3, 5).

Taken together, these observations provide further evidence for the importance of Th2-polarized cells and the associated cytokine profile in the induction and maintenance of inflammatory events within the asthmatic airway.

T cells and airway epithelium interaction

The human airway epithelium, as primary target for heterogeneous external stimuli, has evolved a number of elaborate protective functions: physiologic (including mucus and surfactant production, and changes in ciliary beating), biologic (production and release of inflammatory mediators), and immunologic (expression of accessory molecules, including adhesion proteins involved in cell trafficking). Loss of epithelial integrity results in easier access of allergen/chemicals and microorganisms to underlying tissue.

The airway epithelium exerts effector functions, as epithelial cells synthesize and secrete an array of potent mediators such as leukotrienes (LTC₄ and LTD₄), prostanoids, and cytokines (including IL-1 α , IL-1 β , IL-6, IL-8, TNF- α , TNF- β , GM-CSF, and RANTES) (27). Airway epithelial cells have also been shown to have antigen-presenting capabilities. As epithelial cells line the respiratory tract, they are ideally located to encounter antigens and present them to T cells. The expression of costimulatory molecules important in antigen presentation, such as MHC class II, CD40, B7 molecules, and ICAM-1, also suggests a role as antigen-presenting cells for epithelial cells (28). However, their role in antigen presentation in the lung needs to be further explored.

An important link between epithelial cell function and the pathogenesis of asthma is represented by the expression on their cell surface of adhesion molecules (CAMs), which are important in the phenomena of cell adhesion and recognition. In particular epithelial cells express the intercellular adhesion molecule-1 (ICAM-1), a critical protein in cell-tissue trafficking. This molecule, interacting with the counterreceptor leukocyte function-associated antigen-1 (LFA-1) expressed on leukocytes, is involved in cell migration to the airway epithelium.

The importance of adhesion molecules in asthma has been further highlighted, since ICAM-1 has been implicated as the cell receptor for the most common virus associated with asthma exacerbations: human rhinovirus (HRV) (29–31).

Studies have demonstrated that airway epithelial cells from atopic/asthmatic subjects show a marked upregulation of surface ICAM-1 when compared to epithelial cells from normal healthy subjects (32). On the one hand, this enhanced expression of ICAM-1 is responsible for inflammatory cell recruitment within the airway, while, on the other hand, favoring HRV cell attachment and entry.

The mechanisms by which adhesion molecules are overexpressed on epithelial cells within the asthmatic airway remains to be clarified.

Recently, it has been observed that the Th2-associated cytokines (IL-4, IL-5, IL-10, and IL-13) exert, *in vitro*, a marked upregulation of surface ICAM-1 on epithelial cell (33). In the same studies, it has been shown that HRV further increases Th2-induced ICAM-1 expression on epithelial cells. These observations may explain, in part, ICAM-1 overexpression on the epithelial cells of asthmatics. Moreover, this phenomenon could represent an example of the Th1/Th2 cell interaction with

epithelium resulting in asthma. This evidence supports the importance of the airway epithelium as an active component of the immunobiologic phenomena accounting for ongoing disease in asthma.

Conclusions

The inflammatory process in asthma is believed to be the result of inappropriate immune responses to common aeroallergens in genetically susceptible individuals. Airway inflammation is the result of a complex interplay of leukocytes, epithelial cells, and endothelial cells, regulated by a network of cytokines, growth factors, and adhesion molecules. According to a common view, CD4⁺ cells with a Th2-cytokine profile orchestrate airway inflammation in asthma. This cell subset promotes recruitment and activation of the primary effector cells of the allergic response (mast cells and eosinophils) as well as IgE isotype switching.

The biologic mechanisms promoting expansion of Th2 cells in asthma are still unclear. Current investigations suggest that altered regulations of the genes controlling IL-4/IL-13 or IL-12 production may be critical in Th2 cell expansion. However, the genetic alterations underlying asthma are far from being elucidated. To date, the control of mediators released from mast cells and eosinophils has been considered the principal means to inhibit allergic reactions. The data summarized here suggest that the ability to control T-cell activation upon allergen stimulation may lead to a therapeutic approach able to cure the disease. These findings indicate a new way to clarify the pathophysiology of asthma, suggesting a new approach to develop therapeutic strategies to manipulate the airway cell/cytokine environment.

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